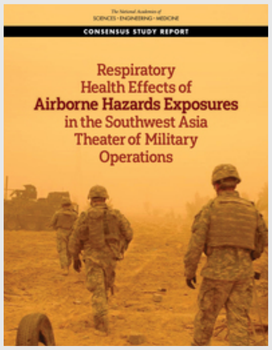

Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations (2020)

DETAILS

270 pages | 8.5 x 11 | PAPERBACK
ISBN 978-0-309-67910-7 | DOI 10.17226/25837

CONTRIBUTORS

Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations; Board on Population Health and Public Health Practice; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine

SUGGESTED CITATION

National Academies of Sciences, Engineering, and Medicine 2020. *Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25837.

Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations

Committee on the Respiratory Health Effects of
Airborne Hazards Exposures in the
Southwest Asia Theater of Military Operations

Board on Population Health and Public Health Practice

Health and Medicine Division

A Consensus Study Report of

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu

THE NATIONAL ACADEMIES PRESS **500 Fifth Street, NW** **Washington, DC 20001**

This activity was supported by Contract Order No. 36C24E18C0068 between the National Academy of Sciences and the Department of Veterans Affairs. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

International Standard Book Number-13: 978-0-309-67910-7
International Standard Book Number-10: 0-309-67910-9
Digital Object Identifier: https://doi.org/10.17226/25837

Additional copies of this publication are available from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

Printed in the United States of America

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2020. *Respiratory health effects of airborne hazards exposures in the Southwest Asia Theater of Military Operations*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25837.

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

The **National Academy of Sciences** was established in 1863 by an Act of Congress, signed by President Lincoln, as a private, nongovernmental institution to advise the nation on issues related to science and technology. Members are elected by their peers for outstanding contributions to research. Dr. Marcia McNutt is president.

The **National Academy of Engineering** was established in 1964 under the charter of the National Academy of Sciences to bring the practices of engineering to advising the nation. Members are elected by their peers for extraordinary contributions to engineering. Dr. John L. Anderson is president.

The **National Academy of Medicine** (formerly the Institute of Medicine) was established in 1970 under the charter of the National Academy of Sciences to advise the nation on medical and health issues. Members are elected by their peers for distinguished contributions to medicine and health. Dr. Victor J. Dzau is president.

The three Academies work together as the **National Academies of Sciences, Engineering, and Medicine** to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The National Academies also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding in matters of science, engineering, and medicine.

Learn more about the National Academies of Sciences, Engineering, and Medicine at **www.nationalacademies.org**.

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Consensus Study Reports published by the National Academies of Sciences, Engineering, and Medicine document the evidence-based consensus on the study's statement of task by an authoring committee of experts. Reports typically include findings, conclusions, and recommendations based on information gathered by the committee and the committee's deliberations. Each report has been subjected to a rigorous and independent peer-review process and it represents the position of the National Academies on the statement of task.

Proceedings published by the National Academies of Sciences, Engineering, and Medicine chronicle the presentations and discussions at a workshop, symposium, or other event convened by the National Academies. The statements and opinions contained in proceedings are those of the participants and are not endorsed by other participants, the planning committee, or the National Academies.

For information about other products and activities of the National Academies, please visit www.nationalacademies.org/about/whatwedo.

COMMITTEE ON THE RESPIRATORY HEALTH EFFECTS OF AIRBORNE HAZARDS EXPOSURES IN THE SOUTHWEST ASIA THEATER OF MILITARY OPERATIONS

MARK J. UTELL (*Chair*), Professor of Medicine and Environmental Medicine, Director of Occupational and Environmental Medicine, former Director of Pulmonary and Critical Care Medicine, University of Rochester Medical Center

LUNG-CHI CHEN, Professor, Department of Environmental Medicine, New York University Grossman School of Medicine

ELLEN A. EISEN, Professor, School of Public Health, University of California, Berkeley

MEREDITH FRANKLIN, Associate Professor, Division of Biostatistics, Keck School of Medicine, University of Southern California; Director of MS Programs in Biostatistics, Health Data Sciences, and Epidemiology

KIRK D. JONES, Clinical Professor, University of California, San Francisco

MEREDITH C. McCORMACK, Associate Professor of Medicine and Medical Director, Pulmonary Function Laboratory, Johns Hopkins University; Vice Chair, American Thoracic Society Committee for Proficiency Standards in Pulmonary Function Testing

CECILE S. ROSE, Professor of Medicine, National Jewish Health, Division of Environmental and Occupational Health Sciences, Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado School of Medicine

FRANK E. SPEIZER, Professor of Environmental Science, Harvard T.H. Chan School of Public Health, Edward H. Kass Distinguished Professor of Medicine, Harvard Medical School

ELAINE SYMANSKI, Professor, Center for Precision Environment Health, Department of Medicine, Baylor College of Medicine

SVERRE VEDAL, Professor Emeritus, Department of Environmental and Occupational Health Sciences, School of Public Health, University of Washington

JODY WIREMAN, Environmental Health Advisor, Defense Health Agency

Study Staff

DAVID A. BUTLER, Scholar and Study Director

ELIZABETH BARKSDALE BOYLE, Program Officer

CHRISTINA R. SAMUEL, Research Associate

REBECCA F. CHEVAT, Senior Program Assistant

ANNE N. STYKA, Senior Program Officer

KRISTIN E. WHITE, Associate Program Officer

ROSE MARIE MARTINEZ, Senior Director, Board on Population Health and Public Health Practice

Reviewers

This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

GEORGIANA BROOKE ANDERSON, Colorado State University
VICTORIA CASSANO, Performance Medicine Consulting, LLC
CAROLYN COMPTON, Arizona State University
SARAH C. R. ELGIN, Washington University in St. Louis
DIANE GOLD, Harvard University
PHILIP I. HARBER, University of Arizona
HOWARD KIPEN, Rutgers University School of Public Health
PETROS KOUTRAKIS, Harvard University
CARRIE A. REDLICH, Yale School of Medicine
RICHARD B. SCHLESINGER, Pace University

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report, nor did they see the final draft before its release. The review of this report was overseen by **SANDRO GALEA,** Boston University School of Public Health, and **DAVID A. SAVITZ,** Brown University. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Acknowledgments

The committee could not have written this report without the help of a number of people. We wish to particularly thank the presenters and participants in our October 2019 workshop—listed in Appendix A—who shared their expertise and perspectives on respiratory health issues in veterans and the research that might allow a better understanding of them. Drs. R. Loren Erickson and Eric Shuping of the Department of Veterans Affairs also briefed the committee and responded to our follow-up questions.

The committee members are very appreciative of the outstanding efforts of the staff of the National Academies of Sciences, Engineering, and Medicine's Health and Medicine Division, who supported us in our work, David Butler, who served as study director; and Elizabeth Boyle, Christina Samuel, Anne Styka, Kristin White, and Stephanie Hanson, who had a daunting task of identifying and culling the large and complex literature we reviewed and more generally guiding and assisting the committee in its mission. We are also very grateful to Rebecca Chevat for capably providing logistical support. Finally, we would like to acknowledge Jorge Mendoza, a senior research librarian who conducted the literature searches for the committee, and Misrak Dabi, the financial business partner for the project.

Mark J. Utell, *Chair*
Committee on the Respiratory Health Effects of
Airborne Hazards Exposures in the
Southwest Asia Theater of Military Operations

Contents

APPENDIXES

Acronyms and Abbreviations

AEP	acute eosinophilic pneumonia
AFRL	Air Force Research Laboratory
AH&OBP	Airborne Hazards and Open Burn Pit
AHBPCE	VA Airborne Hazards and Burn Pits Center of Excellence
AHCE	Airborne Hazards Center of Excellence
ARDS	acute respiratory distress syndrome
ATS	American Thoracic Society
BALF	bronchoalveolar lavage fluid
BMI	body mass index
CARC	chemical agent resistant coating
CBRNE	Chemical, Biological, Radiological, Nuclear, and high yield Explosives
CDC	Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Programs
CHAI	Comparative Health Assessment Interview
CHPPM	U.S. Army Center for Health Promotion and Preventive Medicine
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
COPD	chronic obstructive pulmonary disease
CT	computed tomography
DARPA	Defense Advanced Research Projects Agency
DECAMP	Detection of Early Lung Cancer Among Military Personnel
DHA	Defense Health Agency
DHB	Defense Health Board
DL/VA	the ratio of DLCO to alveolar volume
DLCO	diffusing capacity of the lung to carbon monoxide
DMDC	Defense Manpower Data Center

DMSS	Defense Medical Surveillance System
DoD	Department of Defense
DoDSR	Department of Defense Serum Repository
DOEHRS-IH	Defense Occupational and Environmental Health Readiness System–Industrial Hygiene
DSRR	directly standardized relative risk
DU	depleted uranium
ECG	electrocardiogram
ECRHS	European Community Respiratory Health Survey
EHR	electronic health record
EPA	Environmental Protection Agency
EPMSP	Enhanced Particulate Matter Surveillance Program
ERS	European Respiratory Society
ESA	European Space Agency
FEF	forced expiratory flow
FEV	forced expiratory volume
FEV_1	forced expiratory volume in 1 second
FOT	forced oscillation technique
FRC	functional residual capacity
FVC	forced vital capacity
GINA	Global Initiative for Asthma
GM-CSF	granulocyte-macrophage colony-stimulating factor
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	hazard ratio
HYSPLIT	Hybrid Single Particle Lagrangian Integrated Trajectory
ICD-9-CM	*International Classification of Diseases, Ninth Edition, Clinical Modification*
IgA	immunoglobulin A
IIP	idiopathic interstitial pneumonia
ILER	Individual Longitudinal Exposure Record
IOM	Institute of Medicine
IOS	impulse oscillometry
IPF	idiopathic pulmonary fibrosis
IR	incidence rate
IRB	institutional review board
IRR	incidence rate ratio
JPC	Joint Pathology Center
LCI	lung clearance index
LLN	lower limit of normal
LTBI	latent tuberculosis infection
MAIA	Multi-Angle Imager for Aerosols
MeSH	medical subject heading
miRNA	micro RNA
MISR	Multi-angle Imaging SpectroRadiometer

MODIS	Moderate Resolution Imaging Spectroradiometer
MOS	military occupational specialty
MRE	meals, ready-to-eat
MRR	mortality rate ratio
n	population size
NAAQS	National Ambient Air Quality Standards
NAS	National Academy of Sciences
NASA	National Aeronautics and Space Administration
n.d.	no date
NewGen	National Health Study for a New Generation of U.S. Veterans
NF-κB	nuclear factor kappa B
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NHS	National Health Survey of Gulf War Veterans and Their Families
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NOAA	National Oceanic and Atmospheric Administration
NRC	National Research Council
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OMI	Ozone Mapping Instrument
OND	Operation New Dawn
OR	odds ratio
p	p-value
PAH	polycyclic aromatic hydrocarbon
PAP	pulmonary alveolar proteinosis
PCB	polychlorinated biphenyl
PCDD/F	polychlorinated dibenzo-*p*-dioxin and dibenzo-*p*-furan
PDF	portable document format
PET	positron emission tomography
PFT	pulmonary function test
pIgR	polymeric immunoglobulin receptor
PIR	proportional incidence ratio
PL	Public Law
PM	particulate matter
POEMS	periodic occupational and environmental monitoring summary
PTSD	posttraumatic stress disorder
RAC	Research Advisory Committee on Gulf War Veterans' Illnesses
R_{aw}	airways resistance
RD	rate difference
RFI	request for information
RR	rate ratio
RV	residual volume
SHADE	Service and Health Among Deployed Veterans

SIR	standardized incidence ratio
SMR	standardized mortality ratio
SPIROLA	Spirometry Longitudinal Data Analysis
SSIC	signs, symptoms, and ill-defined conditions
STAMPEDE	Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures
TB	tuberculosis
TBI	traumatic brain injury
TLC	total lung capacity
TSP	total suspended particles
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
VO_2	volume of oxygen (O_2)
VOC	volatile organic compound
WHO	World Health Organization
WRIISC	VA War Related Illness and Injury Study Center

Summary

More than 3.7 million U.S. service members have participated in operations taking place in the Southwest Asia Theater of Military Operations since 1990. These operations include the 1990–1991 Persian Gulf War, a post-war stabilization period spanning 1992 through September 2001, and the campaigns undertaken in the wake of the September 11, 2001, attacks.

Deployment to the Southwest Asia theater—which for the purposes of this report is defined as Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Gulf of Aden, Gulf of Oman, Oman, Qatar, the United Arab Emirates, and the waters of the Persian Gulf, the Arabian Sea, and the Red Sea—exposed service members to a number of airborne hazards, including oil-well fire smoke, emissions from open burn pits, dust and sand suspended in the air, and exhaust from diesel vehicles. The effects of these were compounded by stressors like excessive heat and noise that are inevitable attributes of service in a combat environment.

During and after the initial Gulf conflict, veterans began reporting a variety of health problems. In response to the concerns raised, Congress has passed laws mandating the study of health outcomes in theater veterans, and the Department of Defense (DoD) and the Department of Veterans Affairs (VA) have undertaken their own initiatives to address outstanding questions.

In September 2018, VA requested the National Academies of Sciences, Engineering, and Medicine to form an expert committee to undertake a study of the evidence regarding respiratory health outcomes in veterans of the Southwest Asia conflicts and to identify gaps in this evidence, research that could feasibly be conducted to address outstanding questions and generate answers, newly emerging technologies that could aid in these efforts, and organizations that VA might partner with to accomplish this work. Its full Statement of Task is reproduced as Box S-1. This report, prepared by the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations, provides responses to the elements of that task.

INFORMATION-GATHERING EFFORTS

The committee formed to address VA's charge comprised 11 experts in epidemiology, pulmonology, pathology, exposure assessment, military and veterans' health, and toxicology. It held five in-person meetings between March 2019 and February 2020; additional, later meetings were conducted remotely. One meeting included a workshop where the investigators involved in the epidemiologic studies named in the Statement of Task were invited to give updates on their work and other experts presented the latest scientific and medical developments regarding

BOX S-1
Statement of Task

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will comprehensively review, evaluate, and summarize the available scientific and medical literature regarding the respiratory health effects of exposure to airborne hazards encountered during service in the Southwest Asia Theater of Military Operations and Afghanistan. The report will pay particular attention to:

- hazards associated with burn pit exposures;
- excess mortality, cancer, bronchial asthma, chronic bronchitis, sinusitis, constrictive bronchiolitis, and other respiratory health outcomes that are of great concern to veterans; and
- emerging evidence on respiratory health outcomes in service members from research such as the Millennium Cohort Study, Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE), National Health Study for a New Generation of U.S. Veterans, Comparative Health Assessment Interview (CHAI) Study, Pulmonary Health and Deployment to Iraq and Afghanistan Objective Study, Effects of Deployment Exposures on Cardiopulmonary and Autonomic Function Study, and research being conducted by the Department of Veterans Affairs (VA) War Related Illness and Injury Study Center (WRIISC) Airborne Hazards Center of Excellence (AHCE) in New Jersey.

It will evaluate the extent to which existing knowledge base informs the understanding of the potential adverse effects of in-theater military service on respiratory health, identify gaps, research that could feasibly be conducted to address outstanding questions and generate answers, newly emerging technologies that could aid in these efforts, and organizations that VA might partner with to accomplish this work.

The committee shall produce a final report detailing the conduct of these activities and offering any findings, conclusions, and recommendations it deems appropriate.

respiratory health, airborne exposure assessment, and exposure characterization research. Veterans and veteran service organization representatives also presented their views.

Several other activities were undertaken to develop the scientific foundation for the report's findings, conclusions, and recommendations. These included detailed searches of the published peer-reviewed literature dating back to 1991, requests for information from VA and from authorities in the fields under consideration, and examination of additional pertinent publicly available literature, including relevant National Academies reports. This report builds on earlier literature reviews published as part of the *Gulf War and Health* series of National Academies reports—in particular, *Volume 4: Health Effects of Serving in the Gulf War*; *Volume 8: Update of Health Effects of Serving in the Gulf War*; and *Volume 10: Update of Health Effects of Serving in the Gulf War, 2016*—as well as two related reports: *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan* and *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry*.

THE COMMITTEE'S APPROACH TO ANALYZING THE AVAILABLE INFORMATION

The committee's literature review was a targeted examination of epidemiologic studies of respiratory health outcomes—including excess mortality due to respiratory disease—in military and veteran populations potentially exposed to airborne hazards in the Southwest Asia theater. It was focused on studies of these populations that had not been previously summarized in earlier National Academies reports. The committee considered whether there were any other non-military population groups that might provide supplemental information but concluded that the differences in the airborne exposures encountered by such groups—specifically, differences in the composition of the chemical agents and particulates and in the duration, intensity, and other circumstances of exposure—were too great to justify their use in evaluations of the health effects of military service in Southwest Asia.

Toxicologic studies, which include studies of laboratory animals and cell cultures, focus on mechanisms rather than clinical outcomes. As such these studies were included as supplemental sources of information where relevant, but they were not reviewed in a comprehensive manner as the epidemiologic literature was.

The committee's evaluation of the evidence considered the extent to which a particular study was well designed and methodologically sound. This included whether it specifically examined respiratory health outcomes; identified an appropriate comparison group; had an adequate sample size and power to detect an effect if one existed; characterized the airborne exposure(s) it considered as thoroughly as the available data permitted; performed rigorous health outcome assessment based, to the extent possible, on objective measures and tests over an appropriate time period; ascertained and factored known and potential confounders; and used appropriate statistical analyses. All of these considerations were taken in account when weighing how much a study should contribute to the committee's overall evaluation of the literature base.

Categories of Association

A system of four categories of association was used to classify the strength of scientific evidence of respiratory health outcomes following exposure to airborne hazards in the Southwest Asia theater. These categories were adapted from a system used by the International Agency for Research on Cancer. They have gained wide acceptance by Congress, VA, researchers, and veterans groups and have been used in several previous National Academies reports addressing health issues for veterans of the Southwest Asia theater conflicts and Vietnam. The criteria for each of the four categories of association define a degree of confidence with which a conclusion can be drawn based on the extent to which bias and other sources of error could be reduced and thus on the quality of the evidence. Implicit in these categories is the idea that "the absence of evidence is not evidence of absence." That is, based on the currently available literature that met the committee's criteria for inclusion, a lack of informative data does not mean that there is no increased risk of a specific adverse event, only that the available evidence does not allow a conclusion to be drawn regarding an association.

The committee considered the full body of available information, including supplemental evidence, when reaching a judgment about association for a given outcome. Where the literature base allowed, separate conclusions were made for 1990–1991 Gulf War veterans and post-9/11 veterans. Four categories of association were used to classify outcomes.

For effects to be classified as having "sufficient evidence of an association," a positive association between one or more in-theater airborne exposures and a respiratory health outcome in humans must have been observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence.

For health outcomes in the category of "limited or suggestive evidence of an association," the evidence must suggest an association between an in-theater exposure and a respiratory outcome in studies of humans, but it can be limited by an inability to confidently rule out chance, bias, or confounding. Because there are a number of agents of concern whose toxicity profiles are not expected to be uniform—specifically, the many airborne hazards that may be encountered in theater—apparent inconsistencies can be expected among study populations that have experienced different exposures.

By default, any health outcome is placed in the category of "inadequate or insufficient evidence to determine an association" unless enough reliable scientific data have accumulated to categorize it elsewhere. In this category, the available human studies of exposure to airborne hazards in the Southwest Asia theater and respiratory conditions may have inconsistent findings or be of insufficient quality, validity, consistency, or statistical power to support a conclusion regarding the presence of an association. Such studies might have failed to control for confounding factors (such as smoking) or might have had an inadequate assessment of exposure. In some cases, the body of evidence is too small to permit firm conclusions, such as when there are no available studies to validate or corroborate the findings of a single study. In other cases, some evidence from human studies exists, but the heterogeneity of exposures, outcomes, and methods leads to inconsistent findings that preclude a more definitive conclusion. If a respiratory condition or outcome is not addressed specifically in this report, then it can be considered to be in this category.

The category of "limited or suggestive evidence of no association" is used for health outcomes for which several adequate studies covering the full range of human exposure were consistent in showing no association or a reduced risk with an exposure to airborne hazards encountered in the Southwest Asia theater at any concentration, with the studies having relatively narrow confidence intervals. A conclusion of "no association" is inevitably limited to the conditions, exposures, and observation periods covered by the available studies, and the possibility of a small increase in risk related to the magnitude of exposure studied can never be excluded.

AIRBORNE HAZARDS ENCOUNTERED IN THE SOUTHWEST ASIA THEATER

Southwest Asia theater veterans were exposed to a broad range of potentially hazardous airborne agents. These include such regional environmental exposures as air pollution from dusts; local point and area sources such as traffic, waste management, and local industries; and the aeroallergens and microbial agents present in the theater. Exposures related to military operations are also contributors, such as exhaust from heaters, military vehicles, and aircraft as well as smoke from structural fires, explosions, burning oil wells, or burn pits. One of these exposures, particulate matter, has received special attention because a growing body of literature suggests that it is associated with a number of adverse respiratory and other health effects. Additionally, some service members had occupations, job duties, or tasks that exposed them to a variety of vapors, gases, dusts, and fumes. Exposures differed by conflict and varied by location and over time. For example, 1990–1991 Gulf War veterans are more likely to have been exposed to smoke from oil-well fires, which were set by Iraqi forces as they retreated. In 2003 a fire ignited at the Mishraq State Sulfur Mine Plant near Mosul, Iraq, and burned for almost 1 month, releasing high concentrations of sulfur dioxide and hydrogen sulfide into the surrounding area. Veterans of the post-9/11 conflicts are more likely to have been exposed to emissions from burn pits, which were in operation for extended periods on bases where large numbers of personnel worked and lived.

The health effects of these airborne hazards were likely influenced by factors common to military operations in Southwest Asia. These effect modifiers include temperature extremes, psychosocial stress, sleep deprivation, and noise.

CONCLUSIONS REGARDING THE ASSOCIATION BETWEEN IN-THEATER AIRBORNE HAZARDS AND RESPIRATORY HEALTH OUTCOMES

The committee formulated a list of 27 health outcomes for their literature review, delineated in Box S-2. The list included the conditions explicitly listed in the Statement of Task and those that the committee believed to be "of great concern to veterans."

Of these outcomes, none met the criteria for sufficient evidence of an association. The evidence for respiratory symptoms—which included chronic persistent cough, shortness of breath (dyspnea), and wheezing—met the criteria for limited or suggestive evidence of an association for both veterans who served in the 1990–1991 Gulf War and those who served in the post-9/11 conflicts. Studies considered in previous National Academies reports were relatively consistent in reporting associations between deployment and more prevalent self-reported respiratory symptoms in theater veterans, and outcomes from more recent studies are largely in line with those findings. Importantly, a recent study that compared symptom reporting before, during, and after deployment found that the self-reported frequency of symptoms was increased both during and after deployment relative to pre-deployment.[1] Many of the studies considered, however, were weakened by bias induced by the self-selection of their participants (which may have led to people being more likely to participate if they had respiratory symptoms than if they did not) and by the lack of control for cigarette smoking, which is known to exacerbate symptoms. These concerns, while serious, were consistent with a classification in the limited or suggestive category. Lastly, the committee

[1] Morris, M. J., A. J. Skabelund, F. A. Rawlins III, R. A. Gallup, J. K. Aden, and A. B. Holley. 2019. Study of Active Duty Military Personnel for Environmental Deployment Exposures: Pre- and Post-Deployment Spirometry (STAMPEDE II). *Respiratory Care* 64(5):536–544.

BOX S-2
Respiratory Health Outcomes Addressed

Non-Cancer Respiratory Disorders

Upper Airway Disorders

- Rhinitis
- Sinusitis
- Sleep apnea
- Vocal cord dysfunction

Non-Infectious Lower Airway

- Asthma
- Chronic bronchitis
- Chronic obstructive pulmonary disease
- Constrictive bronchiolitis
- Emphysema

Interstitial Lung Diseases

- Acute eosinophilic pneumonia
- Hypersensitivity pneumonitis
- Idiopathic interstitial pneumonia
- Idiopathic pulmonary fibrosis
- Pulmonary alveolar proteinosis
- Sarcoidosis

Infectious Lower Airway

- Acute bronchitis
- Pneumonia
- Tuberculosis

Respiratory Symptoms

- Chronic persistent cough
- Shortness of breath (dyspnea)
- Wheeze

Respiratory Cancers

- Esophageal cancer
- Laryngeal cancer
- Lung cancer
- Oral, nasal, and pharyngeal cancers

Other Outcomes

- Changes in pulmonary function
- Mortality due to diseases of the respiratory system

concluded that there is limited or suggestive evidence of no association between deployment to the 1990–1991 Gulf War and changes in lung function.

The committee found that there was inadequate or insufficient information to evaluate the association between service in the Southwest Asia theater and all of the remaining respiratory health outcomes it examined. While there are a variety of reasons for this that vary by the outcome under consideration, one prominent cause was the lack of good exposure characterization. Many studies used deployment to the theater as their only metric of exposure, and this undoubtedly led to people with widely different exposure experiences being grouped together for analysis purposes. Such grouping would be expected to diminish the possibility of observing an effect if one existed if there were large numbers of those with relatively low exposure compared with those with relatively high exposure.

Another reason for conclusions of inadequate or insufficient evidence of associations was the widespread use of self-reported health outcomes and exposures. In the military deployment setting, this can be an issue if, for example, those who have a respiratory health problem are more likely to recall airborne exposures than those who do not or, alternatively, if those who experienced airborne exposures are more likely to report a respiratory health problem.

CHALLENGES AND OPPORTUNITIES FOR ADVANCING THE UNDERSTANDING OF RESPIRATORY HEALTH ISSUES IN SOUTHWEST ASIA THEATER VETERANS

The committee's Statement of Task requested it to "pay particular attention to hazards associated with burn pit exposures" and to use the results of its comprehensive review to "identify knowledge gaps, research that could feasibly be conducted to inform the field and generate answers, newly emerging technologies that could aid in these efforts, and organizations that VA might partner with to accomplish this work." Its information-gathering efforts included extensive efforts to develop information that would inform responses to these queries.

Hazards Associated with Burn Pit Exposures

Concerns have long been raised over the hazards associated with exposure to emissions from the open burn pits used in theater for waste management. These exposures have been the primary topic of earlier National Academies reports and are the focus of VA's Airborne Hazards and Open Burn Pit Registry effort, which had more than 200,000 participants as of spring 2020. Concern over burn pit exposures is understandable, given their prominence as a source of smoke and fumes in military facilities where large numbers of service members were present and the known toxic effects of the byproducts of combustion of the materials that were burned in them. However, an examination of the literature on the topic reveals that there is very little evidence addressing how hazards associated with burn pit exposures may result in adverse respiratory health outcomes, and the epidemiologic literature to date has not found an association. The committee believes that existing research efforts on the health of theater personnel are inadequate to shed light on this question and that bringing resolution to the issue will require new research addressing the existing efforts' deficiencies—such as the study approach for evaluating the health effects of burn pit exposures at the former Joint Base Balad in Iraq proposed in the 2011 Institute of Medicine report *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan*—in combination with various advances such as the identification and use of biomarkers of burn pit exposures.

Knowledge Gaps and Research That Could Feasibly Be Conducted to Address Them

The committee identified a large number of gaps in the current information base regarding respiratory health outcomes in the population of veterans who served in the Southwest Asia theater. These can be grouped as gaps in knowledge concerning adverse respiratory health outcomes in theater veterans, gaps in knowledge concerning in-theater airborne exposures, and gaps in knowledge about the biologic and toxicologic effects of in-theater airborne exposures. There are three circumstances where the committee offers recommendations for actions by VA.

The first concerns constrictive bronchiolitis, a disorder that includes several small airway diseases that are defined by the presence of bronchiolar inflammation, fibrosis, or both. The interpretation of lung biopsies for constrictive bronchiolitis has proven to be controversial, leading to uncertainty over the diagnoses of veterans exposed to airborne agents encountered in the Southwest Asia theater. Given the interest surrounding the question of whether in-theater exposures may be responsible for an increase in the prevalence of constrictive bronchiolitis in veterans of these conflicts, the committee concludes that actions to resolve this issue should be given a high priority by VA. Much of the current debate regarding the prevalence of constrictive bronchiolitis is the result of uncertainty and disagreement over the interpretation of the pathologic findings in symptomatic individuals. In order to better manage these circumstances, **the committee recommends that VA establish an expert panel to advise it on issues related to the diagnosis of constrictive bronchiolitis in veterans and its possible relationship to military service.** This panel should be external to VA and should include members with a range of expertise, including expertise in such areas as pulmonary medicine, toxicology, epidemiology, exposure assessment, and radiology, but with the primary membership consisting of experienced pulmonary pathologists. Veterans should also be part of the panel.

The expert advisory panel would be charged with developing specific guidelines for the evaluation of symptomatic Southwest Asia theater–deployed veterans in whom the differential diagnosis includes constrictive bronchiolitis. Its short- and longer-term tasks would include

- Determination of the adequacy of various lung biopsy approaches for the diagnosis of constrictive bronchiolitis and recommendations for best practices.
- Development of recommendations for consistently processing, handling, and storing lung biopsy materials.
- Development of consistent histologic/pathologic criteria to be used for confirming a diagnosis of constrictive bronchiolitis in theater veterans with suspected cases who present at a VA facility or who apply for disability compensation for the disease.
- Review—by the pathology working group within the panel—of biopsy slides from cases in which the issue of a diagnosis of constrictive bronchiolitis related to service has been raised. This review should not be limited to controversial cases but instead be applied to all such cases that fall under VA's areas of responsibility. The working group should be charged with providing a written summary report of each case in a timely manner.
- Establishment of criteria for the evidence base for determining whether an association exists between a veteran's military service and constrictive bronchiolitis, including the types and sources of information that could be considered.
- Recommendations for the research that would help resolve outstanding questions regarding constrictive bronchiolitis in veterans.
- Revision of the guidelines as new evidence becomes available.

The committee recognizes that the creation of this advisory committee and its role in peer review is not without controversy or cost, but it believes that such a committee is critical to ensuring that VA has a consistent approach in establishing or denying a diagnosis and evaluating its possible service connection. The presence of such a committee should also reassure veterans that they are receiving a fair review that uses the best science.

A second knowledge gap that could be filled by appropriate research concerns the question of whether Southwest Asia theater veterans are experiencing excess mortality from respiratory diseases. The committee's review of the literature found that the most recently published mortality study of 1990–1991 Gulf War veterans, which included death due to chronic obstructive pulmonary disease and from respiratory system diseases in general, used 2004 as its cutoff date, while the last salient study of post-9/11 veterans who had been deployed to the theater was generated using data from 2011 and offered no breakout of respiratory disease mortality. It is important to revisit this issue in order to identify whether there are respiratory health outcomes that warrant more intense study or surveillance of this population. Therefore, **the committee recommends that an updated analysis of mortality in Southwest Asia theater veterans be conducted.** Future mortality studies need to be based on analyses that compare higher- and lower-exposed veterans, rather than analyses comparing all veterans to the general population. This in turn will require that a retrospective exposure assessment be included so that the study can produce useful estimates of exposure-related mortality risk. An informative new study to determine whether there is excess mortality in deployed veterans should also consider not just the cause of death and contributing causes of death but also other underlying health conditions that might not be listed as a cause or contributing cause of death but that might confound an association as well as detailed demographic and service information on the veterans and their circumstances of deployment.

The third area where action by VA could fill a knowledge gap involves taking advantage of existing DoD and VA health record integration efforts. DoD and VA have been working toward a modernized and interoperable electronic health record (EHR) since at least 2013, and those efforts are scheduled to come to fruition in summer 2020 when such a system will be rolled out at some initial test sites. An integrated system such as this—in addition to its primary goal of facilitating a secure and seamless transfer of the medical records of active-duty service members as they transition to veteran status—has the potential to enable investigators, with proper human subjects assurances, to far more easily access these data for research purposes. An integrated EHR system would also simplify the monitoring of respiratory health status (including lung function) over time, which is needed for investigations of outcomes that have long latency periods.

In order to accomplish these objectives, **the committee recommends that VA and DoD explicitly integrate research access considerations into their planning as they refine the implementation of their new interoperable electronic health record system.** The committee further suggests that, as part of this effort, VA and DoD commit resources to developing a database of research study data derived from the integrated records. Data integration is still at a relatively early stage, and it is important for VA to be planning now for how it might use the information derived from EHRs so that it can properly configure the system for access.

In addition, the committee identified a number of more general opportunities for advancing knowledge regarding respiratory outcomes in theater veterans for VA's consideration as it establishes its overall health research agenda. Among these are opportunities for promoting research on biomarkers of effect, exposure, and susceptibility, which would allow better characterization of exposures and health status by establishing objective measures. Recent advances in the analysis of satellite data are allowing retrospective estimates of airborne particulates concentrations that may in turn make possible more accurate estimates of exposures of deployed personnel. VA is already sponsoring some work in these areas and will benefit from the information derived from it.

Newly Emerging Technologies to Address Knowledge Gaps

In addition to the aforementioned newly emerging technologies related to biomarker discovery and measurement and advances in remote measurement and estimation of airborne pollutants via satellites, the committee thought it appropriate to touch on some of the new technologies that might be brought to bear to gather information during active duty that would aid in the future evaluation of airborne exposures and health outcomes by VA. In particular, the committee points to three efforts. The first is silicone wristbands for exposure detection, a nascent technology that might allow for individual-level exposure information derived from an easily worn device. There have already been proof-of-concept studies suggesting that these wristbands may have utility. Second, DoD is in the initial stages of sponsoring research on low-cost technologies that could be used to support real-time health risk assessment and mitigation decision making and to generate data that could be made a part of individual longitudinal exposure records. Third, a separate DoD effort is aimed at developing a field-deployable epigenome "reader" for the real-time evaluation of exposures.

The challenge is that any technology, no matter how effective or well-intentioned it is, will take a back seat to the exigencies of operating in the field. It will not gain acceptance unless it can be seamlessly incorporated into operations, can be used in a way that does not encumber or otherwise limit personnel, and does not compromise their security. That said, there appear to be multiple technologies that hold the promise of developing information on active-duty personnel that would later aid VA in its evaluation of the health effects of military exposure to airborne agents. While it will be the responsibility of DoD to develop and deploy these technologies and to gather and maintain the information they generate, VA has a role to play in defining the type and form of that information that would be most useful, fostering studies that take advantage of the information to better understand health outcomes in veterans, and keeping abreast of advancements in domains that they do have responsibility for, such as patient care that might feed into exposure technology development.

Organizations That the Department of Veterans Affairs Might Partner with to Address Knowledge Gaps

A number of federal agencies, investigators in the United States and abroad, and other governmental and private-sector organizations are currently conducting research relevant to theater veterans' health or else have information that could improve the conduct of such work. The committee offers one specific recommendation for VA regarding partnering. It identifies a broad range of organizations that have potentially useful exposure or health information that VA should consider collaborating with in order to address specific needs and pursue new research opportunities.

The specific recommendation concerns DoD, an organization that VA already partners extensively with on issues related to the effects of occupational and environmental exposures on military and veteran health. The partnerships include VA's work with the Defense Health Agency, with which VA collaborates on the individual longitudinal exposure record, a web-based application that provides DoD and VA with the ability to link information on an individual to military exposures and health information. DoD maintains or supports a number of biorepositories that store materials of potential utility to studies of respiratory health outcomes in theater veterans, including biomarkers research. And two research organizations—the Air Force Research Laboratory and the Defense Advanced Research Projects Agency—conduct or support research relevant to the evaluation of the effects of airborne exposures. VA's existing collaborations with DoD are yielding benefits for both service members and veterans in the form of information that can be used to identify, manage, and cope with potentially harmful exposures. **The committee recommends that VA continue and expand its partnership with DoD on environmental health issues, focusing on the free flow of information on exposures encountered during military service and on the health of personnel before, during, and after deployment and after transition to veteran status. This partnership should include cooperation on identifying which respiratory health status information should be gathered during active duty for later use as baseline data in evaluating veterans' health for treatment, benefits, and research purposes.**

The committee also notes that other federal agencies, including the National Aeronautics and Space Administration, National Oceanic and Atmospheric Administration, National Institute of Environmental Health Sciences, and National Institute for Occupational Safety and Health, hold data and conduct research on airborne exposures. Much of this work addresses particulate matter, a well-established airborne hazard.

CONCLUDING REMARKS

Although most of the committee's conclusions regarding health outcomes fall under the category of "inadequate or insufficient evidence to determine an association," it wishes to emphasize that this should not be interpreted as meaning that there is no association between respiratory health outcomes and deployment to Southwest Asia, but rather that the available data are, on the whole, of insufficient quality to make a scientific determination. Existing studies suffer from limitations in

- exposure estimation;
- the availability of pertinent health, physiologic, behavioral, and biomarker data, especially data collected both pre- and post-deployment;
- the amount of time that has passed since exposure; and
- the use of additional or alternate sources of data that might enrich analyses.

Given these limitations, the committee concludes that a new approach is needed that will allow researchers to better examine and answer the question of whether certain respiratory outcomes are associated with deployment. This new approach is not one that is intended to reprise the common theme of "more research is needed" or to suggest that the only alternative is to undertake work that will take many years to bear fruit. Rather, well-conducted epidemiologic studies are possible today using retrospective designs that better account for confounding factors such as smoking habits, combine and analyze existing data in innovative ways, standardize outcome ascertainment methods to allow for better comparability of results, and improve the estimation of exposure.

While burn pit–related research will certainly be a part of this work, it will likely be challenging to attribute specific respiratory effects to this exposure alone. The more important question is whether deployment to the Southwest Asia theater—with all of the hazardous airborne exposures it entailed—may be responsible for adverse respiratory outcomes. The report's observations, conclusions, and recommendations identify not just the existing knowledge gaps but the many means that VA and the organizations that it can partner with inside and outside the government have for addressing them and providing veterans with the health information they need.

1

Introduction

More than 3.7 million U.S. service members have participated in operations taking place in the Southwest Asia Theater of Military Operations[1] and Afghanistan since 1990. These operations comprise the 1990–1991 Gulf War (Operation Desert Shield and Operation Desert Storm), the post-war stabilization period (1992–September 2001), and the post-9/11 conflicts: Operation Enduring Freedom (OEF);[2] Operation Iraqi Freedom (OIF); Operation New Dawn (OND); Combined Joint Task Force–Operation Inherent Resolve; and Operation Freedom's Sentinel. Figure 1-1 presents a map of the location where these operations took place.

Deployment to Southwest Asia exposed service members to a number of airborne hazards, including oil-well fire smoke, emissions from open burn pits, dust and sand suspended in the air, and exhaust from diesel vehicles. The effects of these were compounded by factors such as temperature extremes, stress, and noise, which are almost inevitable during service in a combat environment.

Soon after the 1990–1991 Gulf War, veterans began to seek medical treatment for a variety of symptoms and illnesses. Initially the Department of Defense (DoD) and the Department of Veterans Affairs (VA) responded to these health issues by establishing voluntary clinical examination programs. By 1994 these had been formalized under the Comprehensive Clinical Evaluation Program and the Persian Gulf Registry and Uniform Case Assessment Protocol (IOM, 1998). The programs began with an initial physical examination, including patient and exposure history and screening laboratory tests, followed by an opportunity for referral to more specialized testing and consultation if needed. Similar efforts continued and expanded during the post-9/11 period.

This chapter provides introductory material on U.S. deployments to the theater, the laws that stimulated the National Academies involvement in studies of theater veterans' health, and the impetus for and conduct of the current study. It sets the stage for an evaluation of the available scientific and medical literature regarding the respiratory health effects of exposure to airborne hazards encountered during service in the Southwest Asia theater, which is presented in later chapters of the report.

[1] The Department of Veterans Affairs defines the Southwest Asia Theater of Military Operations as comprising Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Gulf of Aden, Gulf of Oman, Oman, Qatar, the United Arab Emirates, and the waters of the Persian Gulf, the Arabian Sea, and the Red Sea (VA, 2019). For the sake of brevity, this report refers to this region plus Afghanistan as the "Southwest Asia theater" or simply the "theater."

[2] Originally called Operation Infinite Justice.

FIGURE 1-1 The Southwest Asia Theater of Military Operations and Afghanistan.
SOURCE: GAO, 2017, Figure 1.

U.S. DEPLOYMENTS TO THE SOUTHWEST ASIA THEATER

This section provides a brief overview of the deployments of U.S. service members to conflicts in Southwest Asia from 1990 through early 2020. The deployments span seven military operations.

1990–1991 Gulf War

U.S. military operations during the 1990–1991 Gulf War took place in two phases: Operation Desert Shield and Operation Desert Storm. Operation Desert Shield, the preparation and positioning phase, began on August 2, 1990, and ended on January 16, 1991. More than 500,000 American troops were deployed to Saudi Arabia during this period (Collins, 2019). Operation Desert Storm, the combat phase, began on January 17, 1991, and ended on April 6, 1991. A total of approximately 697,000 U.S. troops took part, with ground forces operating in Kuwait and southern Iraq (Collins, 2019).

Post-9/11 Operations

OEF commenced in Afghanistan on October 7, 2001, in response to the September 11, 2001, terrorist attacks in the United States, and it formally ended on December 28, 2014 (CRS, 2019a). OIF began in Iraq on March 20, 2003, initially as a response to perceived threats to U.S. interests, and ended August 31, 2010 (CRS, 2019a). OND overlapped the final stages of OIF and marked the transition of the United States from combat operations to stability-building in Iraq. It began on September 1, 2010, and ended on December 15, 2011, with the withdrawal of the U.S. military mission (CRS, 2019a). These operations were fundamentally different from the 1990–1991 Gulf War in their heavy dependence on the National Guard and reserves and in the pace of deployments, the duration of deployments, the number of redeployments, the short dwell time between deployments, and the type of warfare (IOM, 2010b).

The numbers of individuals and total numbers of deployments to OEF/OIF/OND have not been available since 2017, when these data were removed from public access (Mosbergen, 2018). A 2018 report from RAND Corporation found that from September 11, 2001, to September 2015, across all branches and components, 2.77 million service members had served on more than 5.4 million deployments (Wenger et al., 2018). Table 1-1, which was adapted from that report, indicates that the proportion of those deployed from the regular units ranged from 64% in the Army to 91% in the Navy and Marine Corps. Those in the National Guard and reserves units constituted one-quarter of all those deployed. The average age for those deployed was 29.0 years. Those deployed from the Marine Corps had the lowest average age (25.0 years), and those deployed from the Air Force had the highest average age (31.1 years). Of those deployed, 89.6% were male and 10.4% were female.

Two smaller-scale operations have taken place in the theater in more recent years. Combined Joint Task Force–Operation Inherent Resolve began on October 17, 2014, in Iraq and Syria as a result of threats posed by

TABLE 1-1 Characteristics of U.S. Service Members Deployed to OEF, OIF, or OND as of September 2015

Characteristics	Army	Air Force	Marine Corps	Navy	All Services
		Individuals Deployed by Component and by Service			
Regular	855,000	397,000	333,000	515,000	2,100,000
Reserve	156,000	47,000	38,000	55,000	295,000
National Guard	344,000	84,000	N/A	N/A	428,000
Total[a]	1,326,000	518,000	367,000	563,000	2,774,000
		Number of Deployments by Rank, Gender, and Family Structure			
Commissioned Officer	325,000	284,000	73,000	172,000	854,000
Warrant Officer	73,000	0	6,000	7,000	86,000
Enlisted	1,938,000	968,000	597,000	1,009,000	4,512,000
Male	2,096,000 (90.0%)	1,089,000 (87.2%)	652,000 (96.6%)	1,034,000 (87.5%)	4,871,000 (89.6%)
Female	232,000 (10.0%)	160,000 (12.8%)	23,000 (3.4%)	148,000 (12.5%)	563,000 (10.4%)
Age at time of deployment (average, in years)	29.3	31.1	25.0	28.7	29.0
Married at time of deployment	1,389,000 (59.7%)	768,000 (61.5%)	305,000 (45.2%)	622,000 (52.7%)	3,085,000 (56.8%)
Had children at time of deployment	1,164,000 (50.0%)	606,000 (48.5%)	198,000 (29.4%)	492,000 (41.6%)	2,460,000 (45.3%)
Total[a]	2,335,972	1,252,424	676,351	1,187,932	5,452,679
		Average Number of Cumulative Months Deployed, Among Those Who Have Deployed			
Regular	17.8	12.0	12.0	9.9	
Reserve[b]	12.5	8.8	8.1	8.9	
National Guard[b]	12.8	7.3	N/A	N/A	

NOTES: In contrast with the Army and the Air Force, the Navy and the Marine Corps do not have National Guard components. N/A, not available; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; OND, Operation New Dawn.

[a] Total figures are lower than the sum across rows because some service members deployed with multiple components or ranks.

[b] Nearly 25% of cumulative months deployed in the U.S. Army Reserve and the U.S. Army National Guard were accrued in the U.S. Regular Army.

SOURCES: Wenger et al., 2018, Table 1, used with permission from RAND Corporation; derived from Defense Manpower Center's Contingency Tracking System Deployment File (September 2001 through September 2015; 2001 and 2015 represent partial calendar years).

terrorist organizations (DoD, n.d.). Operation Freedom's Sentinel began on January 1, 2015, following the end of OEF in December 2014 (DoD OIG, 2019). It was launched to train and assist the Afghan National Defense and Security Forces through the NATO-led Resolute Support Mission while simultaneously conducting counterterrorism operations against terrorist groups in Afghanistan. An April 2019 Congressional Research Service publication indicated that approximately 7,200 U.S. forces were serving in Iraq and Syria and 15,000 in Afghanistan at that time (CRS, 2019b). Both Operation Inherent Resolve and Operation Freedom's Sentinel were ongoing as of early 2020.

AFTERMATH OF SOUTHWEST ASIA THEATER DEPLOYMENT

This section addresses some of the legislative consequences of the deployments to the Southwest Asia theater of military operations. Beginning in 1991, Congress passed a number of pieces of legislation in reaction to concerns regarding the health of service members and veterans. These laws led to the involvement of the National Academies in reviews of the scientific literature on this topic. Previous studies that examined respiratory health issues among U.S. veterans deployed to Southwest Asia are noted below.

Legislative Actions

Following the Gulf War, in December 1991 Congress mandated via Public Law (PL) 102-190 that DoD establish the Persian Gulf Registry to assist in addressing health concerns in veterans who had been exposed to burning oil plumes during Operation Desert Storm (IOM, 1995). Later, a provision of PL 102-585—passed in November 1992—expanded the registry to "any other members who served in the Operation Desert Storm theater of operations during the Persian Gulf conflict" (§ 704(a)(2)) and renamed it the Persian Gulf War Veterans Health Registry.

In 1998 Congress passed two statutes: PL 105-277, the Persian Gulf War Veterans Act, and PL 105-368, the Veterans Programs Enhancement Act. These laws were intended to facilitate the identification of health outcomes that might result from exposure to environmental agents during deployment. As part of this effort, the laws directed the Secretary of Veterans Affairs to enter into a contract with the National Academy of Sciences to review and evaluate the scientific and medical literature regarding associations between illness and exposure to toxic agents, environmental or wartime hazards, or preventive medicines or vaccines associated with Gulf War service. The Secretary was further instructed to consider the conclusions offered by the National Academies when making decisions about compensation.

The National Academies were tasked to study a diverse set of biologic, chemical, and physical agents and their possible effects on the health of service members and veterans. The resulting series of reports, entitled *Gulf War and Health*, consists of 11 volumes (to date) on various exposures and health outcomes. Additionally, several other reports that were not part of the series were published on specific exposures and health outcomes among theater veterans. Exposures to many of the agents encountered in the theater have been extensively studied and characterized, primarily in occupational settings (e.g., exposure to pesticides, solvents, and fuels), but exposures to others have not been as well studied and characterized in human populations (e.g., exposure to nerve agents and oil-well fire smoke).

The Veterans Programs Enhancement Act of 1998 (PL 105-368) established the federal Research Advisory Committee on Gulf War Veterans' Illnesses (RAC). The RAC, which includes researchers who are studying the health of these veterans, clinicians who have treated them, and members of the general public (including veterans), has published several reports on the scientific literature related to the health of Gulf War veterans. These are available via the RAC website.[3]

A later set of laws addressed concerns over possible adverse effects of exposure to smoke from trash burning in the theater. Bills were introduced by Congress in 2009 and 2010 to sharply curtail the use of open-air burn pits and to establish a medical surveillance system to identify health effects attributed to exposure to the burning of

[3] See https://www.va.gov/RAC-GWVI/index.asp (accessed August 10, 2020).

solid waste (IOM, 2011). A provision of PL 111-84 (§ 317), the National Defense Authorization Act for Fiscal Year 2010, prohibited the use of burn pits for medical waste disposal except in cases where there was no alternative.[4] The act also required DoD to take several actions, including reporting to Congress regularly whenever burn pits were used, developing a plan for alternatives to burn pits, assessing existing medical surveillance programs of burn pits exposure and making recommendations to improve them, and studying the effects of burning plastics in open pits and evaluating the feasibility of prohibiting the burning of plastics. In 2009 congressional hearings on the proposed bill included testimony from both military officials and veterans groups and focused on the U.S. Army Center for Health Promotion and Preventive Medicine screening study, with DoD and VA officials emphasizing the study's conclusion that Joint Base Balad (one of the largest U.S. military bases in Iraq) exposures fell within military exposure guidelines and the Environmental Protection Agency values for acceptable risk. In response, VA asked the Institute of Medicine to determine the long-term health effects from exposure to burn pits in Iraq and Afghanistan (IOM, 2011).

On January 10, 2013, PL 112-260 was signed, and § 201 of that law directed VA to establish an open burn pit registry within 1 year after its enactment (NASEM, 2017). The law directed the VA secretary to coordinate with DoD to establish and maintain an open burn pit registry for eligible individuals who may have been exposed to toxic airborne chemicals and fumes created by open burn pits. It specified that the registry should include information that would be necessary to ascertain and monitor the health effects of members of the armed forces exposed to toxic airborne chemicals and fumes caused by open burn pits. The law instructed VA to develop a public information campaign to inform eligible individuals about the registry and to periodically notify eligible individuals of significant developments in the study and treatment of conditions associated with exposure to toxic airborne chemicals. It also called for an independent scientific organization to prepare a report addressing issues related to the establishment and conduct of the registry and the use of its data, and VA contracted with the National Academies to conduct the work.

Previous Studies That Examined Respiratory Outcomes Among Military Personnel Deployed to Southwest Asia

The National Academies has convened a number of expert consensus committees to examine health issues in U.S. veterans of conflicts in Southwest Asia. The reports that most directly address environmental exposures are listed in Appendix B. Studies that examined respiratory health outcomes are cited below.

In one of the earliest efforts to address respiratory health issues—*Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Immediate Action* (IOM, 1995)—a committee was tasked to evaluate VA actions to collect and maintain health information for assessing the health consequences of Gulf War deployment and to recommend further studies. That committee specifically noted the need to more adequately characterize the hazards of oil-well fires; it also recommended carrying out epidemiologic studies with better designs and statistical power to make associations between specific exposures encountered in theater and health outcomes and included chronic respiratory effects among the "putative outcomes" that the committee would continue to evaluate. A follow-up report (IOM, 1996) recommended that military medical preparedness for deployments include "detailed attempts to monitor natural and man-made environmental exposures and to prepare for rapid response, early investigation, and accurate data collection, when possible, on physical and natural environmental exposures that are known or possible in the specific theater of operations." It also recommended that the mortality experience of Persian Gulf War veterans be monitored for up to 30 years.

Gulf War and Health, Volume 3: Fuels, Combustion Products, and Propellants (IOM, 2005) contained a comprehensive review of the literature addressing the association between exposure to fuels, combustion products, and propellants present in the 1990–1991 Gulf War and health outcomes. Combustion products were defined as

[4] The National Defense Authorization Act used the definition of hazardous wastes from the 2002 Solid Waste Disposal Act, Section 1004(5): "a solid waste, or combination of solid wastes, which because of its quantity, concentration, or physical, chemical, or infectious characteristics may—(A) cause, or significantly contribute to an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness; or (B) pose a substantial present or potential hazard to human health or the environment when improperly treated, stored, transported, or disposed of, or otherwise managed" (https://public.ornl.gov/sesa/environment/policy/rcra.html [accessed May 10, 2020]).

"smoke from fires, exhaust from burning fuels, and products of other combustion sources," and it was noted that these are also constituents of air pollution in general. Using information from studies of military populations, occupational cohorts, and others, the committee reached conclusions on the association between these exposures and several respiratory health outcomes, details of which are presented in Chapter 4.

The committee responsible for *Gulf War and Health, Volume 4: Health Effects of Serving in the Gulf War* (IOM, 2006) evaluated the overall health status of 1990–1991 Gulf War veterans by reviewing epidemiologic literature to compare the incidence and prevalence of health outcomes in veterans deployed to the region with veterans not deployed there. The committee found it "striking" that while self-reported respiratory symptoms were strongly associated with deployed veterans, objective measures of pulmonary function failed to show increased respiratory illnesses in this population compared with nondeployed veterans. When examining specific exposures and using objective measures, the committee found an indication of an association between asthma exacerbation and oil-well fire smoke; however, the committee did not find nerve agents present in the theater as the result of the destruction of a munitions storage facility at Khamisiyah, Iraq, in March 1991 to be associated with changes in pulmonary function. The committee also provided recommendations for pre- and post-deployment screening of health status, assessment of exposures, and surveillance for adverse health outcomes.

Gulf War and Health, Volume 8: Update of Health Effects of Serving in the Gulf War (IOM, 2010a)—an update to *Volume 4*—reviewed the studies in the earlier report together with literature published since that volume's literature search. The committee assessed and compared health outcomes in veterans deployed to the 1990–1991 Gulf War with veterans who were not deployed or who were deployed elsewhere. Its main focus was diseases that *Volume 4* reported as having occurred with greater prevalence in Gulf War–deployed veterans, which did not include respiratory conditions, but it was also asked to identify emerging health outcomes. The committee concluded that there was inadequate or insufficient evidence to determine whether an association existed between Gulf War deployment and respiratory disease and that there was limited or suggestive evidence of no association between deployment to the Gulf War and decreased lung function in the first 10 years after the war.

The *Review of the Department of Defense Enhanced Particulate Matter Surveillance Program Report* (NRC, 2010) evaluated a report (Engelbrecht et al., 2008) that summarized the results of DoD's Enhanced Particulate Matter Surveillance Program, which was an effort to characterize and quantify particulate matter in the ambient environment at 15 sites[5] in the Middle East over 12 months in 2006–2007. The committee's evaluation included a consideration of the potential acute and chronic health implications based on information presented in the Engelbrecht et al. (2008) report. The committee was also asked to consider epidemiologic and health-surveillance data collected by the U.S. Army Center for Health Promotion and Preventive Medicine (since renamed the U.S. Army Public Health Center) to assess potential health implications for deployed personnel, and to make recommendations for reducing or characterizing health risks. The committee found that while the design and conduct of the Enhanced Particulate Matter Surveillance Program limited its usefulness in health studies, the data showed that "a large-scale assessment of the air-pollution exposures of military personnel and associated health risks is feasible and needed," and it made recommendations regarding, among other things, data re-analysis, improving surveillance study design, and analysis of DoD database medical data. The committee concluded that it was plausible that exposure to ambient pollution in the Middle East theater was associated with adverse health outcomes. It recommended that "[a] more complete inventory of all major sources of ambient pollutants and potential emissions in the theater should be constructed before assessment of health effects to ensure that all relevant pollutants are monitored."

Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan (IOM, 2011) summarized the health effects associated with exposures to 51 pollutants that were detected in air samples taken at Joint Base Balad in Iraq in 2007–2009 or thought to be in emissions, as well as health-effects information on populations considered to be surrogates of military personnel exposed to combustion products from burn pits (firefighters, municipal incinerator workers, and veterans of the 1990–1991 Gulf War exposed to oil-well fire smoke) because there were few studies on post-9/11 veterans exposed to burn pit emissions. The committee concluded that burn pits were not a major source of the pollutants of greatest concern but also noted that there were many air pollut-

[5] The 15 sites were in the following countries: Djibouti (one), Afghanistan (two, in Bagram and Khowst), Qatar (one), United Arab Emirates (one), Iraq (six, in Balad, Baghdad, Tallil, Tikrit, Taji, and Al Asad), and Kuwait (four, in northern, central, coastal, and southern Kuwait).

ants present in the theater that had not been measured by the surveillance campaigns. Based on the epidemiologic literature, the committee concluded that there was inadequate or insufficient evidence of an association between exposure to combustion products and cancer or respiratory disease in the populations studied; however, it found limited or suggestive evidence of an association between exposure to combustion products and reduced pulmonary function. The committee concluded that additional study of health effects specifically in OEF and OIF veterans was necessary. Based on the information that was available, the committee was unable to say whether long-term health effects were likely to result from exposure to emissions from the burn pit at Joint Base Balad. It also stated that none of the individual chemical constituents of the combustion products emitted at Joint Base Balad appeared to have been present at concentrations likely to be responsible for the adverse health outcomes studied in the report. However, the committee's review also suggested that service in Iraq or Afghanistan—taking into account exposure to air pollution not limited to that generated by burn pit emissions—might be associated with long-term health effects, particularly in highly exposed populations (such as burn pit workers) or susceptible populations (such as those with asthma), mainly because of the high ambient concentrations of particulate matter from both natural and anthropogenic (including military) sources. It concluded that respiratory effects and cancer could result in circumstances where exposure to air pollution was sufficiently high.

Gulf War and Health, Volume 10: Update of Health Effects of Serving in the Gulf War, 2016 (NASEM, 2016) was an update to *Volume 4* (IOM, 2006) and *Volume 8* (IOM, 2010a) on the health effects in the 1990–1991 Gulf War veterans that included literature published since those reports were assembled. The committee was charged to pay particular attention to certain disorders, including lung cancer. The thorough literature search conducted by the committee (including studies of experimental toxicology, neuroimaging, and genetics) found little evidence to warrant changes to the conclusions of *Volume 8*. The Volume 10 committee concluded that there was inadequate or insufficient evidence to determine whether an association existed between Gulf War deployment and any cancer or respiratory conditions and concluded that there was limited or suggestive evidence of no association between deployment and decreased lung function. The committee noted that with the exception of cancer, enough time had passed to determine whether veterans had an increased incidence of respiratory conditions compared with non-deployed counterparts, and it concluded that further studies to examine the incidence or prevalence of respiratory conditions due to deployment in the Gulf War should not be undertaken. The committee also posited that as recall bias likely increases with time, further collection of self-reported exposure information from Gulf War veterans was unnecessary but that in the future collecting exposure information before, during, and after deployment as well as information on troop locations and toxicant concentrations would enable a more accurate assessment of actual exposures. The committee noted that efforts to model or reconstruct the exposures of Gulf War deployment were unlikely to yield useful results, and it recommended that without definitive and verifiable individual veteran exposure information, further studies to determine cause-and-effect relationships between Gulf War exposures and health conditions in Gulf War veterans should not be undertaken. It recommended that VA and DoD develop a joint strategy on incorporating emerging diagnostic technologies and personalized approaches to medical care into sufficiently powered future research to inform studies of Gulf War illness and related health conditions.

The committee that authored *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry* (NASEM, 2017) was asked to analyze the data collected by a VA environmental health registry—the Airborne Hazards and Open Burn Pit Registry—created for military personnel who might have been exposed to airborne hazards generated by open burn pits, fumes, and other toxic chemicals during deployment to Southwest Asia from August 1990 onward. The committee was also asked to recommend ways to improve the registry and to suggest how the data could best be used. The information that the committee reviewed had been collected over the registry's first 13 months and included data from about 46,400 participants who had completed the questionnaire[6] during that time. These participants represented about 1% of 1990–1991 Gulf War veterans and 1.7% of post-9/11 veterans. The committee found that the registry questionnaire exhibited problems arising from the basic weaknesses of voluntary, self-report registries and that these were exacerbated by flaws in the registry's structure and operation and the type and manner of questioning. To evaluate the data, the committee focused on health outcomes related to the symptoms, conditions, and diseases associated with the respiratory and the cardio-

[6] In that time period, roughly 40% who began a registry questionnaire did not complete it.

vascular systems since these were the most plausible and well-documented potential health effects of the exposures of concern, but the committee found that the limitations of the registry questionnaire and the data collected by it were too great to allow any firm conclusions. Moreover, the committee concluded that the exposure data were of insufficient quality or reliability to make them useful in anything other than the most general assessments of exposure potential. Within this context,

> [g]enerally speaking, the committee found that the observed prevalences of respiratory and cardiovascular outcomes appear consistent with what would be expected in a population that is predominantly male, aged 25–60, and for whom about one-third report a current or former history of smoking.

The committee recommended that questions about specific health outcomes be expanded and sharpened to improve the tool; regarding respiratory outcomes, it suggested adding

> reduced lung function, eosinophilic pneumonia, other lung infections (such as tuberculosis, fungal pneumonia, community-acquired pneumonia), lung scarring or fibrosis (a more inclusive diagnosis than idiopathic pulmonary fibrosis), bronchiolitis other than constrictive bronchiolitis (respiratory or obliterative), sarcoidosis/hypersensitivity pneumonitis, rhinosinusitis, and vocal cord dysfunction.

The committee found that the registry's primary usefulness was as a vehicle by which "the self-reported signs, symptoms, and diseases identified by registrants constitute a record that can alert providers to concerns and problems that may be forgotten about or missed during clinical encounters." The committee recommended that VA clarify the intent and purpose of the registry before moving forward, while noting that even a well-designed and executed registry would have little value as a scientific tool for health effects research compared with a well-designed epidemiologic study. In the time since this report was completed, the number of registry participants has surpassed 200,000 (VA, 2020). A National Academies report updating the 2017 assessment is scheduled for completion in 2022.

CHARGE TO THE COMMITTEE

The committee's Statement of Task is shown in Box 1-1. In brief, it directs the National Academies to convene an expert committee to evaluate the available scientific and medical literature and to identify gaps, research that could feasibly be conducted to address outstanding questions and generate answers, newly emerging technologies that could aid in these efforts, and organizations that VA might partner with to accomplish this work.

COMMITTEE'S APPROACH TO ITS CHARGE

The committee formed to address this task included experts in epidemiology, pulmonology, pathology, exposure assessment, military and veteran's health, and toxicology. It comprised 11 members who held five in-person meetings between March 2019 and February 2020. Two of these in-person meetings included public open sessions, with one of them including a presentation from VA staff who elucidated the charge to the committee and the other consisting of an information-gathering workshop to help clarify and inform the committee's work.[7] Between and after the in-person meetings, groups of committee members held virtual meetings to review specific studies, discuss the evidence base on a particular health outcome or topic, and facilitate the writing of its report.

Several activities were undertaken to develop the scientific foundation for the report's findings, conclusions, and recommendations. These included detailed searches (discussed in detail in Chapter 3) of the published literature, beginning in 1991; requesting information directly from VA and from experts in the field; examining other pertinent published literature, government documents, and reports; attending professional meetings; and consulting relevant National Academies reports. Background information on topics such as the use of military burn pits and the health effects of exposure to combustion products in general and burn pit emissions in particular has been

[7] Chapter 3 includes a section that details the information presented at this workshop.

BOX 1-1
Statement of Task

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will comprehensively review, evaluate, and summarize the available scientific and medical literature regarding the respiratory health effects of exposure to airborne hazards encountered during service in the Southwest Asia Theater of Military Operations and Afghanistan. The report will pay particular attention to:

- hazards associated with burn pit exposures;
- excess mortality, cancer, bronchial asthma, chronic bronchitis, sinusitis, constrictive bronchiolitis, and other respiratory health outcomes that are of great concern to veterans; and
- emerging evidence on respiratory health outcomes in service members from research such as the Millennium Cohort Study, Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE), National Health Study for a New Generation of U.S. Veterans, Comparative Health Assessment Interview (CHAI) Study, Pulmonary Health and Deployment to Iraq and Afghanistan Objective Study, Effects of Deployment Exposures on Cardiopulmonary and Autonomic Function Study, and research being conducted by the Department of Veterans Affairs (VA) War Related Illness and Injury Study Center (WRIISC) Airborne Hazards Center of Excellence (AHCE) in New Jersey.

It will evaluate the extent to which existing knowledge base informs the understanding of the potential adverse effects of in-theater military service on respiratory health, identify gaps, research that could feasibly be conducted to address outstanding questions and generate answers, newly emerging technologies that could aid in these efforts, and organizations that VA might partner with to accomplish this work.

The committee shall produce a final report detailing the conduct of these activities and offering any findings, conclusions, and recommendations it deems appropriate.

covered by previous National Academies reports, as summarized in the previous section (specifically, IOM, 2011; NASEM, 2016, 2017). With an eye to respiratory health outcomes, the committee considered all epidemiologic studies that had been reviewed in *Gulf War and Health* series Volumes 4, 8, and 10 (IOM, 2006, 2010a; NASEM, 2016) as well as the two reports that focused on exposures to burn pits (IOM, 2011; NASEM, 2017).

Most of the in-person information-gathering occurred during the first and third in-person committee meetings. At its first meeting, the committee heard from VA representatives R. Loren Erickson, M.D., Dr.P.H.—then the chief consultant with the Post Deployment Health Patient Care Services in the Veterans Health Administration—and Eric Shuping, M.D., M.P.H., FAAFP—director of the Post-9/11 Era Environmental Health Program. Drs. Erickson and Shuping elaborated on VA's charge to the committee and on the expectations for the final report. Additionally, National Academies staff briefed the committee on earlier studies of the respiratory health effects of in-theater exposures.

ORGANIZATION OF THE REPORT

This report is organized into five chapters (including this one) and four appendixes. Chapter 2 provides a detailed description of airborne hazards in Southwest Asia, including regional environmental exposures, exposures associated with the operation of in-theater military sites, occupational exposures encountered by military personnel while deployed, and the exposure tracking performed by DoD. The chapter also identifies other factors that may increase an individual's risk to these hazards.

Chapter 3 explains how the committee carried out its evaluation of the evidence base. It describes the approach and process used by the committee to identify and evaluate the scientific and medical literature on the association between exposure to airborne hazards and respiratory health outcomes and the classification system that the committee used to draw conclusions about the strength of the evidence for each respiratory health outcome it considered. The chapter also provides background descriptions of the major epidemiologic cohorts and research initiatives that the committee was tasked to pay particular attention to or that are referenced three or more times in Chapter 4.

Chapter 4 provides a detailed evaluation of the scientific literature addressing respiratory health outcomes in service members and veterans who served in the Southwest Asia theater. This begins with an overview of the condition—its symptoms, diagnostic criteria and pathology, and prevalence. This is followed by a summary of findings on that condition from epidemiologic studies organized by conflict and cohort and the committee's conclusion regarding the strength of the evidence associating deployment to the theater with the outcome. Where the data permit, separate conclusions are drawn for those deployed to the 1990–1991 Gulf War and the post-9/11 conflicts.

Chapter 5 describes the challenges and opportunities for advancing the understanding of respiratory health issues in theater veterans. It addresses the hazards associated with burn pit exposures and uses the results of its comprehensive literature review to fulfill the Statement of Task's directive to "identify knowledge gaps, research that could feasibly be conducted to inform the field and generate answers, newly emerging technologies that could aid in these efforts, and organizations that VA might partner with to accomplish this work."

The report's appendixes present supplemental information on the conduct of the study. Appendix A contains the agendas of the committee's open meeting and workshop. Appendix B lists National Academies reports related to Southwest Asia theater veterans' health. Appendix C is a table of all the new literature on respiratory health outcomes that was reviewed by the committee. Appendix D provides the committee and staff biographies.

REFERENCES

Collins, S. 2019. *Desert Storm: A look back*. https://www.defense.gov/Explore/Features/story/Article/1728715/desert-storm-a-look-back (accessed April 12, 2020).

CRS (Congressional Research Service). 2019a. *U.S. periods of war and dates of recent conflicts*. Updated August 27, 2019. CRS Report RS21405. https://crsreports.congress.gov/product/pdf/RS/RS21405 (accessed May 10, 2020).

CRS. 2019b. *U.S. war costs, casualties, and personnel levels since 9/11*. CRS Report IF11182. https://crsreports.congress.gov/product/pdf/IF/IF11182 (accessed May 10, 2020).

DoD (Department of Defense). n.d. *About CJTF-OIR*. https://www.inherentresolve.mil/About-CJTF-OIR (accessed May 10, 2020).

DoD OIG (Office of Inspector General). 2019. *Lead inspector general for Operation Freedom's Sentinel I quarterly report to the United States Congress I April 1, 2019–June 30, 2019*. https://www.dodig.mil/In-the-Spotlight/Article/1938932/lead-inspector-general-for-operation-freedoms-sentinel-i-quarterly-report-to-th (accessed May 10, 2020).

Engelbrecht, J. P., E. V. McDonald, J. A. Gillies, and A. W. Gertler. 2008. *Department of Defense Enhanced Particulate Matter Surveillance Program (EPMSP): Final report*. Desert Research Institute, Reno, NV. February [online]. https://pdfs.semanticscholar.org/18af/a824db71d54eb0242659b5b224c71e32aaba.pdf (accessed May 10, 2020).

GAO (Government Accountability Office). 2017. *Gulf War illness—improvements needed for VA to better understand, process, and communicate decisions on claims*. GAO-17-511. June. https://www.gao.gov/assets/690/685582.pdf (accessed May 10, 2020).

IOM (Institute of Medicine). 1995. *Health consequences of service during the Persian Gulf War: Initial findings and recommendations for immediate action*. Washington, DC: National Academy Press.

IOM. 1996. *Health consequences of service during the Persian Gulf War: Recommendations for research and information systems*. Washington, DC: National Academy Press.

IOM. 1998. *Adequacy of the VA Persian Gulf Registry and uniform case assessment protocol*. Washington, DC: National Academy Press.

IOM. 2005. *Gulf War and health: Volume 3: Fuels, combustion products, and propellants*. Washington, DC: The National Academies Press.

IOM. 2006. *Gulf War and health: Volume 4: Health effects of serving in the Gulf War.* Washington, DC: The National Academies Press.

IOM. 2010a. *Gulf War and health: Volume 8: Update of health effects of serving in the Gulf War*. Washington, DC: The National Academies Press.

IOM. 2010b. *Returning home from Iraq and Afghanistan: Preliminary assessment of readjustment needs of veterans, service members, and their families*. Washington, DC: The National Academies Press.

IOM. 2011. *Long-term health consequences of exposure to burn pits in Iraq and Afghanistan*. Washington, DC: The National Academies Press.

Mosbergen, D. 2018. After promises of "transparency," Pentagon under scrutiny for troop number blackout. July 4. *HuffPost*. https://www.huffpost.com/entry/pentagon-troop-number-blackout-iraq-syria-afghanistan_n_5b3c6a27e4b07b827cbc12e4 (accessed July 1, 2020).

NASEM (National Academies of Sciences, Engineering, and Medicine). 2016. *Gulf War and health: Volume 10: Update of health effects of serving in the Gulf War, 2016*. Washington, DC: The National Academies Press.

NASEM. 2017. *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry*. Washington, DC: The National Academies Press.

NRC (National Research Council). 2010. *Review of the Department of Defense Enhanced Particulate Matter Surveillance Program report*. Washington, DC: The National Academies Press.

VA (Department of Veterans Affairs). 2019. *Gulf War service*. https://www.publichealth.va.gov/exposures/gulfwar/military-service.asp (accessed May 10, 2020).

VA. 2020. *Airborne hazards and open burn pit registry*. https://veteran.mobilehealth.va.gov/AHBurnPitRegistry (accessed May 10, 2020).

Wenger, J. W., C. O'Connell, and L. Cottrell. 2018. *Examination of recent deployment experience across the services and components*. RAND Corporation. https://www.rand.org/content/dam/rand/pubs/research_reports/RR1900/RR1928/RAND_RR1928.pdf (accessed May 10, 2020).

2

Airborne Hazards in Southwest Asia

An *airborne hazard* is any chemical, physical, or biological agent in the air that has a potential to cause harm. There are numerous airborne hazards that military personnel may have experienced when deployed to Southwest Asia, including regional environmental exposures, such as air pollution from dusts, and local point and area sources, such as traffic, waste management, or local industries. Exposures related to military operations are also contributors, such as exhaust from heaters, military vehicles, and aircraft and smoke from structural fires, blasts, burning oil wells, and burn pits (VA, 2018). The exposures from military operations differ by conflict and vary by location and over time; for example, veterans of the post-9/11 conflicts are more likely to have been exposed to burn pits, whereas the 1990–1991 Gulf War veterans are more likely to have been exposed to smoke from oil-well fires. Additionally, some military personnel have occupations, job duties, or tasks that expose them to a variety of vapors, gases, dusts, and fumes. All these airborne hazards meet the definition of "hazard" in that they have the potential to cause harm and may influence the health of military personnel. The definition of "hazard" differs from "risk," which is the probability that the hazard will cause harm and is a function of the extent of exposure (NRC, 1996).

The Statement of Task charges the committee to "comprehensively review, evaluate, and summarize the available scientific and medical literature regarding the respiratory health effects of exposure to airborne hazards encountered during service in the Southwest Asia theater of military operations." Exposures from the regional environment in Southwest Asia—and those that occur specifically from military operations—are thus the most relevant to the committee's charge. However, military occupational exposures may compound the effects of other environmental and military exposures. Figure 2-1 provides a framework of how complex exposures from multiple sources and environments may influence the health of military personnel.

This chapter characterizes and describes airborne hazards related to military operations, military occupations, and regional environmental exposures that might be encountered by personnel deployed to the Southwest Asia theater.[1] These hazards are listed in Box 2-1.

The following sections provide information on the levels of the hazards from military reports or the published literature, and where applicable they provide a summary of studies that have aimed to characterize the hazards using toxicity studies. The committee took a broad view of what might constitute an in-theater airborne hazard but notes that information on some these—occupational exposures, for example—is lacking.[2]

[1] Cigarette smoking, an airborne hazard that has been shown to be associated with deployment (Krefft et al., 2015), is addressed in Chapters 4 and 5.

[2] Studies of the health effects of some of the airborne exposures noted in Table 2-1 are in some cases available in the (non-military) occupational health literature, as are Material Safety Data Sheets that summarize the state of toxicologic and epidemiologic knowledge on these exposures.

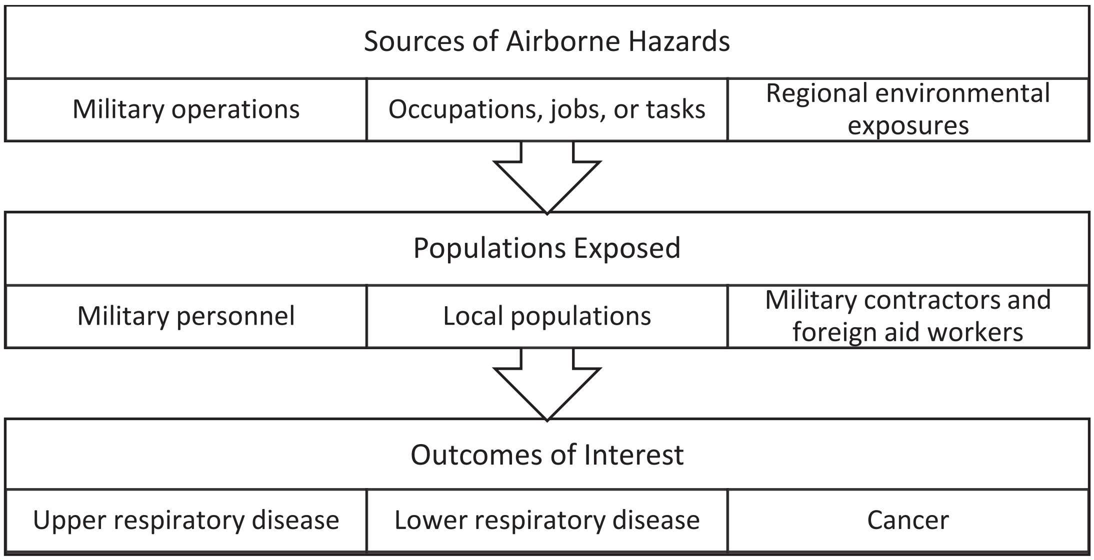

FIGURE 2-1 Conceptual diagram of how exposures in the Southwest Asia theater may be linked to adverse respiratory health outcomes.

BOX 2-1
Airborne Hazards in the Southwest Asia Theater of Military Operations

Exposures Associated with Military Operations
- burn pit emissions
- smoke from oil-well fires (1990–1991)
- nerve agents released during the demolition of the Khamisiyah, Iraq, storage complex (1991)
- airborne depleted uranium particles liberated from munitions and armor
- emissions from the Al-Mishraq, Iraq, sulfur plant fire (2003)
- vehicular (diesel) exhaust and emissions from other fuels (JP-8 and other jet fuels)

Regional Environmental Exposures
- particulate matter, desert dust, sand
- air pollution from local and regional source (industries, power generation, vehicles, agriculture, etc.)
- indigenous biologic agents and allergens

Occupational Exposures
- vapors, gases, dusts, and fumes from agents used in job tasks (paints, solvents, pesticides, welding, etc.)

Factors That May Lead to Increased Vulnerability to Airborne Hazards
- temperature extremes
- stress
- noise

The chapter ends with a brief discussion of factors that may increase the vulnerability of military personnel to airborne exposures while in theater and a description of how the committee approached the task of considering the respiratory health effects of these exposures.

EXPOSURES ASSOCIATED WITH MILITARY OPERATIONS IN THE SOUTHWEST ASIA THEATER

Military operations generate airborne hazards. While these operations are in some respects similar to those encountered in some occupational settings, military personnel are likely to be exposed to hazards not just at work but also at leisure and when sleeping due to the circumscribed realities of deployment to a location such as the Southwest Asia theater. This section provides an overview of some the primary airborne exposures of concern.

Open Burn Pits

One source of combustion-related air pollution that is central to the charge of the committee is the military burn pits used for open-air waste burning. The military has long used burn pits when other waste-disposal options have not been available. Technologic advances and changes in military practices in recent conflicts mean that items are being burned—plastic bottles and electronics, for example—that present new health risks (IOM, 2011). Burn pits were the primary solid-waste management solution in Afghanistan and Iraq from the beginning of the conflicts in 2001 and 2003, respectively. However, their use was restricted by law in 2009 (Public Law [PL] 111-84, § 317). By the end of 2010 their use in Iraq had been phased out, but it continues in Afghanistan. The Department of Defense (DoD) reported that as of March 2019 there was still one U.S.-operated open burn pit in Afghanistan and eight more in other DoD operations locations (DoD, 2019). In addition, that report indicated that "in countries such (as) Iraq, Syria, or Afghanistan it is common practice to burn waste in open pits. Our host nation partners dispose of waste for us; however, there are many cases where trash is burned just outside the gate by contractors" (DoD, 2019). DoD Instruction 4715.19 governs the circumstances under which a burn pit may be operated (DoD, 2018).

DoD estimates that an average of 8–10 lb of waste is generated each day by each person in theater. On the basis of the average populations of large bases in Iraq and Afghanistan (those with more than 1,000 personnel), an average of about 30–42 tons of solid waste per day might be produced on a base. Joint Base Balad, with a population that sometimes surpassed 25,000, including U.S. troops, host-nation soldiers, coalition troops, civilians, and contractors, burned perhaps 100–200 tons of waste per day in 2007. In 2009, three incinerators were operational at Joint Base Balad and burned about 10 tons of waste per day in the pit; the burn pit ceased operation on October 1, 2009. A 2010 Army Institute of Public Health study of burn pits in Iraq and Afghanistan reported that large bases burned waste that consisted generally of 5–6% plastics, 6–7% wood, 3–4% miscellaneous noncombustibles, 1–2% metals, and 81–84% combustible materials. While the mixture of materials that enter a burn pit waste stream remains complex and is not consistent day to day, efforts have been made to reduce or eliminate wastes "covered" under PL 113-66, § 314, such as

> tires; treated wood; batteries; plastics … ; munitions and explosives … ; compressed gas cylinders … ; fuel containers … ; aerosol cans; polychlorinated biphenyls; petroleum, oils, and lubricants, other than waste fuel for initial combustion); asbestos; mercury; and foam tent material. (PL 113-66, § 314)

In response to complaints of odor, poor visibility, and health effects attributed to burn pit emissions, the U.S. Army Public Health Command and the Air Force Institute for Operational Health conducted ambient-air sampling and screening health-risk assessments of burn pit exposures at Joint Base Balad in 2007 and again in 2009. The assessments were designed to detect potentially harmful inhalation exposures of personnel at Joint Base Balad to chemicals expected to be released by the burn pit.

A 2011 review of air monitoring efforts at Joint Base Balad conducted by the Institute of Medicine (IOM) found that:

- Particulate matter (PM) concentrations in ambient air were on average higher than U.S. pollution standards. The air samples taken at Joint Base Balad in 2007 and 2009 were analyzed for PM_{10}. The average of the 90 PM_{10} measurements at Joint Base Balad in 2007 was 126 $\mu g/m^3$ (range 2–535 $\mu g/m^3$); the 24-hour National Ambient Air Quality Standards (NAAQS) limit of 150 $\mu g/m^3$ for PM_{10} was exceeded 26 out of 90 times at the three measurement locations. In 2009 the average of the 51 PM_{10} measurements (excluding those that the 2011 committee considered unusable; see IOM, 2011, Appendix B) was 709 $\mu g/m^3$ (range 104–9,576 $\mu g/m^3$), and NAAQS was exceeded for 49 of the 51 samples. The three highest measured PM_{10} values (9,576, 2,481, and 1,951 $\mu g/m^3$) occurred on the same day during a sandstorm (USAPHC, 2010). The committee concluded that the measured PM was primarily from local sources (vehicle traffic, aircraft emissions) and regional sources (long-range anthropogenic sources, dust storms), although the burn pit likely made some contribution.
- Polychlorinated dibenzo-*p*-dioxins and dibenzo-*p*-furans (PCDD/Fs) were detected at low concentrations. Although the levels of species associated with greater toxicity were higher in these samples than in the air generally found in the United States or urban environments worldwide, they were lower than levels associated with some non-military sources present in the theater.
- Concentrations of volatile organic compounds (VOCs) and polycyclic aromatic hydrocarbons (PAHs) were similar to those reported in major urban areas outside the United States, with the major sources being regional background, ground transportation, stationary power generation, and the airport at Joint Base Balad (IOM, 2011).

Subsequent studies also noted the contribution of the Joint Base Balad burn pit to PCDD/Fs on base as well as the important role of other sources of emissions, including the airfield, as the primary source of PAHs. Other important contributors to PAH levels were aircraft, vehicle emissions, space heaters, and diesel generators (Masiol et al., 2016a,b).

The Joint Base Balad observations were limited to the pollutants that were targeted by DoD. Thus, the available monitoring data provide information on exposures to the major types of constituents from burn pit emissions, but they lack information on other chemicals that were likely present as well as on the exposure variability among burn pits and over time (IOM, 2011; NASEM, 2017a). Further details on the strengths and weaknesses of the pollutant measurements and exposure assessment are available from these publications.

Other data collected as part of a monitoring program for a solid waste disposal facility at the Bagram Airfield in Afghanistan underline the variability of exposures associated with burn pits (Blasch et al., 2016). That facility operated a burn pit from 2005 to 2012. Investigators collected breathing zone samples, unlike the case with Joint Base Balad, but only PM and VOCs were studied. Sampling was conducted at four security locations (up to 125 meters from the burn pit) and a control location (4 km from the burn pit) during 30 12-hour shifts. Among the VOCs detected, only Acrolein exceeded the 1-year military exposure guideline, but benzene was detected in all samples. The range of PM concentrations varied considerably in association with airfield activity (vegetation removal, demining, road construction, vehicle traffic, industrial activity, and air traffic). The highest recorded concentrations of environmental $PM_{2.5}$ (615 $\mu g/m^3$) occurred at the solid waste disposal facility where the burn pit and incinerators were located. High $PM_{2.5}$ and PM_{10} concentrations were also noted at the bazaar, a highly populated site with unpaved roads and considerable vehicular traffic. The investigators concluded that "[t]he diversity of results support the concept of a complex environment with multiple polluting sources and changing meteorological and operational conditions" (Blasch et al., 2016, p. S38). The committee responsible for the 2011 report did not identify other systematic sampling data on in-theater burn pit emissions.

Toxicity Studies of Open Burn Pits

Scientists at Wright-Patterson Air Force Base in Dayton, Ohio, have conducted several experimental animal studies to evaluate the toxicity of burn pits compared with the PM collected in 2013 by the U.S. Army Corps of Engineers from Camp Slayer (in Camp Victory), Iraq, and a soil sample from an undisturbed area. The burn pit exposures were from a simulated burn pit that is designed to reflect solid waste combusted in-theater as based on the U.S. Army

Central Area of Responsibility contingency base waste stream analysis (USALIA, 2013). The burned waste included cardboard, food waste, mixed paper, non-combustibles, plastics, textiles, wood, and miscellaneous wastes. Studies have evaluated the impact of burn pits on epigenetic changes, proteomic changes, and metabolomic changes as well as the impacts on the lung microbiome using the same set of exposures and experimental groups (Mauzy, 2019).

In an investigation of epigenetic changes, the results of which were presented to the committee at its October 2019 meeting, Air Force Research Laboratory researchers used four groups of rats, one of which was an unexposed control group, for the 127-day study (Mauzy, 2019). Rats in the three other groups were exposed to Southwest Asia sand only (20 days), sand (20 days) followed by burn pit emissions (5 days), or burn pit emissions only (5 days). All three exposure groups were also exposed to sand from days 67 to 127. Blood, urine, bronchiolar aspiration fluid, and tissue samples were collected from the animals at various time increments based on the endpoints of interest. Burn pit emission exposures were found to initiate molecular host responses much more strongly than sand inhalation exposures. Exposure to the 5 days of burn pit emissions had a greater impact on epigenomic markers than 20 days of sand exposure. The researchers observed that these acute exposures initiated strong host responses—as would also be expected from chronic exposures—and the results indicated a need for concern with even shorter exposures. The sand exposure response was stronger at 90 days post-exposure than at 1 day post-exposure. Based on this work, host response to emissions exposure is relatively fast, whereas host response to sand inhalation is slower. The chronically exposed groups showed more epigenetic changes than those exposed acutely. The data did not indicate any additive effect of sand and burn pit emission exposures. There were sets of differentially expressed micro RNAs (miRNAs) identified in lung tissue. Two chemical species were found in both Affymetrix and sequence-based discovery data sets, both of which are seen in pathways leading to lung cancer or disease (Mauzy, 2019).

The study of proteomic changes again used four groups of rats: a control and three exposure groups: Southwest Asia sand, burn pit emissions, and burn pit emissions followed by sand. Tissues and blood samples were collected from the animals at baseline (both at the start of the study and prior to the burn pit exposure) and at days 4, 30, and 90 after the exposure periods ended. Samples were analyzed using the SEQUEST algorithm in the Proteome Discoverer 2.2 software suite (ThermoFisher, San Jose, California). In the sand-only group, seven burn pit emissions-based markers and four sand-based markers were observed. In the group exposed to sand and emissions, 24 sand and emissions markers were observed but only in the combination exposure group, which may indicate an additive effect. In the burn pit emissions-only group, 20 other markers were found that were not seen in the combination exposure set (Mauzy, 2019).

The metabolomic study evaluated whether changes in urinary metabolite profiles would correlate with exposures and adverse health effects. Again, the researchers used four groups of rats: a control, Southwest Asia sand, burn pit emissions, and burn pit emissions followed by sand. Animals were continuously monitored for 90 days following the exposure period. A cohort of rats provided urine samples at specific times during the 127-day protocol at 12 specific time points. The largest observed effect on urinary metabolite profiles was time, in both the control group and the experimental exposure groups. The greatest difference in urine metabolite profiles occurred during the exposure timeframe (days 1–38) and the least during the recovery period (days 39–97) (DelRaso et al., 2018).

In the microbiome study, the aim was to evaluate whether the burn pit emissions and sand exposures resulted in changes to the lung microbiome. This study also used four groups of rats: a control, Southwest Asia sand, burn pit emissions, and burn pit emissions followed by sand. Following exposure, the researchers removed bronchoalveolar lavage from the left lung of each rat. DNA was extracted from the samples and sequenced to evaluate the diversity of the lung microbiome. The two groups with emissions exposure had the most differences in microbial diversity compared with the control group (Mauzy, 2019).

Taken together, these toxicity studies provide some evidence that exposure to burn pits may have different toxicologic effects than exposure to other airborne hazards in Southwest Asia. These experiments have some advantages over observational studies because the investigators know the nature and temporal pattern of the exposure. However, the outcomes ascertained are mechanistic and not clinically relevant. Additionally, the doses used in the studies may be higher than those experienced by military personnel in theater, and differences in the deposition and clearance of particulates from rat and human lungs (Schlesinger, 1988) affect the interpretation of their results.

Emissions from the 2003 Al-Mishraq Sulfur Plant Fire

On June 24, 2003, U.S. military field reports indicated that a large fire had started at the state-run Al-Mishraq Sulfur Plant near Mosul, Iraq. The fire burned continuously for almost 1 month, until approximately July 21, 2003, and emitted dense clouds of sulfur dioxide, a byproduct of the combustion of elemental sulfur piles. Hydrogen sulfide (H_2S) was also released. Calculations from the Earth Probe Total Ozone Mapping Spectrometer, a National Aeronautics and Space Administration satellite-based instrument, estimated that the amount of SO_2 released averaged 21 kilotons/day over the time that the facility burned—a daily total similar to the amount of SO_2 emitted from a highly polluting plant in the United States in 1 year. At the time of this incident, thousands of U.S. military personnel were deployed to the area in support of Operation Iraqi Freedom. Troops in the area were called on to assist local Iraqis fighting the fire, others assisted in evacuating civilians from local towns nearby, and others continued their military missions and transport operations in the area (Baird et al., 2012).

Fuels

Several petroleum-derived fuels were present in Southwest Asia during U.S. military operations, including gasoline, kerosene, diesel, and jet propellant fuels (JP-4, JP-5, and JP-8). These fuels powered aircraft, ground vehicles, tent heaters, and cooking stoves. They were also used for less conventional purposes, such as suppressing sand and dust aerosolization, cleaning equipment, and burning trash. Other exposures include diesel exhaust from motor pools and diesel-powered vehicles and emissions from the kerosene heaters used in sleeping quarters for warmth. There are anecdotal reports of personnel sleeping in or on running vehicles when other sources of warmth were not available. Deployed military personnel may also experience exposure to exhaust from fixed- and rotary-wing flight-line activities and to complex airborne mixtures, such as those associated with a burn pit.

Military personnel serving in the theater could thus have been exposed to the uncombusted fuels, the combustion products from the burning of those fuels, or a combination of uncombusted and combusted materials. No studies evaluating fuel exposures or their associated combustion byproducts in theater were identified, although, based on the reported widespread use, these are likely a significant source of exposures to airborne hazards in theater (Masiol et al., 2016a).

Oil-Well Fires

Oil-well fires and the smoke they emitted were the most visually dramatic environmental event of the 1990–1991 Gulf War (IOM, 2005). A DoD online publication reported that smoke from the burning oil wells was first visible from satellite images as early as February 8, 1991 (Rostker, 2000). Satellite images showed that the number of oil fires peaked during February 22–24, 1991. In total, Iraqi forces ignited or damaged more than 750 of Kuwait's 943 oil wells distributed among eight fields. The first fires were extinguished in early April 1991, with the last well capped on November 6, 1991. During this period, various sources estimated that the damaged well heads had released approximately 4–6 million barrels of crude oil and 70–100 million cubic meters of natural gas per day. The burning crude oil smoke was a mixture of heated, potentially noxious gases and coated carbon particles, including a wide range of combustion products: carbon dioxide (CO_2) and carbon monoxide (CO), sulfur dioxide (SO_2), oxides of nitrogen (NO_x), VOCs, hydrogen sulfide (H_2S), ozone (O_3), various PAHs, and acid aerosols. The smoke also contained other components that are common impurities in crude oil, such as vanadium, iron, nickel, aluminum, beryllium, cadmium, calcium, chromium, arsenic, silicon, zinc, and lead (Rostker, 2000).

No systematic monitoring of the airborne hazards from the fires occurred until May 1991, when several independent teams from multiple U.S. agencies (including the Army Public Health Agency and the Environmental Protection Agency [EPA]) and international agencies went into Kuwait to monitor the ambient air contamination due to oil-well fire emissions (Spektor, 1998). The monitoring data indicate that concentrations of NOx, CO, SO_2, H_2S, other pollutant gases, and PAHs did not exceed those in the air of a typical U.S. industrial city (IOM, 2006). PAH concentrations in the samples were low (PAC, 1996). High concentrations of PM from sand and soot were often observed at multiple monitoring sites; an estimated 20,000 tons of soot, or fine-particle mass, was generated by the fires (Thomas et al., 2000) and made up about 23% of the PM in the Persian Gulf, often at concentrations twice those considered acceptable (Rostker, 2000).

The potential exposures of troops to smoke and combustion products from the oil-well fires were also modeled (Draxler et al., 1994). Daily and seasonal normalized air concentrations due to emissions from the oil-well fires were computed using a modified Lagrangian transport, dispersion, and deposition model for the period of February through October 1991. The highest normalized concentrations were located near the coast between Kuwait and Qatar, with peak values moving farther west and inland with each season (i.e., the smoke and combustion products moved from over the Gulf in the spring to the west over the Saudi Peninsula by autumn).

Nerve Agents

Another hazard specific to the 1990–1991 Gulf War was exposure to nerve agents following the demolition of a large storage complex at Khamisiyah, Iraq, which occurred during a cease-fire period in March 1991. The total amount released, according to estimates, was 371 kg of sarin and cyclosarin combined (Winkenwerder, 2002). U.S. troops performing the demolitions were unaware of the presence of nerve agents, and no air monitoring was conducted at the time of the demolition. Exposure models estimated that the exposures were low, and there were no medical reports at the time of any cases exhibiting signs or symptoms of exposure to sarin or acute cholinergic syndrome (IOM, 2004).

Depleted Uranium

Depleted uranium (DU) is a weakly radioactive, chemically toxic heavy metal derived from natural uranium which is used by the U.S. military for munitions and for armor on some tanks. DU is well suited as a munition because of its high density and "self-sharpening" nature, both of which help it to penetrate armor. Its high density also makes DU an effective shield. DU has been used by all branches of the U.S. military since the 1980s and was used on the battlefield in the 1990–1991 Gulf War and the post-9/11 conflicts (NRC, 2008).

Concern about the adverse health effects on survivors of combat exposure to DU arose in response to "friendly-fire" incidents in which U.S. vehicles were accidentally struck with DU rounds. In the Gulf War, about 115 U.S. soldiers in or on 6 Abrams tanks and 14 Bradley fighting vehicles were caught in friendly-fire events that involved the use of large-caliber munitions containing DU penetrators. Some of the soldiers were injured by DU shrapnel. Most of the large metal embedded fragments in the surviving 104 soldiers were removed during treatment for their injuries. However, many small fragments were left embedded in their muscle tissue because their removal might lead to other health complications (NRC, 2008).

When used as an antitank armor-piercing munition, a DU penetrator can create an airborne spray of uranium with particles of various sizes that can be inhaled by the tank crew or escape into the environment (NRC, 2008). Studies in uranium miners found associations between exposure to uranium and respiratory diseases, including pneumoconiosis, chronic obstructive pulmonary disease, pulmonary fibrosis, and tuberculosis (Hines et al., 2013). However, the committee responsible for *Gulf War and Health: Updated Literature Review of Depleted Uranium* concluded that there was inadequate or insufficient evidence to determine whether exposure to DU is associated with long-term health problems (IOM, 2008).

REGIONAL ENVIRONMENTAL EXPOSURES

The Southwest Asia regional climate is hot and arid, which exposes military personnel to intense heat and sunlight during the day, while nights are cool. Pressure gradients cause frequent and severe dust storms in the region, and the relative lack of vegetation permits large areas of loose soil to be moved great distances (Goudie, 2014). Variations in climatic and vegetation conditions are associated with changes in dust levels in arid regions (Li et al., 2020). In some instances, winds are high enough to cause larger dust and sand particles to impact and eject smaller particles into the air via a process called "saltation,"[3] which can lead to the large-scale transport of particulate matter across several hundred miles (Jayaratne et al., 2011). Wildfires, in which forests, crops, and brush can catch fire and which result from natural drought and human activity, also contribute to air pollution. And Southwest Asia is becoming increasingly industrialized, with more vehicle traffic, and the only country within the theater of operations with air quality standards is Saudi Arabia. The region is resource rich, and thus its primary industries are extractive, such as mining and oil and gas development, which affects air quality (Tsiouri et al., 2015).

Toxicity of Air Pollution Exposures

Traffic-related air pollution has been associated with a variety of respiratory effects. In 2010, a panel of the Health Effects Institute reviewed more than 700 studies on the health effects of traffic-related air pollution and concluded that the evidence is sufficient to support a causal relationship between exposure to traffic-related air pollution and exacerbation of asthma. It also found suggestive evidence of a causal relationship between traffic-related air pollution and both nonasthma respiratory symptoms and impaired lung function (HEI, 2010).

Exposures to emissions from diesel engines and their potential impact on human health have also been of concern. Epidemiologic and toxicologic studies have reported associations between short- and long-term exposures to diesel exhaust and its components and a range of acute and chronic adverse health effects, including lung cancer. In 2012 the International Agency for Research on Cancer reviewed the body of scientific evidence on the carcinogenicity of diesel exhaust and concluded that there was sufficient evidence in humans and experimental animals to classify diesel exhaust as a Group 1 carcinogen (carcinogenic to humans) (Benbrahim-Tallaa et al., 2012).

Particulate Matter

Particulate matter is characterized by its physical size and chemical properties and includes total suspended particles (TSP), inhalable particles with aerodynamic diameters less than 10 micrometers (PM_{10}), coarse particles with aerodynamic diameter between 10 and 2.5 micrometers ($PM_{10-2.5}$), and fine inhalable particles with diameters less than 2.5 micrometers ($PM_{2.5}$). In Southwest Asia, PM sources may include dust storms, dust from motor-vehicle disturbance of the desert floor, agricultural activities, lead–zinc smelters, battery-processing facilities, refineries, power stations, fertilizer plants, and emissions from vehicles (UNEP, 2007). Dust storms may carry large amounts of PM great distances, and the chemical composition can change during transport (Mori et al., 2003). The long-range transport of desert dusts significantly affects the air-quality over large regions. Dust transport and anthropogenic emission sources (petrochemical and power plants and industrial operations) have affected the levels of TSP throughout Southwest Asia and neighboring countries, and dust storms increase the concentrations of PM_{10} and $PM_{2.5}$ (Querol et al., 2019).

There have been several efforts to characterize ambient PM levels in Southwest Asia. These studies vary in a number of ways, particularly in terms of the exposure assessment methods used and the time, location, and area. In general, the studies have found that PM exposures in Southwest Asia appear higher than those generally observed in the United States and that they often exceed the NAAQS for $PM_{2.5}$ (12 $\mu g/m^3$ [annual average]; 35 $\mu g/m^3$ [24-hour average]) and PM_{10} 150 $\mu g/m^3$ (24-hour average not to exceed more than once per year over 3 years) (see Table 2-1).

Masri et al. (2017b) published $PM_{2.5}$ exposure estimates that have the most coverage to date in terms of time and geography throughout the region. They determined the relationship between daily airport visual range measurements and $PM_{2.5}$ samples collected during 2004–2005 (Brown et al., 2008) to develop a $PM_{2.5}$ prediction model that could be applied more generally to airport visual range data. In their application, the prediction model was used on location-specific visibility data at 104 regional sites in Iraq, Afghanistan, United Arab Emirates, Kuwait, Djibouti, and Qatar during the period 2000–2012 to estimate monthly average $PM_{2.5}$ concentrations. Predicted

[3] "Saltation is the movement of large particles (about 100–500 µm) that bounce a few centimeters above the surface and then fall back down, thereby bombarding the surface; upon impact, they dislodge smaller particles (less than 100 µm) from the surface, which can be entrained in the prevailing airflow" (NASEM, 2017b, p. 35).

TABLE 2-1 Summary of Studies That Measured Particulate Matter in Southwest Asia

Reference	Sample Type	Location	Year	$PM_{2.5}$ µg/m^3 Mean (SD)	PM_{10} µg/m^3 Mean (SD)	TSP µg/m^3 Mean (SD)
Brown et al. (2008)	24-hr samples, Rupprecht and Patashnick Co., Inc., Model 3500 ChemCombs speciation samplers	Northern Kuwait	2004–2005	30.8 (16.6)	65.8 (37.0)	
		Kuwait City	2004–2005	37.6 (17.3)	92.8 (38.9)	
		Southern Kuwait	2004–2005	36.5 (18.2)	90.4 (52.1)	
Engelbrecht et al. (2008)	24-hr active air sampling with Airmetrics MiniVol particulate sampler, one each for TSP, PM_{10}, and $PM_{2.5}$ using a 1-in-6 day sampling schedule across the sites	Djibouti	2006–2007	33	72	94
		Bagram, Afghanistan	2006–2007	40	120	174
		Khowst, Afghanistan	2006–2007	75	126	185
		Qatar	2006–2007	67	166	282
		United Arab Emirates	2006–2007	52	140	196
		Balad, Iraq	2006–2007	56	183	242
		Baghdad, Iraq	2006–2007	103	250	371
		Tallil, Iraq	2006–2007	65	303	411
		Tikrit, Iraq	2006–2007	114	300	628
		Taji, Iraq	2006–2007	81	213	348
		Al Asad, Iraq	2006–2007	38	96	142
		Northern Kuwait	2006–2007	67	211	416
		Central Kuwait	2006–2007	117	298	352
		Coastal Kuwait	2006–2007	60	180	264
		Southern Kuwait	2006–2007	62	199	290
Javed et al. (2019)	24-hr $PM_{2.5}$ and PM_{10} samples were collected on pre-weighed, polypropylene-ring-supported 2-µm pore-size Teflon 37 mm filters, using a low-volume air-sampling pump	One site in Doha, Qatar	May to December 2015	40 (15)	145 (70)	
Lim et al. (2018)	PM samples were collected onto Teflon filters (GelmanTeflo, 37-mm, 0.2-µm pore-size) using $PM_{2.5}$ and PM_{10} Harvard impactors connected to calibrated vacuum pumps, at a rate of 10.0 L/min	Jeddah, Saudi Arabia	2011–2012	21.9 (11.6)	107.8 (72.6)	
Masri et al. (2017a)	Monthly predicted $PM_{2.5}$ using airport visual range measurement calibrated and aerosol optical depth	17,000 km^2 region surrounding Joint Base Balad and Baghdad, Iraq	2005–2008	45.4		
Masri et al. (2017b)	Compared daily airport visual range measurements with $PM_{2.5}$ samples collected from 2004–2005 develop a model to predict monthly $PM_{2.5}$ using ground-level airport visual range data	104 sites in Iraq, Afghanistan, United Arab Emirates, Kuwait, Djibouti, and Qatar	2000–2012	42.8 (22.7)		

continued

TABLE 2-1 Continued

Reference	Sample Type	Location	Year	$PM_{2.5}$ µg/m^3 Mean (SD)	PM_{10} µg/m^3 Mean (SD)	TSP µg/m^3 Mean (SD)
Nayebare et al. (2017)	24-hr $PM_{2.5}$ samples were collected on pre-weighed, sequentially numbered polypropylene-ring-supported Whatman 2-µm pore-size PTFE 46.2 mm filters, using a low-volume air-sampling pump	One site in Rabigh, Saudi Arabia	May to June 2013	37 (16.2)		

NOTE: PM, particulate matter; PTFE, polytetrafluoroethylene; SD, standard deviation; TSP, total suspended particle.

$PM_{2.5}$ concentrations averaged from 10–365 µg/m^3 across the locations, with an overall mean of 42.8 µg/m^3 and a standard deviation of 22.7 µg/m^3.

In a related study, visibility data obtained for 2006–2007 from seven U.S. Air Force 14th Weather Squadron sites located in a 17,000-km^2 region in Iraq that includes Joint Base Balad were used to predict $PM_{2.5}$. The authors coupled visibility measurements with aerosol optical depth observed by satellite to create a visibility prediction model, and then, using the previously defined calibration between visibility and $PM_{2.5}$ (Masri et al., 2017b), they converted the spatially and temporally resolved satellite observations to ground-level $PM_{2.5}$ concentrations over the region (Masri et al., 2017a). Predicted $PM_{2.5}$ was variable across space and time, but overall the highest concentrations were in the Baghdad and Balad regions. Two-year average predicted $PM_{2.5}$ ranged from 34.79 µg/m^3 to 231.30 µg/m^3. At the Air Force sites, mean predicted $PM_{2.5}$ was 45.4 µg/m^3 (min [December]: 32.7 µg/m^3, max [June]: 63.5 µg/m^3). The advantage of this study is that employing both satellite aerosol optical depth observations and airport visibility data provides a measure of particle abundance near the ground with fine (1 × 1 km) resolution (Masri et al., 2017a).

Other studies have measured PM in the region, including the aforementioned study by Brown et al. (2008), who characterized PM concentrations by collecting 24-hour samples at varying frequencies at three sites in Kuwait in 2004–2005, and DoD's Enhanced Particulate Matter Surveillance Program, which characterized PM (TSP, PM_{10}, $PM_{2.5}$) in ambient air at 15 sites in 2006–2007 (Engelbrecht et al., 2008). DoD's program was limited in that the sampler used for this study (the Airmetrics MiniVol portable air sampler) was not well suited to sampling in circumstances where concentrations may be excessively high, for example, during a dust storm, so that the samplers may have been overloaded, leading to overestimated exposures (NRC, 2010).

Between May 6 and June 17, 2013, Nayebare et al. (2017) collected 40 24-hour $PM_{2.5}$ samples on pre-weighed, sequentially numbered polypropylene-ring-supported Whatman 2-µm pore-size polytetrafluoroethylene 46.2-mm filters, using a low-volume air-sampling pump at a location in Rabigh, Saudi Arabia. They observed significant variability in concentrations, ranging from 12.2 µg/m^3 to 75.9 µg/m^3, with an average of 37 µg/m^3 and a standard deviation of 16.2 µg/m^3.

At a location in Jeddah, Saudi Arabia, Lim et al. (2018) collected $PM_{2.5}$ and PM_{10} samples on Teflon filters (GelmanTeflo, 37-mm, 0.2-µm pore-size) using Harvard impactors connected to calibrated vacuum pumps, at a rate of 10.0 L/min, from midnight to midnight over a year-long period from June 2011 to May 2012. They collected samples once on a Thursday or Friday and twice on Saturday through Wednesday to capture both variation through the week and seasonal differences. The annual average concentrations of $PM_{2.5}$ were 21.9 µg/m^3 with a standard deviation of 11.6 µg/m^3, and the annual average PM_{10} concentration was 107.8 µg/m^3 with a standard deviation of 72.6 µg/m^3. Seasonally, the highest concentrations for both PM_{10} and $PM_{2.5}$ were observed in spring (due to dust storm activity), while the lowest concentrations were observed in autumn. Coarse particles were predominant in Jeddah, with a smaller $PM_{2.5}/PM_{10}$ mass ratio (0.20) observed there than in other cities.

Regardless of the temporal, geographical, and compositional variations of airborne PM in Southwest Asia, the concentrations of PM often exceeded EPA's NAAQS or the World Health Organization's air quality guideline values for $PM_{2.5}$ and PM_{10}. Relying on the extrapolation of results derived from studies performed in the United

States to estimate the health effects attributed to air pollution in this area seems inappropriate (Li et al., 2019). The only airborne hazard that has complexity similar to those encountered in Southwest Asia by military personnel during service in the Southwest Asia theater was the smoke and dust discharged into the air after the collapse of the World Trade Center twin towers and a number of surrounding skyscrapers on September 11, 2001. The unprecedented event released millions of tons of material into the air from pulverized and incinerated building materials, furniture, equipment, and unburned jet fuels (Maciejczyk et al., 2005). The plume from the collapse covered a large area around the World Trade Center and penetrated many buildings in downtown Manhattan (CDC, 2002). Additional pollutants were released by the ensuing fire, which persisted until December 20, 2001, and by the recovery and clean up processes that followed (Lioy et al., 2002; Maciejczyk et al., 2005).

A 2002 EPA analysis estimated that "individuals engulfed in the initial dust/smoke cloud may have been exposed for several hours to concentrations of both fine and coarse inhalable particles anywhere in the range from milligrams per cubic meter (>1,000 $\mu g/m^3$) to perhaps hundreds of milligrams per cubic meter (>100,000 $\mu g/m^3$)" (EPA, 2002, p. 30). Concentrations had decreased to near ambient levels in December 2001, with a few peak concentrations ranging from 20 to 55 $\mu g/m^3$ (Maciejczyk et al., 2005). Numerous World Trade Center–related health effects research studies have shown increased incidences of respiratory and other illnesses in World Trade Center responders, who were exposed to extremely high concentrations of dust (in the >15,000 $\mu g/m^3$ range) (Li et al., 2016; Lippmann et al., 2015; Singh et al., 2018; Solan et al., 2013). Studies of residents near the former World Trade Center site, who were exposed to much lower concentrations of World Trade Center dust than the responders, showed an increased rate of new-onset and persistent bronchial hyperresponsiveness and symptoms as compared with a control population (Reibman et al., 2005). These studies provide biologic plausibility for the claim that exposures to airborne hazards in Southwest Asia have the potential to influence the health of military personnel, although clearly the World Trade Center exposure was much more intense and over a shorter time period.

Source Apportionment Studies

Several studies have investigated the sources and chemical composition of PM and dusts in Southwest Asia. Brown et al. (2008) conducted source apportionment using specimens that the authors collected in 2004–2005. The investigators analyzed for the presence of elemental and organic carbon and calculated the fraction of PM that was contributed by coarse particles. They found that coarse particles made up 50–60% of PM_{10}. The high levels of PM_{10} and the large fraction of coarse particles making up PM_{10} are an indication that resuspension of dust and soil from the desert crust was a significant source. However, levels of elemental carbon, organic carbon, and most of the elements—including toxic heavy metals—that were identified were higher in urban location specimens, indicating contributions from local mobile and stationary sources.

Alolayan et al. (2013) investigated $PM_{2.5}$ in the atmosphere of Kuwait based on the sampling program described in Brown et al. (2008). They used three methods of source identification; a positive matrix factorization model; backward trajectory profiles; and concentration rose plots. Contributions from five major sources of $PM_{2.5}$ were estimated: sand dust or sandstorms; oil combustion or power plants; petrochemical industry, fertilizer, nylon or catalyst regeneration facilities; traffic, vehicle emissions, and road dust; and transported emissions (that is, emissions from outside Kuwait). The researchers found that 54% of $PM_{2.5}$ emissions were from sand dust, 18% from oil combustion, 12% from the petrochemical industry, 11% from traffic, and 5% from sources transported from outside the country. The contributions from oil combustion, petrochemical industry, and traffic were found to originate from local sources, whereas sand dust and some emissions from traffic, and possibly smelters, appeared to originate from sources outside of Kuwait.

Engelbrecht et al. (2009) conducted a source apportionment analysis of the samples collected as part of DoD's Enhanced Particulate Matter Surveillance Program. The researchers used trace-element analysis to measure the concentrations of metals and major elements and ion-chemistry analyses to estimate the mineral components. Scanning electron microscopy with energy dispersive spectroscopy was used to analyze the chemical composition of small individual particles. The three main air pollutant types found were geological dust, smoke from burn pits, and heavy metal condensates. Non-dust-storm events resulted in elevated trace metal concentrations in samples from Baghdad, Balad, and Taji in Iraq. In all instances, quartz grains had rounded edges, and mineral grains were generally coated by clay minerals and iron oxides. The design of the sampling schema in this study does not permit complete characterization of the particle mass for any given set of samples because there needed to be more clearly defined objectives of the sampling and analysis scheme at the outset of the program (NRC, 2010). While the study provides a perspective on the airborne sources present in the Southwest Asia theater, there is reason to be skeptical of the conclusions drawn, which were based on a pooled analysis of sites that were widely separated in space (Djibouti, Afghanistan, Qatar, United Arab Emirates, Iraq, and Kuwait) and time (over an approximately 1-year period).

Lim et al. (2018) conducted source apportionment analysis of the samples they collected in Jeddah, Saudi Arabia. Using absolute principal component analysis, concentration roses, and backward trajectories, they identified the following source categories for both $PM_{2.5}$ and $PM_{2.5–10}$: soil/road dust; incineration; and traffic; and for $PM_{2.5}$ only, residual oil burning. Soil/road dust accounted for a major portion of both the $PM_{2.5}$ (27%) and $PM_{2.5–10}$ (77%) mass, and the largest source for $PM_{2.5}$ was residual oil burning (63%).

Javed et al. (2019) examined PAHs, n-alkane homologs, hopanes, and steranes in airborne $PM_{2.5}$ and PM_{10} specimens collected in Doha, Qatar. This organic pollutant apportionment study was conducted in May–December 2015. Analyses indicated that the primary sources of these pollutants were fossil fuel combustion (emissions from vehicles, shipping, and petroleum refineries), fugitive dust, and vegetative and other biogenic sources.

Biologic Agents and Allergens

Biologic agents can contribute to disease in military personnel through causing infections or by initiating an allergic response from the immune system. A previous National Academies committee found that several infections endemic to Southwest Asia could have long-term adverse outcomes, including brucellosis, Campylobacter infection, leishmaniasis, malaria, Q fever, salmonellosis, and shigellosis. Of these, only brucellosis was found to be associated with a respiratory health outcome: respiratory system infections (IOM, 2007).

In addition, numerous aeroallergens have been observed across Southwest Asia: pollen from hundreds of different grasses, weeds, shrubs, and trees; spores from hundreds of species of molds; allergens from insects such as cockroaches and mosquitos; dander from domestic animals, rodents, and farm animals; and dozens of types of house dust mites and storage mites. Among the pollens specific to the region are those from the date palm and from the invasive shrub *Prosopis juliflora* (Goronfolah, 2016).

Toxicity of Sand and Dusts

Concerns about the toxicity of the sand and dusts encountered in the Southwest Asia theater have led to various studies to characterize the composition and the toxicity of dusts from the region. In 2004 the U.S. Central Command Area of Responsibility began Operation Sandbox to characterize the mineral, chemical, physical, and microbiologic composition of airborne Kuwaiti and Iraqi dust surface soil or dust samples normally encountered in other desert regions. The study found a number of bioavailable metals, including arsenic, chromium, lead, nickel, cobalt, strontium, tin, vanadium, zinc, manganese, barium, and aluminum. The investigators also identified more than 147 different microbial isolates (six different genera), of which about 30% are known human pathogens; 13 isolates were α- or β-hemolytic species (Lyles, 2018). These data suggest that the microbial and metal content of the mineralized dust could pose an inhalation hazard due to the presence of metals and pathogens.

There has also been research to characterize the toxicity using both in vitro (cell-based) and in vivo (animal) toxicity studies. Szema et al. (2014) obtained dusts from a grab sample taken from Camp Victory, Iraq, and examined the dusts using X-ray diffraction and X-ray fluorescence. They then conducted a small toxicity study using male C57BL/6 mice to compare the toxicity of the Camp Victory dust (n = 3) with that of untreated controls (n = 5) and of two positive control groups, a group treated with Montana mining dust (n = 2) and an inert negative-control soil sample from San Joaquin, California (n = 3). Both control dusts were obtained from the National Institute of Standards and Technology. The dust was administered intratracheally to age-matched C57BL/6 mice. The authors found increased interleukin-2 (IL-2) from bronchiolar lavage in the mice treated with Iraq dust compared with the control groups, demonstrating that Iraq dust may lead to lung inflammation. This small study provides some information with respect to the possible histologic and immunologic effects of Iraq dusts; however; the route of exposure—intratracheal administration—does not correspond well with the exposure route experienced by humans in real-world situations.

Dorman et al. (2012) conducted a study in adult rats to characterize the respiratory toxicity of inhaled Iraqi sand. Adult rats underwent a 6-week inhalation regimen exposing them to air or to common cigarette smoke (3 hours per day, 5 days per week) that included exposure to Iraqi or crystalline silica (1 mg/m^3, 19 hours per day, 7 days per week) or air during the last 2 weeks. Assessments included motor activity, whole-body plethysmography, cytological and biochemical analysis of bronchoalveolar lavage fluid, lung metal burden, nasal and lung pathology, and changes in lung protein and gene expression. Chemical analysis of the Iraqi sand showed that it contains nickel, manganese, vanadium, and chromium. The authors found evidence that the metals in Iraqi sand are bioavailable because they observed elevated lung parenchyma aluminum, silica, barium, manganese, and vanadium concentrations in Iraqi sand–exposed rats. Rats exposed to Iraqi sand only developed mild inflammation in the anterior nose and lung. Rats exposed to silica inhalation had some pulmonary responses that were not seen in Iraqi sand–exposed rats, such as mild laryngeal and tracheal inflammation, mild tracheal epithelial hyperplasia, and elevated lung silica concentrations. Cigarette smoke inhalation with or without co-exposure to either Iraqi sand or silica resulted in changes consistent with pulmonary inflammation and stress response. Rats exposed to cigarette smoke and silica had more widespread airway lesions than rats exposed to cigarette smoke only. Silica-exposed rats had more robust pulmonary gene expression and proteomic responses than seen in Iraqi sand–exposed rats. This study showed that the respiratory toxicity of Iraqi sand is similar to that of silica. It has the advantage of being an inhalation study that evaluated for interactions with cigarette smoking, a common exposure in military personnel. However, the exposure duration was only 6 weeks, which may not be representative of the exposure durations that service members experience during their deployments to the theater.

In a third experimental study using rats, Taylor et al. (2013) evaluated the respiratory toxicity of sand particles collected at military bases near Fort Irwin in Barstow, California; camps Victory, Taji, and Tallil in Iraq; and Khost, Afghanistan. The goal of the study was to assess the role of soluble metals in the respiratory toxicity of the sand particles using cell lines and animal models. Rat type II alveolar cell cultures were exposed to sand extracts or vehicle control in serum-free media for up to 24 hours. The researchers then determined cytotoxicity using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay and assessment of lactate dehydrogenase leakage. Male Crl:CD(SD) rats were used to assess the acute and delayed pulmonary toxicity of extracts of sand from Camp Victory, Camp Taji, and Khost, Afghanistan, and of Taji sand following intratracheal administration. Assessments included a biochemical analysis of bronchoalveolar lavage fluid (BALF) and lung histopathology. Based on the cell-culture assays, the researchers found that the sand from Taji and Tallil was the most toxic, followed by the sand from Khost, Afghanistan, Camp Victory, and Fort Irwin. The in vitro cytotoxicity assay results were partially predictive of in vivo responses. The more cytotoxic Taji sand extract induced an acute irritant response in rats following intratracheal administration. Rats that were administered the less cytotoxic Camp Victory sand extract had minimal biochemical or cytologic BALF changes, whereas rats given either the Afghanistan or the Taji sand extracts demonstrated BALF changes that were suggestive of mild lung inflammation. Similar lung pathologies were observed in all extract-exposed rats.

Taken together these toxicity studies provide some evidence that sands and dusts in Southwest Asia may have different toxic effects than dusts found in other regions. Such experiments have some advantages over observational studies because investigators have control over a number of influential factors, including the nature and temporal pattern of the exposure; the selection of the test subjects in terms of species, ages, gender, and known or suspected susceptibilities; and the nature and timing of the response assays before, during, and after the exposures. It is also the case that animal studies can have a good correlation with human disease; acutely toxic doses are similar in human and a variety of animal systems, and many respiratory system anatomic, physiologic, and biochemical parameters are similar in humans and other mammals. However, it is unclear how relevant these studies are for understanding human exposures. The outcomes ascertained are mechanistic in nature and provide evidence of harmful toxicological effects, but they lack clinical relevance. Two of the studies reviewed by the committee used intratracheal administration as the exposure method, which is of low relevance to human exposures. Additionally, the doses used in the studies may be higher than those experienced by military personnel in theater.

OCCUPATIONAL EXPOSURES

Occupational exposures akin to those experienced in civilian settings also occur in the Southwest Asia theater. For example, a military mechanic will experience exposures to fuels, engine fluids, and solvents just as that person's civilian counterpart would, and military and civilian facilities management personnel may be exposed to both insecticides and pesticides as part of their duties. Exposure to such hazards has been associated with long-term adverse health outcomes (IOM, 2011). The military occupations with the highest exposure to vapors, gases, dusts, and fumes include firefighters; ground crew; fuel handlers; maintenance workers; infantry/combat engineers; artillery; motor transport; aviation; special forces; combat medicine; ordinance disposal; maintenance of vehicle, aircraft, or weapons systems; airfield services; and military police (Zell-Baran, 2018).

Certain job duties or tasks can also increase exposures to vapors, gases, dusts, and fumes. For example, military personnel who painted combat vehicles and equipment during their military service may have been exposed to chemical agent resistant coating (CARC) paint or to vapors. CARC is used on military vehicles to make metal surfaces more highly resistant to corrosion and to the penetration of chemical agents. CARC paints contain several inhalation hazards, including hexamethylene di-isocyanate, toluene diisocyanate, and other solvents.

While a number of papers considered by the committee mention military occupational exposures among the many airborne hazards experienced by deployed personnel, the committee did not identify any studies that specifically examined these exposures and adverse respiratory health outcomes.

EXPOSURE TRACKING BY THE DEPARTMENT OF DEFENSE

DoD and the Department of Veterans Affairs are working on a number of information management and technology efforts to support linking exposure and health effects information. The Individual Longitudinal Exposure Record (ILER) is a web-based application that provides the ability to link an individual to occupational and environmental exposures to improve the efficiency, effectiveness, and quality of health care. ILER is supposed to create a complete record of a service member's occupational and environmental health exposures over the course of his or her career by linking individuals to known exposure events and incidents and compiling the exposure history in order to distill and report the relevant data and information (e.g., handling, diagnosis, and action thresholds). ILER uses multiple data sources, such as the Defense Manpower Data Center, Defense Occupational and Environmental Health Readiness System–Industrial Hygiene, and the Military Health System Data Repository. The goal of ILER is to provide epidemiologists, researchers, and policy makers with greater access to and insights on exposure events and to give them the ability to develop cohorts more efficiently by reducing the number of external information management and information technology systems they need to access in order to assess exposure impacts. ILER is planned to have full operating capability by September 2023 (Shuping, 2019).

FACTORS THAT MAY LEAD TO INCREASED VULNERABILITY TO AIRBORNE HAZARDS

There are factors that are common to military operations in Southwest Asia that, while they are not airborne hazards, may modify the relationship between exposure to airborne hazards and respiratory health effects. These include temperature extremes, stress, and noise. Other influences, such as obesity and poor diet, may also increase the individual susceptibility to some airborne hazards but are not discussed in this brief overview of the topic because they are less directly related to military service in theater. The risks from these hazards may have been increased due to the personnel having co-occurring exposures from their military occupations, tasks, or job duties that act on similar targets. The committee did not identify any literature that addressed the effect of these factors on respiratory health outcomes in deployed personnel but notes them here for completeness.

In addition to these, deployed military personnel may also be at higher risk than their nondeployed counterparts because of the characteristics of the structures in which they work, eat, and sleep. The committee could not identify any literature on this subject with the exception of a conference paper (Aldred and Corsi, 2011) that suggested that PM exposure in indoor environments in the Middle East might pose serious health problems because of high outdoor PM levels and high outdoor-indoor penetration factors in military buildings. This was also pointed out in the 2011 IOM report *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan* (IOM, 2011), which observed that it was likely that much of the available in-theater housing would allow penetration of fine particles into the living spaces. However, neither of these sources cites data on penetration factors nor measurements in indoor environments. Information on this would help to better characterize potential airborne exposures encountered in indoor spaces in theater.

Temperature Extremes

Heat may increase exposure to air pollution through increased respiration, and prolonged exposure to extreme heat can cause heat exhaustion, heat cramps, heat stroke, and—in severe cases—death. It can also exacerbate pre-existing chronic conditions, including respiratory diseases (WHO, 2019). In a study of heat illness hospitalizations and deaths in the U.S. Army from 1980–2002, infantry soldiers and gun crewman were found to have the greatest rate of heat illness among all military occupational specialties that were examined (Carter et al., 2005). Low temperatures may also have an effect on health. When temperatures drop, heat may rapidly leave the body, which can lead to shivering, fatigue, loss of coordination, or, in more serious cases, hypothermia. Epidemiologic literature shows growing evidence of the acute effects of high and low temperatures in the United States, Europe, and other parts of the world (Baccini et al., 2008; Turner et al., 2012; Zanobetti and Schwarz, 2008). More recently, in a time series analysis, Alahmad et al. (2019) found that both high and low ambient temperatures were significantly associated with an increased risk of short-term mortality in Kuwait. Another analysis of this population (Alhamed et al., 2020a) showed a U-shaped exposure–response relationship to heat and cardiovascular mortality, with the risk tripling at extreme high temperature (108° Fahrenheit), and males showing a higher risk than females. In those aged 15–64 years, which encompasses the age span of U.S. military personnel, risk was significantly increased. After further stratifying the 15–64 age group, there was a significantly increased risk of cardiovascular and non-accidental mortality at extreme high temperature in those most likely to work outside and perform demanding jobs (Alahamed et al., 2020b). These results suggest that in-theater ambient conditions may represent a risk even for young and healthy people. There have been some studies of how hot temperature modify the health effects of air pollutants in non-military populations, but the findings have been equivocal (Analitis et al., 2018; Lee, 2019).

Stress

Acute and chronic stress affect health through a wide range of biological pathways, including the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes and other key regulatory systems of the body, including respiratory, immune, endocrine, central nervous system, cardiovascular, and metabolic functions (Clougherty and Kubzansky, 2009). The body's response to stress is adaptive, meaning it responds to changing conditions and demands. However, over-extension of an acute stress response over time (also known as chronic stress) and the consequent failure to achieve homeostasis lead to physiologic damage and increase an individual's susceptibility to injury from exposures to social and environmental stressors (Payne-Sturges et al., 2018). This condition is commonly referred to as "allostatic load" and includes systemic impacts to cardiovascular, immune, endocrine, and metabolic function as well as neurodevelopmental and cognitive effects (McEwen, 1998). A contrasting model in which cortisol production lessens following chronic stress has been proposed to explain the pro-inflammatory effects of chronic stress (Hannibal and Bishop, 2014). Chronic, repeated activation of acute stress responses may down-regulate, or blunt, adaptive acute stress responses either via dis-regulation of cortisol or catecholamine release at the target tissue. Psychosocial stressors and chemical pollutants affect many of the same physiologic systems (e.g., neurologic, metabolic, immune, and cardiovascular), which are key regulatory systems of the body. Therefore, it is highly plausible that combined psychosocial and environmental exposures may interact to increase or amplify the risks of adverse respiratory health outcomes.

Noise

Chronic environmental noise is associated with a wide variety of adverse health effects, including sleep disturbance, annoyance, noise-induced hearing loss, cardiovascular disease, endocrine effects, and diabetes (Hammer et al., 2014). Also, service members have a significantly increased risk of hearing impairment (Lie et al., 2016). Contemporaneous exposures to particulate matter and noise may contribute to an increased susceptibility to the development or exacerbation of cardiopulmonary diseases. In a small study of male highway workers in the United States, increased levels of $PM_{2.5}$ and noise were associated with increased heart rate variability, but no effects were observed with lung function or nitric oxide concentrations in exhaled air (Meier et al., 2014).

FINAL OBSERVATIONS ON AIRBORNE HAZARDS

The information developed in this chapter is used to inform the evaluation of respiratory outcomes evidence that is reviewed in Chapters 3 and 4. Some of the studies considered in these chapters examine the potential association between a particular exposure—burn pit emissions, for example—and a health effect or outcome. However, the committee is mindful of the fact that everyone who was deployed to the theater was potentially exposed to a broad range of airborne hazards, whether these were explicitly considered in an epidemiologic analysis or not. This is particularly true of airborne particulate matter, which was ubiquitous and ever-present in the form of environmental dust and sand. The committee therefore does not draw conclusions on the influence of specific exposures on specific outcomes in deployed personnel, an exercise that is in any case rendered largely impractical by the current lack of good exposure information. Chapter 5 goes on to address how some of the knowledge deficits identified here could be addressed.

REFERENCES

Alahmad, B., A. Shakarchi, M. Alseaidan, and M. Fox. 2019. The effects of temperature on short-term mortality risk in Kuwait: A time-series analysis. *Environmental Research* 171:278–284.

Alahmad, B., H. Khaishah, A. F. Shakarchi, M. Albagdadi, S. Rajgopalan, P. Koutrakis, and F. A. Jaffer. 2020a. Cardiovascular mortality and exposure to heat in an inherently hot region implications for climate change. *Circulation Research Letter* 141:1271–1273.

Alahmad, B., A. F. Shakarchi, H. Kharaisah, M. Alsaidan, J. Gasana, A. Al-Hemoud, P. Koutrakis, and M. A. Fox. 2020b. Extreme temperatures and mortality in Kuwait: Who is vulnerable? *Science of the Total Environment* 732:139289.

Aldred, J. R., and R. L. Corsi. 2011, December. Investigating the exposure of military personnel serving in the Middle East to ambient particulate matter. In *12th International Conference on Indoor Air Quality and Climate 2011*. Pp. 143–148. https://www.isiaq.org/docs/presentations/0102_Aldred.pdf (accessed July 16, 2020).

Alolayan, M. A., K. W. Brown, J. S. Evans, W. S. Bouhamra, and P. Koutrakis. 2013. Source apportionment of fine particles in Kuwait City. *Science of the Total Environment* 448:14–25.

Analitis, A., F. De'Donato, M. Scortichini, T. Lanki, X. Basagana, F. Ballester, C. Astom, A. Paldy, M. Pascal, A. Gasparrini, P. Michelozzi, and K. Katsouyanni. 2018. Synergistic effects of ambient temperature and air pollution on health in Europe: Results from the PHASE Project. *International Journal of Environmental Research and Public Health* 15(9):1856.

Baccini, M., A. Biggeri, G. Accetta, T. Kosatsky, K. Katsouyanni, A. Analitis, H. R. Anderson, L. Bisanti, D. D'Ippoliti, J. Danova, B. Forsberg, S. Medina, A. Paldy, D. Rabczenko, C. Schindler, and P. Michelozzi. 2008. Heat effects on mortality in 15 European cities. *Epidemiology* 19:711–719.

Baird, C. P., S. DeBakey, L. Reid, V. D. Hauschild, B. Petruccelli, and J. H. Abraham. 2012. Respiratory health status of U.S. Army personnel potentially exposed to smoke from 2003 Al-Mishraq sulfur plant fire. *Journal of Occupational and Environmental Medicine* 54(6):717–723.

Benbrahim-Tallaa, L., R. A. Baan, Y. Grosse, B. Lauby-Secretan, F. El Ghissassi, V. Bouvard, N. Guha, D. Loomis, K. Straif, and International Agency for Research on Cancer Monograph Working Group. 2012. Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes. *Lancet Oncology* 13(7):663–664.

Blasch, K. W., J. E. Kolivosky, and J. M. Heller. 2016. Environmental air sampling near burn pit and incinerator operations at Bagram Airfield, Afghanistan. *Journal of Occupational and Environmental Medicine* 58(8 Suppl 1):S38–S43.

Brown, K.W., W. Bouhamra, D. P. Lamoureux, J. S. Evans, and P. Koutrakis. 2008. Characterization of particulate matter for three sites in Kuwait. *Journal of the Air and Waste Management Association* 58(8):994–1003.

Carter, R., S. N. Cheuvront, J. O. Williams, M. A. Kolka, L. A. Stephenson, M. N. Sawka, and P. J. Amoroso. 2005. Epidemiology of hospitalizations and deaths from heat illness in soldiers. *Medicine & Science in Sports & Exercise* 37(8):1338–1344.

CDC (Centers for Disease Control and Prevention). 2002. Occupational exposures to air contaminants at the World Trade Center Disaster Site–New York, September–October, 2001. *JAMA* 287(24):3201–3202.

Clougherty, J. E., and L. D. Kubzansky. 2009. A framework for examining social stress and susceptibility to air pollution in respiratory health. *Environmental Health Perspectives* 117:1351–1358.

DelRaso, N. J., C. A. Mauzy, B. A. Wong, and N. V. Reo. 2018. *Burn pit emission and respirable sand exposures in rats: NMR-based urinary metabolomic assessment*. No. AFRL-RH-WP-TR-2018-0061. Henry M. Jackson Foundation for the Advancement of Military Medicine. Wright-Patterson Air Force Base United States.

DoD (Department of Defense). 2018. *DOD Instruction 4715.19: Use of open-air burn pits in contingency operations*. Office of the Under Secretary of Defense for Acquisition and Sustainment. https://fas.org/irp/doddir/dod/i4715_19.pdf (accessed May 22, 2020).

DoD. 2019. *Open Burn Pit Report to Congress: April 2019*. Office of the Under Secretary of Defense for Acquisition and Sustainment. https://www.acq.osd.mil/eie/Downloads/Congress/Open%20Burn%20Pit%20Report-2019.pdf (accessed May 22, 2020).

Dorman, D. C., V. Mokashi, D. J. Wagner, A. O. Olabisi, B. A. Wong, O. R. Moss, J. A. Centeno, G. Guandalini, D. A. Jackson, W. E. Dennis, J. A. Lewis, R. S. Thomas, and G. D. Chapman. 2012. Biological responses in rats exposed to cigarette smoke and Middle East sand (dust). *Inhalation Toxicology* 24(2):109–124.

Draxler, R. R., J. T. McQueen and B. J. B. Stunder. 1994. An evaluation of air pollutant exposures due to the 1991 Kuwait oil fires using a Lagrangian model. *Atmospheric Environment* 28(13):2197–2210.

Engelbrecht, J. P., E. V. McDonald, J. A. Gillies, and A. W. Gertler. 2008. *Department of Defense Enhanced Particulate Matter Surveillance Program (EPMSP): Final report*. Desert Research Institute, Reno, NV. February. https://pdfs.semanticscholar.org/18af/a824db71d54eb0242659b5b224c71e32aaba.pdf (accessed June 17, 2020).

Engelbrecht, J. P., E. V. McDonald, J. A. Gillies, R. K. M. Jayanty, G. Casuccio, and A. W. Gertler. 2009. Characterizing mineral dusts and other aerosols from the Middle East—Part 1: Ambient sampling. *Inhalation Toxicology* 21(4):297–326.

EPA (Environmental Protection Agency). 2002. *Exposure and human health evaluation of airborne pollution from the World Trade Center disaster (External review draft)*. Washington, DC: Environmental Protection Agency.

Goronfolah, L. 2016. Aeroallergens, atopy and allergic rhinitis in the Middle East. *European Annals of Allergy and Clinical Immunology* 48(1):5–21.

Goudie, A. S. 2014. Desert dust and human health disorders. *Environment International* 63:101–113.

Hammer, M. S., T. K. Swinburn, and R. L. Neitzel. 2014. Environmental noise pollution in the United States: Developing an effective public health response. *Environmental Health Perspectives* 122(2):115–119.

Hannibal, K. E., and M. D. Bishop. 2014. Chronic stress, cortisol dysfunction, and pain: A psychoneuroendocrine rationale for stress management in pain rehabilitation. *Physical Therapy* 94(12):1816–1825.

HEI (Health Effects Institute). 2010. *Traffic-related air pollution: A critical review of the literature on emissions, exposure, and health effects*. Special Report 17. Health Effects Institute. https://www.healtheffects.org/publication/traffic-related-air-pollution-critical-review-literature-emissions-exposure-and-health (accessed May 23, 2020).

Hines, S. E., P. Gucer, S. Kligerman, R. Breyer, J. Centeno, J.Gaitens, M. Oliver, S. Engelhardt, K. Squibb, and M. McDiarmid. 2013. Pulmonary health effects in Gulf War I service members exposed to depleted uranium. *Journal of Occupational and Environmental Medicine* 55(8):937–944.

IOM (Institute of Medicine). 2004. *Gulf War and health: Updated literature review of sarin*. Washington, DC: The National Academies Press.

IOM. 2005. *Gulf War and health: Volume 3: Fuels, combustion products, and propellants*. Washington, DC: The National Academies Press.

IOM. 2006. *Gulf War and health: Volume 4: Health effects of serving in the Gulf War.* Washington, DC: The National Academies Press.

IOM. 2007. *Gulf War and health: Volume 5: Infectious diseases*. Washington, DC: The National Academies Press.

IOM. 2008. *Gulf War and health: Updated literature review of depleted uranium*. Washington, DC: The National Academies Press.

IOM. 2011. *Long-term health consequences of exposure to burn pits in Iraq and Afghanistan*. Washington, DC: The National Academies Press.

Javed, W., M. Iakovides, R. Garaga, E. G. Stephanou, S. H. Kota, Q. Ying, J. M. Wolfson, P. Koutrakis, and B. Guo. 2019. Source apportionment of organic pollutants in fine and coarse atmospheric particles in Doha, Qatar. *Journal of the Air & Waste Management Association* 69(11):1277–1292.

Jayaratne, E. R., G. R. Johnson, P. McGarry, H. C. Cheung, and L. Morawska. 2011. Characteristics of airborne ultrafine and coarse particles during the Australian dust storm of 23 September 2009. *Atmospheric Environment* 45(24):3996–4001.

Krefft, S. D., C. S. Rose, S. Nawaz, and Y. E. Miller. 2015. Deployment-related lung disorders. *Federal Practitioner* 32(6):32–38.

Lee, W. 2019. Synergic effect between high temperature and air pollution on mortality in Northeast Asia. *Environmental Research* 178:108735.

Li, J., R. M. Brackbill, T. S. Liao, B. Qiao, J. E. Cone, M. R. Farfel, J. L. Hadler, A. R. Kahn, K. J. Konty, L. T. Stayner, and S. D. Stellman. 2016. Ten-year cancer incidence in rescue/recovery workers and civilians exposed to the September 11, 2001 terrorist attacks on the World Trade Center. *American Journal of Industrial Medicine* 59(9):709–721.

Li, J., E. Garshick, A. Al-Hemoud, S. Huang, and P. Koutrakis. 2020. Impacts of meteorology and vegetation on surface dust concentrations in Middle Eastern countries. *Science of the Total Environment* 712:136597.

Li, X., L. Jin, and H. Kan. 2019. Air pollution: A global problem needs local fixes. *Nature* 570(7762):437–439.

Lie, A., M. Skogstad, H. A. Johannessen, T. Tynes, I. S. Mehlum, K. Nordby, B. Engdahl, and K. Tambs. 2016. Occupational noise exposure and hearing: A systematic review. *International Archives of Occupational and Environmental Health* 89(3):351–372.

Lim, C. C., G. D. Thurston, M. Shamy, M. Alghamdi, M. Khoder, A. M. Mohorjy, A. Alkhalaf, J. Brocato, L. C. Chen, and M. Costa. 2018. Temporal variations of fine and coarse particulate matter sources in Jeddah, Saudi Arabia. *Journal of the Air & Waste Management Association* 68(2):123–138.

Lioy, P. J., C. P. Weisel, J. R. Millette, S. Eisenreich, D. Vallero, J. Offenberg, B. Buckley, B. Turpin, M. Zhong, M. D. Cohen, C. Prophete, I. Yang, R. Stiles, G. Chee, W. Johnson, R. Porcja, S. Alimokhtari, R. C. Hale, C. Weschler, and L. C. Chen. 2002. Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in lower Manhattan after the collapse of the WTC 11 September 2001. *Environmental Health Perspectives* 110(7):703–714.

Lippmann, M., M. D. Cohen, and L. C. Chen. 2015. Health effects of World Trade Center (WTC) dust: An unprecedented disaster's inadequate risk management. *Critical Reviews in Toxicology* 45(6):492–530.

Lyles, M.B. 2018. Chapter 18: Biological, chemical, and environmental hazards of desert dust to military personnel. *Environmental Geochemistry: Site Characterization, Data Analysis, and Case Histories (Second Edition)*. Cambridge, MA: Elsevier. Pp. 467–485.

Maciejczyk, P. B., R. L. Zeisler, J. S. Hwang, G. D. Thurston, and L. C. Chen. 2005. Characterization of size-fractionated World Trade Center dust and estimation of relative dust contribution to ambient particulate concentrations. *Urban Aerosols and Their Impacts: Lessons Learned from the World Trade Center Tragedy (ACS Symposium Series): Volume 919*. Washington, DC: American Chemical Society. Pp. 114–131.

Masiol, M., C. T. M. Mallon, K. M. Haines, Jr., M. J. Utell, and P. K. Hopke. 2016a. Airborne dioxins, furans, and polycyclic aromatic hydrocarbons exposure to military personnel in Iraq. *Journal of Occupational and Environmental Medicine* 58(8S):S22–S30.

Masiol, M., C. T. M. Mallon, K. M. Haines, Jr., M. J. Utell, and P. K. Hopke. 2016b. Source apportionment of airborne dioxins, furans, and polycyclic aromatic hydrocarbons at a United States forward operating air base during the Iraq war. *Journal of Occupational and Environmental Medicine* 58(8S):S31–S37.

Masri, S., E. Garshick, B. A. Coull, and P. Koutrakis. 2017a. A novel calibration approach using satellite and visibility observations to estimate fine particulate matter exposures in Southwest Asia and Afghanistan. *Journal of the Air & Waste Management Association* 67(1):86–95.

Masri, S., E. Garshick, J. Hart, W. Bouhamra, and P. Koutrakis. 2017b. Use of visual range measurements to predict fine particulate matter exposures in Southwest Asia and Afghanistan. *Journal of the Air & Waste Management Association* 67(1):75–85.

Mauzy, C. 2019. *Toxicity evaluation and biomarker identification in rats exposed to burn pit emissions and respirable sand from Afghanistan*. Air Force Research Laboratory. Presentation to the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 4, 2019.

McEwen, B. S. 1998. Protective and damaging effects of stress mediators. *New England Journal of Medicine* 338(3):171–179.

Meier, R., W. E. Cascio, A. J. Ghio, P. Wild, B. Danuser, and M. Riediker. 2014. Associations of short-term particle and noise exposures with markers of cardiovascular and respiratory health among highway maintenance workers. *Environmental Health Perspectives* 122:726–732.

Mori, I., M. Nishikawa, T. Tanimura, and H. Quan. 2003. Change in size distribution and chemical composition of kosa (Asian dust) aerosol during long-range transport. *Atmospheric Environment* 37(30):4253–4263.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2017a. *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry*. Washington, DC: The National Academies Press.

NASEM. 2017b. *Investigative strategies for lead-source attribution at Superfund sites associated with mining activities*. Washington, DC: The National Academies Press.

Nayebare, S. R., O. S. Aburizaiza, A. Siddique, D. O. Carpenter, J. Zeb, A. J. Aburizaiza, C. Pantea, M. M. Hussain, and H. A. Khwaja. 2017. Association of fine particulate air pollution with cardiopulmonary morbidity in Western Coast of Saudi Arabia. *Saudi Medical Journal* 38(9):905–912.

NRC (National Research Council). 1996. *Understanding risk: Informing decisions in a democratic society*. Washington, DC: National Academy Press.

NRC. 2008. *Review of toxicologic and radiologic risks to military personnel from exposure to depleted uranium during and after combat*. Washington, DC: The National Academies Press.

NRC. 2010. *Review of the Department of Defense Enhanced Particulate Matter Surveillance Program report*. Washington, DC: The National Academies Press.

PAC (Presidential Advisory Committee). 1996. Presidential Advisory Committee on Gulf War Veterans' Illnesses: Final Report. Washington, DC: Government Printing Office.

Payne-Sturges, D., M. Scammell, J. Levy, D. Cory-Slechta, E. Symanski, J. C. Shmool, R. Laumbach, S. Linder, and J. Clougherty. 2018. Methods for evaluating the combined effects of chemical and nonchemical exposures for cumulative environmental health risk assessment. *International Journal of Environmental Research and Public Health* 15(12):2797.

Querol, X., A. Tobías, N. Pérez, A. Karanasiou, F. Amato, M. Stafoggia, C. Pérez García-Pando, P. Ginoux, F. Forastiere, S. Gumy, P. Mudu, and A. Alastuey. 2019. Monitoring the impact of desert dust outbreaks for air quality for health studies. *Environment International* 130:104867.

Reibman, J., S. Lin, S.-A. A. Hwang, M. Gulati, J. A. Bowers, L. Rogers, K. I. Berger, A. Hoerning, M. Gomez, and E. F. Fitzgerald. 2005. The World Trade Center residents' respiratory health study: New-onset respiratory symptoms and pulmonary function. *Environmental Health Perspectives* 113(4):406–411.

Rostker, B. 2000. *Environmental exposure report: Oil well fires*. Department of Defense. https://gulflink.health.mil/owf_ii/index.htm (accessed May 12, 2020).

Schlesinger, R. B. 1988. Biological disposition of airborne particles: Basic principles and application to vehicular emissions. In *Air Pollution, the Automobile, and Public Health*, pp. 239–298. https://www.ncbi.nlm.nih.gov/books/NBK218161 (accessed July 16, 2020).

Shuping, E. 2019. *Individual Longitudinal Exposure Record (ILER). Briefing to Office of Research and Development and Clinical Staff*. PowerPoint presentation. Department of Veterans Affairs. https://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/3699-notes.pdf (accessed May 13, 2020).

Singh, A., R. Zeig-Owens, W. Moir, C. B. Hall, T. Schwartz, M. Vossbrinck, N. Jaber, M. P. Webber, K. J. Kelly, V. Ortiz, E. Koffler, and D. J. Prezant. 2018. Estimation of future cancer burden among rescue and recovery workers exposed to the World Trade Center disaster. *JAMA Oncology* 4(6):828–831.

Solan, S., S. Wallenstein, M. Shapiro, S. L. Teitelbaum, L. Stevenson, A. Kochman, J. Kaplan, C. Dellenbaugh, A. Kahn, F. N. Biro, M. Crane, L. Crowley, J. Gabrilove, L. Gonsalves, D. Harrison, R. Herbert, B. Luft, S. B. Markowitz, J. Moline, X. Niu, H. Sacks, G. Shukla, I. Udasin, R. G. Lucchini, P. Boffetta, and P. J. Landrigan. 2013. Cancer incidence in World Trade Center rescue and recovery workers, 2001–2008. *Environmental Health Perspectives* 121(6):699–704.

Spektor, D. M. 1998. *A review of the scientific literature as it pertains to Gulf War illnesses—Volume 6: Oil well fires*. National Defense Research Institute. Santa Monica, CA: RAND Corporation.

Szema, A. M., R. J. Reeder, A. D. Harrington, M. Schmidt, J. Liu, M. Golightly, T. Rueb, and S. A. Hamidi. 2014. Iraq dust is respirable, sharp, metal-laden, and induces lung inflammation with fibrosis in mice via IL-2 upregulation and depletion of regulatory T cells. *Journal of Occupational and Environmental Medicine* 56(3):243–251.

Taylor, K., M. L. Foster, J. M. Law, J. A. Centeno, E. Fornero, M. S. Henderson, S. A. Trager, M. G. Stockelman, and D. C. Dorman. 2013. Assessment of geographical variation in the respiratory toxicity of desert dust particles. *Inhalation Toxicology* 25(7):405–416.

Thomas, R., T. Vigerstad, J. Meagher, and C. McMullin. 2000. *Particulate exposure during the Persian Gulf War.* Washington, DC: Department of Defense.

Tsiouri V., K. E. Kakosimos, and P. Kumar. 2015. Concentrations, sources and exposure risks associated with particulate matter in the Middle East Area—a review. *Air Quality, Atmosphere, and Health* 8:67–80.

Turner, L. R., A. G. Barnett, D. Connell, and S. Tong. 2012. Ambient temperature and cardiorespiratory morbidity: A systematic review and meta-analysis. *Epidemiology* 23(4):594–606.

UNEP (United Nations Environment Programme). 2007. *Air quality and atmospheric pollution in the Arab Region*. Draft. League of Arab States and United Nations Economic and Social Commission for Western Asia. http://www.un.org/esa/sustdev/csd/csd14/escwaRIM_bp1.pdf (accessed May 22, 2020).

USALIA (U.S. Army Logistics Innovation Agency). 2013. *U.S. Army Central area of responsibility contingency base waste stream analysis*. Fort Belvoir, VA: Pacific Northwest National Laboratory. https://apps.dtic.mil/dtic/tr/fulltext/u2/a579439.pdf (accessed May 22, 2020).

USAPHC (U.S. Army Public Health Command). 2010. *Screening health risk assessments, Joint Base Balad, Iraq, 11 May–19 June 2009*. Aberdeen Proving Ground, MD: U.S. Army Center for Health Promotion and Preventive Medicine.

VA (Department of Veterans Affairs). 2018. *Airborne hazards concerns: Information for veterans*. War Related Illness and Injury Study Center. https://www.warrelatedillness.va.gov/education/factsheets/airborne-hazards-concerns-info-for-veterans.pdf (accessed April 7, 2020).

WHO (World Health Organization). 2019. *Information and public health advice: Heat and health*. https://www.who.int/globalchange/publications/heat-and-health/en (accessed May 13, 2020).

Winkenwerder, W. 2002. *Case narrative: US demolition operations at Khamisiyah. Final report*. Washington, DC: Department of Defense. https://gulflink.health.mil/khamisiyah_iii (accessed May 12, 2020).

Zanobetti, A., and J. Schwartz. 2008. Temperature and mortality in nine U.S. cities. *Epidemiology* 19:563–570.

Zell-Baran, L. 2018. *Are military occupational specialty codes (MOS) useful epidemiologic tools to predict inhalational exposures during deployment?* PowerPoint presentation. National Jewish Health. https://cdn.ymaws.com/www.cste.org/resource/resmgr/weston/2018weston/Zell_Baran_20180907.pdf (accessed September 2, 2019).

3

Evaluation of the Evidence Base and Background of Major Studies and Cohorts

This chapter explains how the committee carried out its evaluation of the papers, reports, and other documents that form the foundation of its analyses. It is divided into two primary parts. The chapter begins with a description of the approach and process used by the committee to identify and evaluate the scientific and medical literature on the association between exposure to airborne hazards and respiratory health outcomes among military personnel and veterans who served in Afghanistan and the Southwest Asia Theater of Military Operations[1] from 1990 to the present. The majority of the evidence considered by the committee when making its conclusions on the strength of the evidence of an association between exposure to airborne hazards in theater and a specific respiratory health outcome consisted of published epidemiologic studies. The committee's literature search criteria as well as its process for screening abstracts, conducting full-text review of studies identified as possibly relevant in the abstract screening, and evaluating the final set of studies identified as relevant are described in detail, including the basic methodologic considerations used for assessment of individual studies. This is followed by the classification system, or categories of association, that the committee used to draw conclusions about the strength of the evidence for each respiratory health outcome it considered.

The second part of the chapter provides background descriptions of major cohorts and research initiatives that the committee was tasked with examining. The details of the populations, assessment methods, and outcomes are presented here to minimize repetition when the results of the studies are described in Chapter 4. The section begins with cohorts of post-9/11 operations veterans followed by 1990–1991 Gulf War veterans. Cohorts and large studies of U.S. veterans are presented first, followed by those of foreign coalition forces.

IDENTIFICATION AND SCREENING OF LITERATURE

The committee was tasked with comprehensively reviewing, evaluating, and summarizing the scientific literature regarding associations between airborne hazards and respiratory health outcomes in theater veterans in order to draw conclusions on the strength of the associations between exposure and outcomes. This section describes

[1] The Department of Veterans Affairs defines the Southwest Asia Theater of Military Operations to comprise Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Gulf of Aden, Gulf of Oman, Oman, Qatar, the United Arab Emirates, and the waters of the Persian Gulf, the Arabian Sea, and the Red Sea (VA, 2019). For the sake of brevity, this report refers to this region plus Afghanistan as the "Southwest Asia theater" or simply the "theater."

the extensive searches of the published scientific literature that were conducted using major biomedical databases and the process for screening through the identified titles and abstracts.

Literature Identification

Under the direction of the committee, National Academies staff worked to define and refine searches of the scientific literature. Five databases were examined: Embase, Scopus, Medline, PubMed, and Toxline/Toxnet. These databases index peer-reviewed medical, chemical, biologic, and toxicologic publications. The searches covered the full text of the articles whenever that text was available. If any of the search terms were included in the title or abstract or indexed in the key words or text of the article, the article would be included in the results.

The committee's search included specific exposure and outcome terms indicated in the Statement of Task as well as terms that were not explicitly mentioned but were implied by the scope of the work. The full set of search terms is shown in Box 3-1. That set included full and abbreviated names, common and scientific names,

BOX 3-1
MeSH Search Terms

Respiratory Health Outcomes*
mortality, bronchitis, asthma, bronchiolitis, chronic bronchitis, chronic obstructive pulmonary disease, bronchiolitis obliterans, cough, dyspnea, emphysema, pulmonary eosinophilia, gastroesophageal reflux, extrinsic allergic alveolitis, idiopathic pulmonary fibrosis, obstructive sleep apnea, pneumonia, pulmonary hypertension, respiratory tract diseases, respiratory tract infections, respiratory signs and symptoms, rhinitis, sarcoidosis, sinusitis, spirometry, vocal cord dysfunction, respiratory sounds, esophageal neoplasms, laryngeal neoplasms, lung neoplasms, nose neoplasms, nasopharyngeal neoplasms, mouth neoplasms, oropharyngeal neoplasms, oropharynx neoplasms

Airborne Hazards Exposures
Industrial exposure: industrial environment OR occupational air pollutants OR occupational asthma OR occupational diseases OR occupational illnesses OR occupational exposure

Environmental exposure: air pollutants OR environmental air pollutants OR air pollution OR environmental illness OR environmental illnesses OR environmental hypersensitivities OR environmental hypersensitivity OR environmental pollutants OR environmental carcinogens

Burn pits: incineration OR solid waste incineration OR burn pits OR open burning OR open pits OR open-air burning OR solid waste incineration OR uncontrolled burning OR uncontrolled combustion

Fossil fuels: petroleum OR fuel oils OR gasoline OR diesel OR kerosene OR kerosine OR coal

Geographic Region
Middle East OR Afghanistan OR Bahrain OR Iraq OR Kuwait OR Oman OR Qatar OR Saudi Arabia OR United Arab Emirates OR Djibouti OR Indian Ocean OR Persian Gulf OR Red Sea OR Arabian Sea OR Gulf of Aden OR Gulf of Oman OR Saudi–Iraqi neutral zone

Military Personnel
Air Force OR Armed Forces OR Army OR Navy OR Coast Guard OR Marines OR military OR military deployment OR sailors OR soldiers OR submariners OR veterans

* Primary MeSH listings only.

and Medical Subject Heading (MeSH) descriptors for each of the exposure and health outcome terms. The search terms for respiratory health outcomes included *mortality*, *cancer*, *bronchial asthma*, *chronic bronchitis*, *sinusitis*, *constrictive bronchiolitis*, and other relevant respiratory health outcomes. The airborne hazards exposure terms included *industrial exposures*, *environmental exposures*, and *fossil fuels* as well as hazards associated with burn pit exposures. Other search terms included geographic regions and military- and veteran-specific nomenclature.

The search was limited to articles published in English and was conducted in April 2019. After removing duplicate studies that were identified in multiple databases, 41,646 titles and abstracts were initially identified to be screened.

Literature Screening

The search strategy was devised to ensure that abstracts of all potentially relevant articles were identified, but it also resulted in the identification of a large number of non-relevant studies. Again under direction of the committee, National Academies staff began screening the results of the literature using a web-based platform to systematically screen and review large volumes of literature. Two reviewers reviewed each title or abstract. When the two primary reviewers were not in agreement, a third reviewer made the determination whether to include an article. Articles that did not have abstracts were generally passed to the full-text review stage unless the information included in the title clearly excluded it.

After a preliminary screening of the first few thousand identified studies, the committee deliberated and determined that the exclusion criteria needed to be strengthened. Studies considered not relevant and excluded from further consideration during the screening phase included studies published before 1991 (approximately 7,500), studies focused solely on respiratory outcomes of children and people under the age of 18, and studies that measured exposures without respiratory health outcomes. Studies that examined conditions or diseases that were not part of the respiratory system (such as cardiovascular system diseases) or that caused secondary effects on the respiratory system (such as amyotrophic lateral sclerosis, which causes breathing problems but which is not a respiratory disease), as well as respiratory health issues caused by physical injuries were all excluded. Animal studies were generally excluded. A complete list of exclusion criteria is found in Box 3-2. The committee focused its review

BOX 3-2
Exclusion Criteria

- Therapeutic or treatment studies following intentional or unintentional exposure to an agent found in theater
- Descriptions of intentional acute exposures or poisoning, including suicide
- Narrative or historical accounts of service in theater
- Studies that did not relate an exposure of interest to a health outcome of interest
- Study populations composed solely of people less than 18 years of age
- Exposures that occurred in the Southwest Asia theater prior to 1990
- Respiratory health outcomes resulting from physical injury (e.g., lung injuries due to blast exposure)
- Respiratory health conditions or diseases that occur as a result from diseases that do not primarily affect the pulmonary system (e.g., psychogenic dyspnea and cardiovascular disease)
- Studies of military populations involved in conflicts outside of the Southwest Asia Theater of Military Operations
- Studies of exposures that are not associated with deployment
- Non-human studies that do not aim to specifically evaluate the toxic effects from airborne hazards in theater
- Populations of non-military or veteran personnel, such as populations of civilians in Southwest Asia countries, firefighters, incinerator workers, or people living near incinerators

on epidemiologic studies, rather than medical case studies or animal models because epidemiology deals with the frequency, determinants, and distribution of disease in human populations rather than in individuals or in animal models. Epidemiologic studies effectively integrate any results of exposure to a target substance in combination with other substances that may be etiologically relevant. Several types of epidemiologic studies were captured and evaluated, including cohort, case–control, and cross-sectional designs.

Because Southwest Asia theater veterans are the topic of the charge to the committee, the committee chose not to consider studies of respiratory health outcomes in other non-military populations with ostensibly similar exposures. Such populations would include those exposed to the aftermath of the World Trade Center attacks, incinerator workers, and firefighters. While these populations also had or have exposure to smoke or dust associated with the burning of diverse materials, the composition of the chemical agents and particulates present and the duration, intensity, and other circumstances of exposure are materially different from those experienced by deployed service members. In addition, other characteristics associated with deployment, such as living conditions and combat, may also confound the association between airborne exposures and effects. For these reasons, the committee concluded that the differences between these populations and theater veterans were too great to justify their use in evaluations of the health effects of military service in Southwest Asia.

Of the more than 41,000 study titles and abstracts screened, only fewer than 200 (n = 196) were found to be relevant. Full text articles of the approximately 200 articles that had passed the screening stage were then retrieved and reviewed. Additional studies were dropped from further consideration after their full text had been read if they met one or more of the exclusion criteria.

The committee supplemented the epidemiologic studies identified by the comprehensive literature review with epidemiologic studies found in the reference lists of reviews and relevant studies, book chapters, and government reports as those were presumed to have also undergone some type of review before publication. Additional studies that were published after the April 2019 literature search were also captured by committee members familiar with the literature in the area and by web alerts set to the topic, although the list of publications identified in this manner may not be exhaustive.

Supplemental Evidence Considered

Peer-reviewed studies with original data collection and analyses were preferred over studies that were reanalyses of a population (without the incorporation of additional information), pooled analyses or meta-analyses, reviews, and so on. In general, the committee used only published papers that had undergone peer review as the basis for its conclusions. As a supplement to these published epidemiologic studies, a number of identified case studies, conference abstracts and presentations, topic-specific reviews, and commentaries, letters to the editor, and author responses to an included article were used as supportive information for certain topic areas. These supplemental pieces may be discussed in conjunction with the results from the epidemiologic literature or in synthesis sections on a given exposure or health outcome. Toxicologic studies, which would include studies of laboratory animals and in vitro cultures, focus on mechanisms rather than clinical outcomes, with the latter being the focus of the committee's charge. As such, toxicologic studies were included as supplemental sources of information where relevant, but they were not reviewed in the same comprehensive manner as the epidemiologic literature. The supplemental sources, while providing additional information, did not drive the committee's conclusions. The committee did not collect original data or perform any secondary data analyses.

Invited Presentations

As part of fulfilling its Statement of Task, the committee held two open sessions to assist in information gathering, which served to inform the discussions throughout this report. During the first open session, on March 27, 2019, representatives from the Department of Veterans Affairs (VA) gave a presentation to formally charge the committee with its Statement of Task and to answer clarifying questions related to the charge. The second open session occurred on October 3–4, 2019, when the committee held a workshop as part of its third in-person meeting to assist it in information gathering concerning past and current research efforts that informed discussions throughout this report. The workshop agenda is reproduced in Appendix A. PDF copies of speakers' presentations are posted to the National Academies website;[2] videos of the presentations are also available.[3] Highlights of this information are summarized below.

During the October 3–4, 2019, workshop, seven of the invited workshop presenters discussed the objectives, methodology, and future efforts of major epidemiologic studies on military and veterans' health. Rudolph Rull from the Naval Health Research Center presented on topics related to respiratory health research in the Millennium Cohort Study (Rull, 2019). This included data regarding the study participants' deployment status, combat exposure, combat deployment, burn pit exposure, and biomarkers of burn pit exposure. Aaron Schneiderman from the VA Post-Deployment Health Services Epidemiology Program spoke about the respiratory conditions and diseases, environmental exposures, and deployment status of study participants in the National Health Study for a New Generation of U.S. Veterans (Schneiderman, 2019). He also presented information on the Comparative Health Assessment Interview (CHAI) Study, a national study on the health and well-being of veterans, which was undergoing data cleaning and preliminary analysis in autumn 2019. Drew Helmer from the Michael E. DeBakey VA Medical Center presented work conducted by the VA Airborne Hazards and Burn Pits Center of Excellence (AHBPCE) at the War Related Illness and Injury Study Center (WRIISC) in New Jersey (Helmer, 2019). He discussed the cumulative clinical experience of the WRIISC/AHBPCE post-deployment cardiopulmonary evaluation network, the Airborne Hazards and Open Burn Pit Registry, and other ongoing research at the center. Michael Falvo from WRIISC and the Rutgers New Jersey Medical School discussed the primary outcomes and preliminary data from the Effects of Deployment on Cardiopulmonary and Autonomic Function, a VA pilot study with 50 participants (Falvo, 2019). Michael Morris from the Brooke Army Medical Center presented on the post-deployment respiratory symptoms of the Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE) (Morris, 2019a). This included acute eosinophilic pneumonia, chronic obstructive pulmonary disease (COPD), asthma, and sarcoidosis, among others. Eric Garshick from the Harvard Medical School and the VA Boston Healthcare System addressed the Service and Health Among Deployed Veterans (SHADE) study, VA SHADE ancillary study, and burn pit–related exposures and visibility measurements to predict $PM_{2.5}$ exposures (Garshick, 2019). Rebekah R. Wu from the Duke University School of Medicine and the Durham VA Cooperative Studies Program Epidemiology Center spoke in depth about the Gulf War Era Cohort Biorepository Project to develop a research cohort of Gulf War–era veterans and a biorepository to be made available for future research studies (Wu, 2019). This presentation included information on the eligibility of participants, data collected, participant demographics, respiratory exposures, and respiratory symptoms and conditions.

Five workshop speakers gave presentations on health issues related to in-theater airborne hazards exposures. Timothy Blackwell from the Vanderbilt University Medical Center presented a detailed overview on lung pathology in patients with post-deployment constrictive bronchiolitis, including an analysis of small airways, blood vessels, and parenchyma in the lungs of service members (Blackwell, 2019). Michael Morris gave a second talk, this one addressing pre- and post-deployment spirometry among military personnel (Morris, 2019b). This included pre- and post-deployment spirometry performed as part of the STAMPEDE series of studies and screening and respiratory health investigations conducted in other populations of military personnel. Joan Reibman from the New York University (NYU) Grossman School of Medicine, NYU Langone Health, NYU/Bellevue Asthma Clinic, and the World Trade Center Environmental Health Center, presented on the respiratory health outcomes in community members exposed to environmental toxins from the World Trade Center disaster and its pertinence to Gulf War veterans (Reibman, 2019). Karan Uppal from Emory University explained how the application of high-resolution metabolomics, data science, and integrative omics can be used to evaluate the health effects of environmental exposures (Uppal, 2019). Kimberly Sullivan of the Boston University School of Public Health and Nancy Klimas of the Miami VA Medical Center and NOVA Southeastern University spoke about the use of military veteran biorepositories—particularly the Gulf War Illness Consortium Biorepository and the Boston Biorepository, Recruitment and Integrated Network for Gulf War Illness—in collecting data and conducting research on the respiratory health of military personnel (Klimas, 2019; Sullivan, 2019).

---

[2] See https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019" (accessed May 15, 2020).

[3] See https://www.youtube.com/playlist?list=PLGTMA6QkejfjaqtcHrad0uWZVlMXjB7w3 (accessed May 15, 2020).

Six of the invited workshop presenters expanded on the use of exposure assessment and diagnostic-related innovations to measure in-theater exposures. Steven Patterson and Jennifer Therkorn from the Johns Hopkins University Applied Physics Laboratory gave an overview of exposure assessment in a military environment, covering topics such as burn pits, toxic mixtures, fuel vapor exposures, silicone wristbands, and particulate matter (PM) sensors (Patterson, 2019; Therkorn, 2019). William Funk from Northwestern University talked about emerging biomarker approaches and technologies for exposure assessment (Funk, 2019). This included targeted versus untargeted biomarker approaches and dried blood spot sampling. Eric Hoffman from the University of Iowa explained how computed tomography (CT) and magnetic resonance imaging can serve to provide lung structure–function relationships for the phenotyping of lung disease (Hoffman, 2019). He addressed multi-scale imaging, xenon imaging, and dual energy CT. Camilla Mauzy from the Air Force Research Laboratory gave a presentation on toxicity evaluation and biomarker identification in rats exposed to burn pit emissions and respirable sand from Afghanistan (Mauzy, 2019). She explained how molecular analyses using epigenomics, blood proteomics, urine metabolomics, and lung microbiome can aid with identifying biomarkers. Katrina Waters from the Pacific Northwest National Laboratory also discussed various biomarker strategies for exposure and response outcomes (Waters, 2019).

The workshop open session also included comments from the public. These included presentations made by representatives from two veterans advocacy organizations. Anthony Hardie from the Veterans for Common Sense gave a brief introduction about his organization and spoke about the impact of respiratory health research on veterans like himself (Hardie, 2019). Ronald Brown from the Vietnam Veterans of America gave a presentation on exposure to oil-well fires, chemical weapons, and sandstorms from the perspective of service members (Brown, 2019). He concluded that Gulf War veterans have higher rates of respiratory illnesses after returning from service in the Gulf War.

Information Requests

Additional requests for information on the details of past and planned research and on reports of respiratory health problems in veterans were made to VA and to experts who were consulted or cited in the course of the committee's work. Those requests and the received responses are part of the committee's public access file. This information was integrated with the other evidence and used to form the basis of the report's findings, conclusions, and recommendations.

EVALUATION PROCESS

This section details the methods used by the committee for evaluating and synthesizing the identified studies included in the post-full-text review. As part of its evaluation, the committee first outlined the components of an ideal epidemiologic study so that when individual studies were assessed, these aspects were given the most weight. The categories of association used for making conclusions about the strength of the relationship between exposure to airborne hazards and respiratory health outcomes among Southwest Asia theater veterans are presented as the final topic of this section. The quantitative and qualitative procedures underlying the committee's evaluation of the literature have been made as explicit as possible, but ultimately the conclusions regarding the associations expressed in this report are based on the committee's collective judgment. The committee has strived to express its judgments as clearly and precisely as the data allow.

The full-text articles that met the inclusion criteria were distributed among the committee members based on their areas of expertise, with at least one committee member reviewing each paper. The committee began its assessment of the literature by assuming neither the presence nor the absence of an association between exposure and any particular health outcome. Each study was reviewed and objectively evaluated for each health outcome it presented. If a study examined more than one health outcome, it was considered separately as part of the evidence base for each of those outcomes. All studies were grouped by outcome (e.g., all studies that addressed asthma). For each outcome, the committee members responsible read and evaluated each study and presented the information to the entire committee. Such information included the design; methods used for selecting the study populations, conducting exposure and outcome assessment, and analyzing the association; relevant results; and an assessment of the overall strengths, limitations, and potential biases of the study. Following the discussion of each individual study, the lead committee member for the outcome reviewed and summarized the epidemiologic evidence for the outcome. Using the assessments of the individual studies and supplemental evidence where available, the committee discussed the evidence until it came to a consensus regarding the conclusion and assigned a category of association based on the strength of the evidence of a link between exposure to airborne hazards in the Southwest Asia theater and the respiratory health outcome under scrutiny. The committee did not use a formulaic approach to determining the number of studies that would be necessary to assign a specific category of association. Rather, the committee's review required expert judgment and a nuanced consideration of all the studies.

The committee reviewed all identified studies of U.S. and international Southwest Asia theater veterans published since 1991. In general, few studies included objective measures of the composition and concentrations of airborne hazards. Instead, presence in the Southwest Asia theater was used as a proxy for all military-related and general environmental airborne (and other hazardous) exposures encountered by service members. In some circumstances, a specific potentially harmful exposure was distinguished for analysis, such as proximity to burn pits. Consequently, it is difficult to quantify the risk of a specific respiratory health outcome or the risk of exposure to a specific agent or environmental contaminant. Furthermore, it is reasonable to assume that there were variations in exposures across the populations that were studied. In the absence of actual measures of exposure, comparisons between deployed and nondeployed theater-era veterans are considered a more relevant comparison since this implicitly factors in at least some common military exposures.

In many studies of in-theater veterans, not all health outcomes of interest were reported, or multiple outcomes were grouped (e.g., studies that examined emphysema, bronchitis, and COPD together). For others, there were too few cases to perform an analysis of certain outcomes, and only the number of outcomes observed was reported.

Methodologic Considerations for Assessment

Randomized double-blind controlled studies (also called experimental studies) are often considered the "gold standard" for evaluating the association between an exposure and a health outcome. However, such a design is either not possible or unethical in many circumstances. For example, it is not possible to randomize which service members are deployed for the purpose of later evaluating health outcomes in the population. Observational study designs (cohort or case–control, among others) are thus important epidemiologic tools that can complement randomized controlled studies or be used when the former is not possible.

The basic components of any well-designed and methodologically rigorous study of respiratory health outcomes include

- designing the study to specifically collect data relevant to respiratory health outcomes rather than using a design or sources that collected information on many health outcomes;
- identifying an appropriate comparison group, which should consist of individuals who are similar in both their eligibility for exposure and their baseline risk of developing the outcomes of interest;
- using adequate sample size and power to detect a true effect if one does exist (because statistical power depends on several factors, including how common an outcome of interest is, larger sample sizes are needed to study rarer outcomes, such as constrictive bronchiolitis);
- performing suitable exposure assessment, a task that is especially critical if one is to attribute adverse health outcomes to specific airborne hazards, such as burn pit exposures, rather than to exposures common to combat and desert environments (the assessment should be based on objective measures when possible rather than self-report of specific exposures);
- conducting rigorous outcome assessment based on objective measures and tests, allowing for adequate follow-up time (which could be many years to assess latent effects), and carrying out assessments at multiple time points in order to measure changes in incidence and severity over time;
- factoring information on known and potential confounders, which include demographic characteristics, military characteristics, deployment locations, lifestyle and behavioral factors (such as smoking), and other potential exposures to airborne hazards throughout the life course, such as living in areas with high

air pollution and nonmilitary jobs or hobbies that can entail high airborne exposures (woodworking for asthmatics, for example); and
- using appropriate statistical analysis techniques.

As part of its charge, the committee that authored *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan* assessed the feasibility of designing a prospective longitudinal epidemiologic study to answer the question of whether there are long-term health effects from exposure to burn pits in military personnel—at Joint Base Balad, specifically (IOM, 2011). Although that committee focused on a single base, many of the elements are the same as those needed to design an ideal epidemiologic study of respiratory health outcomes. That committee recommended that pilot studies be conducted to address issues of statistical power and to develop design features for specific health outcomes; it stated that once a prospective cohort infrastructure has been established, multiple health outcomes could be studied in the cohort over time. Intermediate outcomes on the pathway to the development of chronic diseases could also be assessed. That committee also recommended taking a tiered approach to characterizing exposures to the complex mixture of burn pit emissions and separating them from the other sources of air pollutants in the ambient environment. The three tiers of the study recommended by that committee are characterized by decreasing specificity of exposure and would answer different research questions.

As with any literature base, the studies of Southwest Asia theater veterans that have been conducted are quite diverse in both their methods and their quality. To assess their contribution to the overall weight of evidence—given that most did not perform objective exposure assessment—it is essential to consider the quality of the particular methods used to investigate the association because of the substantial unevenness in the rigor and informativeness of specific studies. As already noted, many studies make the implicit assumption that all deployed veterans have the same exposures to airborne hazards. This assumption likely leads to biasing the effect estimate toward the null due to non-differential exposure misclassification. The committee sought to weigh the evidence in the most objective manner possible using methodologic principles.

The summaries of the studies that met the committee's inclusion criteria include the study methodology, the reported results, the implications of the methods (especially when there are shortcomings) on the results and inferences that can be made, and an assessment of the contribution that the study makes individually and in the aggregate to the evidence base. As has been the case with several other National Academies reports, the authoring committee of this report recognizes the challenges in traditional hypothesis testing and in an over-reliance on "statistically significant" p-values that rely on arbitrary cutoffs. In drawing its conclusions, the committee weighted the consistency of direction of associations over specific statistically significant findings, and the body of evidence was considered as a whole. In its examination and assessment of the available evidence, the committee was looking for signals of associations, so even isolated findings that may well reflect random error from making multiple comparisons or findings that have not been corroborated are reported. Ultimately, replications of results were considered indications of stronger evidence for an association that the committee considered in its weighing. The committee notes that most of the studies reported the results of two-sided tests, which formally assess only whether there is a difference between two groups (which could be either a positive or a negative association). For simplicity and readability, the committee generally discusses the results as "increased" or "decreased" based on the magnitude and precision of the point estimate; in doing so, it does not mean to imply that a formal one-sided hypothesis test was done (which was rarely the case).

Categories of Association

To rate the strength of the scientific evidence for respiratory health outcomes following exposure to airborne hazards in Southwest Asia, the committee used a system of four categories of association. These categories were adapted from the categories used by the International Agency for Research on Cancer, which have gained wide acceptance by Congress, VA, researchers, and veterans groups and have been used in report series, including *Veterans and Agent Orange* and *Gulf War and Health* (both of them being 11-volume series), as well as in several stand-alone reports on topics such as adverse health outcomes of antimalarial drugs when used for prophylaxis

(NASEM, 2020). The criteria for each of the four categories of association express a degree of confidence based on the extent to which bias and other sources of error can be reduced and thus on the quality of the evidence.

The coherence of the full body of epidemiologic information, including supplemental evidence, was considered when the committee reached a judgment about association for a given outcome. As was the case with several committees that chose to use these categories of association, criteria identified by Hill were used to frame their evaluation of whether an observed association might be causal (Hill, 1965). These criteria, in brief, consist of nine considerations: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experiment, and analogy.[4] These considerations were not applied, however, as a checklist for strength-of-association assessments because they are not a definitive set of elements for assessing causality, and they vary in the importance or weight that might be assigned to each. Instead, the committee discussed the evidence and reached a consensus on the categorization of the evidence for each respiratory outcome of interest. Their collective judgment is presented in the Conclusions section for each outcome in Chapter 4. Evidence on each respiratory condition was reviewed in detail, but the committee's conclusions are based on the accumulated evidence of published articles, not just on recently published studies. When drafting language for a conclusion, the committee considered the nature of the exposures, the nature of the specific condition, the population exposed, and the quality of the evidence examined. Implicit in these categories is that "the absence of evidence is not evidence of absence." That is, based on the currently available literature that met the committee's criteria for inclusion, a lack of informative data does not mean that there is no increased risk of a specific adverse event, only that the available evidence does not support claims of an increased risk. When the literature base allows, separate conclusions are made for 1990–1991 Gulf War veterans and post-9/11 veterans. The four categories of association and the criteria for each are described below.

Sufficient Evidence of an Association

For effects to be classified as having "sufficient evidence of an association," a positive association between one or more in-theater airborne exposures and a respiratory health outcome in humans must have been observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. For example, the committee might regard evidence from several small studies that have no known bias or confounding and that show an association that is consistent in magnitude and direction to be sufficient evidence of an association. Experimental animal and in vitro data supporting the biologic plausibility of an association strengthen the likelihood of an association but they are not a prerequisite and are not enough to establish an association without corresponding epidemiologic findings.

Limited or Suggestive Evidence of an Association

For health outcomes in the category of "limited or suggestive evidence of an association," the evidence must suggest an association between an in-theater exposure and a respiratory outcome in studies of humans, but it can be limited by an inability to confidently rule out chance, bias, or confounding. Typically, at least one high-quality study indicates a positive association, but the results of other studies could be inconsistent. Because there are a number of agents of concern whose toxicity profiles are not expected to be uniform—specifically, the many airborne hazards that may be encountered in theater—apparent inconsistencies can be expected among study populations that have experienced different exposures. Even for a single exposure, a spectrum of results would be expected, depending on the power of the studies, the inherent biologic relationships, and other study design factors.

Inadequate or Insufficient Evidence to Determine an Association

By default, any health outcome is placed in the category of "inadequate or insufficient evidence to determine an association" unless enough reliable scientific data have accumulated to place it in another of the categories.

[4] A more complete discussion of these criteria and the application of the criteria is contained in *Gulf War and Health: Volume 8*, in a discussion titled "Inferring Causality" (IOM, 2010, pp. 27–28).

In this category, the available human studies of exposure to airborne hazards in the Southwest Asia theater and respiratory conditions may have inconsistent findings or be of insufficient quality, validity, consistency, or statistical power to support a conclusion regarding the presence of an association. Such studies might have failed to control for confounding factors (such as smoking) or might have had an inadequate assessment of exposure. In some cases, the body of evidence is too small to permit firm conclusions, such as when there are no available studies to validate or corroborate the findings of a single study. In other cases, some evidence from human studies exists, but the heterogeneity of exposures, outcomes, and methods leads to inconsistent findings that preclude a more definitive conclusion. Evidence in experimental animal studies may provide insight regarding the biologic plausibility of these associations but, in the absence of human data, is not enough to establish an association. Because the committee could not possibly address every rare condition or disease, it does not draw explicit conclusions about outcomes that are not discussed; thus, this category is the default or starting point for any health outcome. If a respiratory condition or outcome is not addressed specifically in this report, then it can be considered to be in this category.

Limited or Suggestive Evidence of No Association

The category of "limited or suggestive evidence of no association" is used for health outcomes for which several adequate studies covering the full range of human exposure were consistent in showing no association or a reduced risk with an exposure to airborne hazards encountered in the Southwest Asia theater at any concentration, with the studies having relatively narrow confidence intervals. A conclusion of "no association" is inevitably limited to the conditions, exposures, and observation periods covered by the available studies, and the possibility of a small increase in risk related to the magnitude of exposure studied can never be excluded. However, a change in classification from inadequate or insufficient evidence of an association to limited or suggestive evidence of no association would require new studies that correct for the methodologic problems of previous studies and that have samples large enough to limit the possible study results attributable to chance.

BACKGROUND ON EPIDEMIOLOGIC STUDIES AND POPULATIONS

A number of epidemiologic studies have been conducted on the health status of U.S. and other veterans who served in Southwest Asia. The primary objectives of some of the studies have been to determine the nature of the diseases and symptoms experienced by deployed persons, to discern whether symptom clusters represent any new or unique syndromes, and to explore what types of exposures might have produced the health outcomes. The epidemiologic studies of these veterans have contributed to our understanding of veterans' health, although many are beset by the limitations commonly encountered in all epidemiologic studies. In many cases, the studies used deployment as a surrogate of exposure and made comparisons using veterans of the same era who were not deployed to Southwest Asia (they either remained in the United States or deployed to places outside of Southwest Asia such as Bosnia or Korea). This has led to limitations of representativeness. Studies that group veterans according to their deployed or nondeployed status are limited because this has the effect of assuming that all in-theater veterans have the same exposures with respect to their military duties, locations, status during and after deployment (active duty, reserves, or National Guard or separated), and time in theater (days in theater and number of deployments). Many of the studied populations are chosen based on the ease of recruitment or ease of ascertaining data.

This section describes the major studies of service members and veterans as set forth in the Statement of Task as well as others that were identified and are referenced several times in Chapter 4, such as the National Health Survey of Gulf War Era Veterans and Their Families. The accompanying information includes the primary objectives; methods and sources of data collection and timeframes of investigation; populations studied; comparison groups; exposure assessment; the respiratory outcomes of interest and how they were identified, such as by self-reported questions, checklists of outcomes, or clinical examinations; relevant demographic, military, behavioral, and lifestyle information collected; and notable strengths and limitations. Some of this information was previously addressed in *Gulf War and Health* Volumes 4, 8, and 10 (IOM, 2006, 2010; NASEM, 2016) and in the 2017 National Academies report *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry*. New studies on established cohorts are also considered, and the committee has included descriptions of additional cohorts that were not discussed in the previous National Academies reports. However, respiratory health findings from the studies described in this section are presented in Chapter 4. The cohorts were assembled at different times and with different primary intents, but each is important for increasing the understanding of the health of service members and veterans who served in the Southwest Asia theater.

Major studies that collected new data (reference studies) or used previously collected data (derivative studies) to analyze the associations between exposure to airborne hazards in Southwest Asia and respiratory outcomes are listed in this chapter,[5] but the details of the individual analyses and the corresponding results are presented in Chapter 4. Some cohorts, once established, led to numerous studies or multiple publications that examined more detailed questions about specific health outcomes; these derivative studies—which may be publications reporting additional results, subcohort analyses, or nested case–control studies based on the population described by the reference study—are presented under the same heading as the reference cohort from which the study population was drawn. This organization helped the committee identify populations that have been studied and understand which studies were independent of one another. Establishing which studies rely on the same population sample was important because it helped the committee assess the literature base as a whole when weighing the evidence. Some research efforts resulted in only one or a very small number of papers; these are not addressed here but are summarized in Chapter 4.

The Statement of Task directs the committee to

> pay particular attention to … emerging evidence on respiratory health outcomes in service members from research such as the Millennium Cohort Study, Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE), National Health Study for a New Generation of U.S. Veterans, Comparative Health Assessment Interview (CHAI) Study, Pulmonary Health and Deployment to Iraq and Afghanistan Objective Study, Effects of Deployment Exposures on Cardiopulmonary and Autonomic Function Study.

Additionally, research conducted by WRIISC's Airborne Hazards Center of Excellence in New Jersey was to be considered. Information on these research efforts is thus presented in this section.

Studies of Post-9/11 Operations Veterans

The post-9/11 U.S. military operations in the Southwest Asia theater have been Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), Operation New Dawn (OND), Combined Joint Task Force–Operation Inherent Resolve, and Operation Freedom's Sentinel. These operations, details of which are provided in Chapter 1, first began in October 2001 (the start of OEF; an operation that has since concluded) and Combined Joint Task Force–Operation Inherent Resolve and Operation Freedom's Sentinel are still ongoing as of early 2020.

Millennium Cohort Study

The Millennium Cohort Study is an ongoing population-based longitudinal study that was initiated to examine long-term health outcomes among U.S. military members. In response to concerns about the health effects of deployments following the 1990–1991 Gulf War, the Institute of Medicine[6] recommended that the Department of Defense (DoD) conduct prospective epidemiologic research to evaluate the impact of military exposures, including deployment, on long-term health outcomes (IOM, 1999). DoD subsequently launched a large epidemiologic study in 2001 through the Naval Health Research Center. Service members from all branches (Army, Navy, Air Force, Marine Corps, and Coast Guard) and all service components (active duty, reserve, National Guard) of the military were randomly selected to participate (Chesbrough et al., 2002; Porter et al., 2020; Smith et al., 2008). Women, reserve and National Guard service members, along with personnel with past deployment experience,

[5] Additional publications of outcomes not related to respiratory health outcomes may have been conducted, but only those specific to respiratory health outcomes are listed.

[6] As of March 2016, the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine continues the consensus studies and convening activities previously undertaken by the Institute of Medicine.

were oversampled to ensure adequate power for statistical analysis purposes (Smith et al., 2009). The Millennium Cohort Study was designed to have multiple groups (termed *panels*) of participants who were enrolled every 3–4 years and followed up at multiple time points—on average, every 3 years at the same time that the baseline assessment was conducted for the next panel. The first panel consists of 77,047 enrolled participants who were randomly selected from DoD rosters in October 2000. Four additional panels have been recruited since then, and, in total, more than 200,000 service members and veterans have taken part in the study to date.

The study's self-administered questionnaire consists of more than 450 questions and can be completed online or via hardcopy and returned by mail. Questions include information on potential occupational exposures, health behaviors, health conditions, health care use, military life, and other health and well-being concerns at each 3-year interval. Some questionnaire data are linked to administrative records and military databases to collect or verify information on topics such as mortality, demographics, cancer diagnoses (through cancer registries), medical histories, health care use, and deployment status. This allows for investigators to study additional associations or to factor additional covariates into their analyses of health outcomes.

The two most notable advantages of the Millennium Cohort Study are its time period and the size of the sample. Data have been collected in various waves of the study since 2001. The large sample size allows for a more accurate representation of the population of interest. The follow-up surveys allow for the identification of changes in health data over time. As a prospective cohort study, this study reduces the amount of recall bias commonly seen in retrospective studies. Consistent follow-up surveys and the linking of medical databases and deployment records with the responses on the questionnaire further minimizes any significant recall or reporting biases seen in self-reported survey data studies. The study also allows for an examination of multiple outcomes from one or more exposures. Smith et al. (2008) assert that "[p]revious analyses have demonstrated that Millennium Cohort participants well represent the U.S. military, prior health did not influence response rates, and questionnaire data are reliable" (p. 580).

The Millennium Cohort Study, however, does have some limitations. As previously noted, although the amount of recall or reporting bias is designed to be low, it is impossible to completely eliminate bias. Digital military medical records were available only for active-duty military personnel, making it harder to link survey data with military databases for separated military personnel (Rivera et al., 2018). Because data are collected every 3 years, it is often not possible to know the exact timeframe between exposure to a hazard and the onset of a symptom or illness. Additionally, because hazardous exposures are self-reported and validated by deployment status or proximity to a burn pit, the study does not possess accurate information regarding the duration or quantity of exposure to a health hazard. Like all prospective studies, this study is also susceptible to bias resulting from the loss of study participants (illness, death, or refusal to participate) as well as bias between panels and in the overall study.

To date, more than 100 papers using data from the Millennium Cohort Study have been published, but few of these examine respiratory health outcomes or airborne hazards exposures among Southwest Asia theater military personnel. Salient publications are described below, and their results summarized in Chapter 4.

Smith et al. (2008) conducted an assessment to compare the agreement of 38 medical conditions obtained via self-reported, clinician-diagnosed information with that in electronic medical records of regular, active-duty participants from the first panel (2001–2003) of the Millennium Cohort Study (n = 37,798). Reservists and National Guard members were excluded because their electronic medical records are not fully available within the DoD medical record system; cohort members who failed to respond to any of the questionnaire items related to the medical conditions of interest or who had missing covariate data were also excluded. Demographic and military covariates included sex, date of birth, education, marital status, race/ethnicity, previous deployment experience (from January 1, 1998, to September 1, 2000), pay grade, service component, service branch (Army, Navy/Coast Guard, Air Force, and Marine Corps), and occupation. Self-reported medical conditions were based on yes/no responses to a list of conditions. Individual, electronic hospitalization and ambulatory data included diagnoses using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes that were obtained from three sources: the Standard Inpatient Data Record, the Standard Ambulatory Data Record, and the Health Care Service Record. For each participant, all electronic data were scanned for ICD-9-CM codes corresponding to medical conditions from the time that the earliest records were available (1988 for the Standard Inpatient Data Record) up to and including the date of survey submission. ICD-9-CM codes were selected to best represent the 38 medical conditions included in the questionnaire (of interest are sinusitis, sleep apnea, asthma, chronic bronchitis, and emphysema). Annual changes in ICD-9-CM coding up to 2003 (the last year of survey submission) were accounted for in the final list of codes. Electronic medical records were scanned in chronological order, and diagnostic fields were scanned in numerical order for the selected diagnostic codes. Any diagnostic code in any portion of the medical record indicated agreement with a self-reported medical condition. Both positive and negative agreement were used to compare self-reported data with those from electronic medical records. One limitation with the use of ICD-9-CM codes for assessing concordance is that ICD-9-CM codes are not uniquely related to only one condition. Furthermore, the medical conditions of interest in this study are not mutually exclusive of each other or sometimes have symptoms that overlap (such as chronic bronchitis and emphysema). Conditions diagnosed prior to the time of the medical records search or prior to military service may not be identified from DoD records, which may lead to disagreement between self-reported and medical record conditions. The strengths of this study include its large population and its use of a relatively complete information source to examine a wide range of health conditions.

Smith et al. (2009) used responses from 46,077 participants of the Millennium Cohort Study who completed baseline (July 2001–June 2003) and follow-up (June 2004–February 2006) questionnaires to investigate the occurrence of respiratory symptoms, asthma, chronic bronchitis, and emphysema. Respiratory outcome assessments were analyzed by deployment status (deployed versus nondeployed) and by cumulative time deployed, while stratifying by service branch and controlling for military and demographic characteristics and smoking behavior. The length of deployment was calculated in days for each participant and based on the cumulative number of deployments from the first deployment occurring after completion of the baseline questionnaire through the last deployment prior to completion of the follow-up questionnaire, after which it was categorized into quartiles ranging from 0 days (nondeployed, referent group) to greater than 270 days. Multivariable logistic regression adjusted for sex, birth year, marital status, race/ethnicity, education, smoking status, service component, military pay grade, and occupational code was used to compare the adjusted odds of the newly reported respiratory outcomes for deployed versus nondeployed participants. Additional models were used to assess associations between the respiratory health outcomes and cumulative deployment length, adjusted for the same covariates. This study is somewhat limited by its use of self-reported data without validation from clinical exams or medical records. However, the strengths of this analysis include its population-based design; its use of prospectively collected data on the same individuals; its inclusion of personnel from all service branches and components, including those no longer in military service; its use of large sample sizes that allow for adequate statistical power to assess the outcomes of interest; and the use of statistical methods to control for multiple demographic, military, and lifestyle confounders.

Smith et al. (2012) investigated the effects of exposure to documented open-air burn pits within 2, 3, or 5 miles on self-reported respiratory outcomes of symptoms of persistent or recurring cough or shortness of breath, asthma, and chronic bronchitis or emphysema among 22,844 Millennium Cohort Study Army and Air Force participants who were deployed to Iraq or Afghanistan after January 1, 2003, and who completed the baseline questionnaire and one of the follow-up assessment cycles through 2008. This analysis built on those performed by the Naval Health Research Center (AFHSC, 2010), which used a 5-mile radius of burn pit exposure and is detailed later in this chapter under the heading Armed Forces Health Surveillance Center Studies. Three proxy measurements were used to assess exposure: deployments near any of three documented, open-air burn pit sites (Joint Base Balad, Camp Taji, or Camp Speicher) were compared with deployments to other locations that had no known burn pits; cumulative days exposed within the vicinity of any of the burn pits (categorized into quartiles) were compared with no days deployed to the burn pit locations; and to measure whether a specific burn pit site was associated with risk, deployment to one of the three sites was compared with deployments to other locations with no burn pits, where specific burn pit sites were modeled separately and individually. Separate models compared the odds of association between each respiratory outcome and each of the three proxy measures assessing open-air burn pit exposure while adjusting for all demographic (sex, birth year, marital status, race/ethnicity, education), behavioral (smoking status: nonsmoker, past smoker, consistent smoker, or resumed or new smoker; aerobic activity), and military (service branch, military rank, pay grade, occupation, and date of military separation, if applicable) covariates. The demographic and military characteristics for the study participants were provided by the Defense Manpower Data Center (DMDC), and the respiratory outcomes, smoking status, and aerobic activity were collected using the

Millennium Cohort Study questionnaire. Most of the results that were presented focused on analyses using burn pit exposures within 3 miles; the 2-mile analysis was restricted to newly reported respiratory outcomes among Air Force members. The primary purpose of the study was to examine each respiratory outcome by service branch for those with and without exposure to burn pits. This study is limited by its use of self-reported outcomes, which were not confirmed by clinical examinations or a review of medical records. The average follow-up period was 2.9 years, which may not adequately capture the development of more chronic conditions or changes in symptoms (cough or shortness of breath) that may change over time. The exposure assessment was broad and non-specific, and the characteristics of burned materials were not considered. The use of the number of days of exposure and individual camps with documented burn pits and consideration of distance from the burn pit locations strengthened the analysis since individual levels of exposure were not possible; this and the ability to control for multiple confounders, including smoking status, were considered strengths of the study.

In addition to the studies summarized above, other analyses also used data from the Millennium Cohort Study. Rivera et al. (2018) examined risk factors for new-onset asthma, specifically combat deployment, among 75,770 cohort study participants who were deployed to Southwest Asia and participated in the study from 2001 to 2013 (panels 1, 2, and 3). In its analysis of the association between deployment to areas near burn pits and respiratory health outcomes, the Armed Forces Health Surveillance Center (AFHSC, 2010) used merged data from the Millennium Cohort Study as part of their analyses. Abraham et al. (2014) and Sharkey et al. (2015), described later in this chapter under Armed Forces Health Surveillance Center Studies, also built on these analyses.

Study of Active-Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures

STAMPEDE is a series of prospective studies that examine deployment-related respiratory symptoms and pulmonary disease among U.S. service members returning from the Southwest Asia theater—specifically, Iraq, Afghanistan, Kuwait, and Qatar (Morris et al., 2013, 2014, 2019, 2020). Though the three studies in the series have overlapping information, the questionnaires and overall methods used for each differ from one another. In brief, STAMPEDE I participants were asked to complete a deployment questionnaire, STAMPEDE II participants were administered one pre-deployment and one post-deployment questionnaire, and STAMPEDE III participants were asked to submit a deployment questionnaire and answer additional questions related to their potential exposure to burn pits. Three STAMPEDE papers that address outcomes of interest in this report are summarized below.

The STAMPEDE I study (Morris et al., 2014) was a preliminary prospective evaluation of new-onset respiratory symptoms in 50 military personnel deployed to Iraq or Afghanistan whose goal was to determine potential etiologies for symptoms. All study participants were active-duty military personnel who were recruited after deployment to Southwest Asia starting in July 2010. Participants were evaluated for deployment-related pulmonary symptoms after reporting respiratory symptoms within 6 months of returning to their duty station. This relatively small study consisted of multiple study components, such as medical examinations and diagnostic procedures, designed to provide a comprehensive evaluation of pulmonary symptoms. The components included a detailed deployment questionnaire (which included questions concerning deployment history; airborne exposures; smoking; pulmonary symptoms experienced before, during, and post-deployment; and medical treatment data) that was completed by 42 of the participants, a laboratory examination, radiographic imaging, pulmonary function testing, impulse oscillometry, methacholine challenge testing, fiberoptic bronchoscopy with bronchoalveolar lavage, and chest tomography. Lung biopsies were performed if clinically indicated. The majority of participants were male (80%), identified as white (58%), and had deployed to Iraq (64%). The mean age was 31.9 ± 8.4 years, and the mean deployment period was 11.7 ± 3.6 months. Most participants (58%) never smoked, while 26% were previous smokers, and 16% were current smokers, who averaged 0.5 packs per day. The reported airborne hazards exposures included sandstorms and blowing dust (97%), burn pit smoke (92%), smoke/vehicle exhaust (86%), and various chemicals (52%). The differences in lung measures were calculated using t-tests. This primarily descriptive study was limited by its small sample size, which was drawn from a single referral center, which leads to concerns regarding generalizability and statistical power. Although recall bias is another potential concern, diagnostic tests and clinical examinations performed as part of the study help to temper some of the recall bias effects on questionnaire responses. No modeling was performed, and analyses were not adjusted for potential confounders. The study is further limited by the lack of a comparison group. The extensive examinations, procedures, and diagnostic tests performed are an important strength of this study as they provide for more accurate diagnoses of symptoms.

In STAMPEDE II, Morris et al. (2019) conducted a prospective study of pre- and post- deployment lung function among Army personnel deployed to Iraq, Afghanistan, Kuwait, or Qatar. Active-duty soldiers were recruited from the Soldier Readiness Processing Center at Fort Hood, Texas, from 2011 to 2014. Any soldier with a pending deployment to Southwest Asia was eligible to participate. A total of 1,693 participants completed a pre-deployment questionnaire that collected data on demographics, smoking status, and respiratory health and underwent baseline chest radiography, spirometry, and impulse oscillometry. The post-deployment evaluation was conducted within 2 weeks of return from deployment for those individuals who returned to the Fort Hood processing center and included the same questions as on the pre-deployment questionnaire but also included additional questions on current medications; medical history including respiratory illnesses; respiratory symptoms before, during, and after deployment; run time performance on the physical fitness test; and airborne exposures experienced during deployment (dust and/or sand, vehicle exhaust, burning trash, and industrial fumes). Repeated chest radiography, spirometry, and impulse oscillometry were also conducted as part of the post-deployment exam. Only half (n = 843) of the soldiers who completed the baseline examinations also completed the post-deployment testing. The majority of the participants who completed the post-deployment questionnaire and exam were male (83.4%), white (58.4%), never smokers (70.1%), and overweight or obese (76.2%). Soldiers were nearly equally split by component: active duty (29.1%), National Guard (35.1%), and reserve (35.1%). Although only half of the participants who completed the baseline questionnaire and exam also completed them post-deployment, no differences in demographics were found between those who completed the post-deployment questionnaire and exam and those who did not. The mean values ± standard deviation were used as summary statistics for continuous variables, such as spirometry data, and student t-tests were used when appropriate. Odds ratios were calculated using multivariable logistic regression models, which included potential risk factors (smoking, presence of obstruction, increased body mass index [BMI], or self-reported asthma) for spirometric obstruction during deployment and post-deployment symptoms (dyspnea, cough, wheezing, sputum production, and decreased exercise tolerance). STAMPEDE II has the advantages of having a prospective design that assessed respiratory health pre- and post-deployment and using a much larger sample size than STAMPEDE I. Although recall bias is a concern, diagnostic tests and clinical examinations performed as part of the study help to temper some of the possible recall bias effects on questionnaire responses and are a strength of this study as they provide for more accurate diagnoses of symptoms. Because participants were limited to soldiers who were passing through a single processing center, the generalizability of the findings is limited.

The purpose of STAMPEDE III was to enroll active duty and retired military personnel who had deployed to Southwest Asia for a minimum of 6 months with onset of chronic respiratory symptoms (primarily exertional dyspnea or decreased exercise tolerance) temporally related to deployment and to perform a comprehensive clinical cardiopulmonary evaluation on them (Morris et al., 2020). A total of 380 military personnel were recruited from the Brooke Army Medical Center or the Walter Reed National Military Medical Center. Participants completed a deployment questionnaire (deployment history, airborne exposures, smoking status, and pulmonary symptoms before, during, and after deployment), answered questions taken from the VA Airborne Hazards and Open Burn Pit Registry questionnaire, and underwent a history and physical examination. The pulmonary function testing consisted of spirometry, lung volume, diffusing capacity, impulse oscillometry, and bronchodilator testing. Other tests included methacholine challenge, exercise laryngoscopy, high-resolution CT scan, electrocardiography, and transthoracic echocardiography. The deployment questionnaire was completed by 86% of participants. Of the 380 participants, the majority were male (88%), white (70%), and never smokers (64%). The average age of participants who completed testing was 38.5 ± 8.4 years. One-third of the participants were obese. Most participants served in Iraq or Afghanistan, with total deployments of 1.7 ± 2.0 per individual. The reported results were primarily descriptive, with comparisons of the diagnostic categories based on means and standard deviations. Continuous variables were analyzed using the Wilcoxon test with a Steel-Dwass adjustment for pairwise comparisons. The use of several objective pulmonary function tests and the large sample size are strengths of the analysis. However, as in STAMPEDE I, this study is limited by recall bias for reporting the presence and severity of symptoms pre-deployment and is also limited by the fact that the study population was limited to service members with chronic respiratory symptoms who were seen at one of two medical centers, thereby limiting the generalizability of the findings.

National Health Study for a New Generation of U.S. Veterans

The population-based cohort study National Health Study for a New Generation of U.S. Veterans, known as NewGen, was initiated by VA to examine the overall health of a randomly selected sample of 60,000 veterans who served in the military between October 2001 and June 2008 (Eber et al., 2013). All participants were sampled from DoD records. This included 30,000 veterans deployed to OEF or OIF and 30,000 veterans who were not deployed to these conflicts. Service members from each branch and component of the military were included in the study. Female veterans were oversampled by 20%. All veterans participated in the study by completing the 72-item, self-administered questionnaire, which collected a variety of information, including environmental exposures, respiratory conditions, health behaviors, physical parameters, and VA health care use. In addition, the medical records of 2,000 participants were reviewed for certain health conditions. The overall study had a response rate of approximately 34%, or 20,563 participants, and was conducted between August 2009 and January 2011 (Eber et al., 2013).

NewGen has multiple strengths as well as limitations. Although the response rate was just 34.3%, the overall number of survey participants was still more than 20,500, with representation from all branches and components of the military. As with any cohort study that uses self-reported surveys to collect data, this study was likely subject to recall bias in its survey responses, leading to both overreporting and underreporting. Though the study takes into account the number of deployments among OEF and OIF service members, it does not contain data on the total time spent in service or the start date of the participant's entry into the military, leading to inaccurate measurement of exposure to respiratory hazards (Barth et al., 2014, 2016).

Two NewGen studies that report on respiratory health outcomes—Barth et al. (2014), which examined the prevalence of asthma, bronchitis, and sinusitis, and Barth et al. (2016), which determined the lifetime prevalence of respiratory exposures and the, relationship between exposures and respiratory health—are summarized below. The results of their analyses are presented in Chapter 4, along with information from a third NewGen study (Díaz Santana et al., 2017).

Barth et al. (2014) investigated the population prevalence of asthma, bronchitis, and sinusitis using the data from 20,563 veterans who participated in NewGen. The researchers compared veterans deployed to post-9/11 conflicts (n = 13,162) with nondeployed veterans (n = 7,401). Birth year, unit component, and branch of service were all gathered from the administrative records used to design the NewGen survey; all other variables were assessed based on participant self-report on the study questionnaire. Conditions were identified by asking, "Has a doctor ever told you that you have any of the following conditions?" with a follow-up question, "Year first told?" Conditions reported before 2001 were classified as before service. Statistical weights were used to adjust the stratified sampling design for non-response and to improve the precision and accuracy of the population prevalence. Logistic regression was used to produce unadjusted and adjusted odds ratios (adjusted for birth year, sex, service branch, unit component, race/ethnicity, education, and smoking status). Separate models were used to examine diagnoses before 2001 and during or after 2001 because the impact of deployment should differ based on whether the respiratory disease was diagnosed before or after deployment. This study has several strengths. Its weighted effect estimates ensure that the prevalence estimates are a robust representation of the burden of respiratory illnesses. Investigators controlled for confounders during data analysis, although it is unclear if the investigators used causal diagrams to choose the appropriate confounders, which can be important to ensure that model adjustments do not introduce biases (Shrier and Platt, 2008). The study also had a highly relevant comparison group of nondeployed veterans, which was appropriate, although the nondeployed comparison group was much smaller than the deployed group. Furthermore, the data used in this study were not restricted to medical encounter data from within the VA health system. The use of self-reported data has limitations, including the potential for recall bias. The study investigators also did not account for the impact of multiple deployments or deployment during the 1990–1991 Gulf War, which may have affected the study's findings. Finally, the authors did not address whether the deployment occurred during the etiologically relevant time period for the development of the disease. Additionally, although NewGen could be used to evaluate disease changes over time through the collection of repeated measures, this paper is a baseline assessment and cannot calculate those more complex rates.

Barth et al. (2016) expanded on the analysis of NewGen data by Barth et al. (2014) to examine the prevalence of respiratory diseases (asthma, bronchitis, sinusitis) and added a category of "any respiratory disease" and their association with self-reported respiratory exposures during military service for OEF/OIF deployed and nondeployed veterans. Respiratory exposures were collected by self-report responses (yes/no) to five options that were specified to have occurred during military service: dust and sand; burning trash/feces; diesel, kerosene, and/or other petrochemical fumes; smoke from oil fires; and industrial pollution. "Any respiratory exposure" was defined by at least one affirmative response to any of the five exposures. The five respiratory exposures were summed for each individual to create a variable for the number of different exposures, where low exposure was defined as one to two different exposures, and high exposure was defined by three to five different exposures. Of the deployed veterans, approximately 32% were considered to have low exposure, 55% were considered to have high exposure, and 13% had no exposure. Weights were created to improve accuracy of the population prevalence estimates by adjusting for the sample design, non-response, and misclassification in the sampling frame. Logistic regression analyses were used to calculate weighted, adjusted odds of respiratory disease stratified by deployment status and controlled for sex, birth year, race/ethnicity, education, smoking status, unit component, service branch, and number of OEF/OIF deployments. Similar to the other analyses of NewGen data, the population-based sample of veterans included those who accessed VA health care and those who did not, which is more generalizable to the total OEF/OIF and OEF/OIF-era veteran populations than is the group of those who use only VA health care services. As with this group's prior work (Barth et al., 2014), the data were based only on self-report, so recall bias is a factor, especially for individuals who deployed many years before the survey. Other limitations included unknown dates of respondents' entry into the military and not adjusting for respiratory conditions that occurred before or after joining the military or before or after deployments. The survey questions regarding respiratory exposures inquired about exposures during military service, not specifically during OEF/OIF deployment.

Comparative Health Assessment Interview Study

The CHAI Study is a health survey conducted on veterans who served after September 11, 2001, whose goal is to help VA better understand the effects of military service, deployment, and combat on the health and well-being of veterans who served in OEF, OIF, and OND. The study consists of two components: an online or telephone survey and an in-person interview to test neurocognitive function for a subsample of veterans. Out of 38,633 veterans who were invited to participate in the study, 15,166 veterans completed the survey. This 39% response rate included 6,591 veterans who were deployed to Southwest Asia, 4,195 veterans who were not deployed to Southwest Asia, and 4,380 veterans who were never deployed. Of 16,483 civilian controls who were invited to participate in the study as the comparison group, 4,654 (response rate 28%) completed the survey. Women were oversampled by 30%. The investigators have also completed 300 neurocognitive assessments from a subsample of veterans. The study questionnaire collects data on physical health, mental health, social relationships, and occupational well-being. Both the veteran and civilian versions of the survey were framed in a way that provides a direct comparison of health and experiences between the two groups. The latest update on the study suggests that the researchers have completed the survey data collection and the neurocognitive assessments. As of early 2020, the study was in the analysis stage, and no publications related to respiratory health outcomes were available for the committee's review (Schneiderman, 2019; Schneiderman et al., 2020).

Effects of Deployment Exposures on Cardiopulmonary and Autonomic Function Study

The cross-sectional study Effects of Deployment Exposures on Cardiopulmonary and Autonomic Function Study (AirHzds) was conducted by VA's Office of Research and Development to evaluate cardiorespiratory and autonomic function in 32 OEF, OIF, and OND veterans exposed to high levels of PM compared with 18 veterans who were deployed to regions other than Southwest Asia. Cardiopulmonary function was evaluated using a standardized exercise challenge and bronchodilator spirometry, while autonomic nervous system function was evaluated by examining the indices of heart rate variability and cardiovascular reflex regulation during different tasks (Falvo, 2017, 2019). No AirHzds study publications related to respiratory health outcomes were available for the committee's review at the time its work was completed in early 2020.

War Related Illness and Injury Study Center

WRIISC was established in 2001 as part of VA's Post Deployment Health Services as a national research program that focuses on the post-deployment health concerns and health care needs of veterans. Research generated from WRIISC is used to identify new areas of concern and to provide post-deployment health care solutions to "veterans and their health care providers through environmental exposure assessments, medical evaluations, clinical care, education and risk communication" (VA, 2020). WRIISC also provides post-deployment health education to families of veterans who were deployed. The topics of research studies conducted by WRIISC include the long-term health effects of combat; neurological diseases, traumatic brain injuries, and other deployment-related disabilities; the environmental exposures of deployment; and women's health.

The Airborne Hazards Center of Excellence (AHCE), which was designated the Airborne Hazards and Burn Pits Center of Excellence in 2019, is a part of WRIISC. The center works to improve the health of veterans through gaining a better understanding of the potential health effects of exposure to airborne hazards. Its investigators study the impact of exposure to airborne hazards on a variety of health outcomes, including respiratory health. Studies conducted by AHCE involve many of the same tests used in specialty care, such as assessment of cardiopulmonary function and exercise ability. These assessments aid the center in making recommendations regarding the management of symptoms and follow-up care needed to improve the quality of life among veterans exposed to airborne hazards. Research on respiratory health issues conducted by WRIISC and center investigators is summarized in Chapter 4 (Butzko et al., 2019; Falvo et al., 2016a,b; Garshick et al., 2019; Jani et al., 2017; Lindheimer et al., 2019).

Studies of Burn Pit Exposures

Exposure to emissions from burn pits has been of particular concern among those interested in respiratory health. The effects of such emissions have been examined in several publications, including a 2017 National Academies report and an analysis from the Armed Forces Health Surveillance Center (AFHSC, 2010), the latter of which was then used as the basis for additional work. These publications are described next.

Airborne Hazards and Open Burn Pit Registry The committee responsible for the 2017 National Academies report *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry* carried out an analysis of the initial months of data gathered from respondents to the registry questionnaire as part of its Statement of Task (NASEM, 2017). The registry, which was created by Public Law (PL) 112-260, is open to service members who were deployed to the Southwest Asia theater and Djibouti, Africa; participation is voluntary. The data analyzed by the committee were derived from the first 13 months (June 2014–July 2015) of completed questionnaires (n = 46,404), accounting for approximately 1.0% of the 1990–1991 Gulf War veterans and 1.7% of post-9/11 veterans who met the registry's eligibility criteria. As this is a registry, there was no comparison group.

Health outcomes were characterized by self-reports of health care provider–diagnosed conditions, by exposures to burn pits and other airborne hazards based on self-report, and by DoD data on the number and location of deployments. The committee also synthesized exposure metrics by combining the responses to questions regarding specific exposures. For that committee's multivariate analysis of airborne hazards exposure potentials and selected respiratory and cardiovascular health outcomes, the population was limited to post-9/11 conflict respondents. Several metrics of exposure were considered. First, the committee examined exposure to burn pits using three measures that combine the duration and presumed intensity of exposure based on self-reported responses to the questionnaire: (1) cumulative days deployed near a burn pit, derived by summing the number of days of each deployment for which a respondent indicated that he or she was near a burn pit; (2) cumulative days of burn pit duty; and (3) cumulative hours of exposure to smoke from burn pits, created by multiplying the average number of hours each day that smoke or fumes from burn pits entered the worksite or housing by the number of days of deployment. Those measures were presented as quartiles, with the first (lowest exposure) quartile serving as the reference group. Other exposures contribute pollutants that may lead to respiratory distress, and therefore dust, diesel/exhaust/fuel, combat, and construction exposure potential scores were considered in the analysis and were presented as categories ranging from 0 to 6, where 0 was the lowest level of exposure potential and also served as the reference group for comparisons. The committee also used a composite exposure potential measure, which was calculated based on the levels of exposure to the six individual exposure categories (burn pits, dust, diesel, combat, construction, soot) to examine the association between the totality of airborne exposures of concern and each health outcome; those results were presented as quartiles, with the first quartile again serving as the reference.

The respiratory outcomes that were examined included asthma; emphysema, chronic bronchitis, or COPD as a composite variable; any functional limitation due to a lung or breathing problem; and respiratory symptoms as a composite variable. The models excluded respondents who had been diagnosed with a respiratory disease before deployment. Respondents with missing exposure or disease were excluded from the analysis. Sample sizes differed across models and ranged from 32,178 for construction exposure and emphysema, chronic bronchitis, or COPD to 39,271 for each of the three burn pit metrics and any respiratory symptoms. All models were adjusted for sex; age at questionnaire completion in approximate quartiles (19–30, 31–37, 38–44, or ≥45 years); education level (less than college or "some college or more"); race/ethnicity (white or "other"); BMI (underweight/normal [<25 kg/m^2], overweight [25–30 kg/m^2], or obese [>30 kg/m^2]); smoking status (current smoker, former smoker, or never smoker); unit component (active duty, National Guard, or reserve); rank (enlisted, warrant officer, or commissioned officer); service branch (Army, Navy, Marine Corps, Air Force, or Coast Guard); and primary duty occupational specialty (10 broad groups based on the groups used in the Millennium Cohort Study). For covariates with less than 5% missing data, the missing data were imputed with the modal category. For covariates with greater than 5% missing data, a separate "missing" category was included in the analysis. The report detailed a number of issues with the quality and limitations of the registry's information, which led the committee to conclude that the results of the analyses could not be taken at face value and that any identified associations (or lack thereof) might be an artifact of the population's selection and the limitations of the voluntary participation and self-reported exposure and disease data. Specific respiratory health results are discussed in Chapter 4.

Armed Forces Health Surveillance Center Studies An analysis conducted by the Armed Forces Health Surveillance Center (AFHSC, 2010) examined medical encounters at military facilities by Army and Air Force personnel within 36 months of April 2006, after deployment to Joint Base Balad, Camp Taji, or Contingency Operating Base Speicher (which were located in Iraq and which had burn pits), Camp Buehring or Camp Arifjan (which were located in Kuwait and did not have burn pits), or the Republic of Korea (where there was exposure to urban air pollution and other airborne PM) from 2005 to 2007. Personnel who served within 3 miles of burn pits were considered to have been exposed (15,908 at Joint Base Balad and 2,522 at Camp Taji) and were compared with 51,299 personnel at bases without burn pits and 237,714 personnel in the United States who had not deployed as of April 2006. Respiratory outcomes were limited to all diseases of the respiratory system (ICD-9 460–519) and, specifically, acute respiratory infections (ICD-9 460–466), COPD and allied conditions (ICD-9 490–492, 494–496), and asthma (ICD-9 493). Incidence rate ratios were calculated using Poisson regression models and adjusted for age at the start of follow-up, sex, race, military pay grade at the start of follow-up, and service branch to compare the deployed populations to the U.S.-based population. Only the overall results were presented because, as the authors state, service-stratified and time-stratified analyses were similar to the overall cohort.

Additional analyses of respiratory health outcomes were conducted using data merged with those collected as part of the Millennium Cohort Study (described earlier in this chapter). Information from the Millennium Cohort Study included data on smoking status (nonsmoker, past smoker, current smoker, or resumed or new smoker), mental and physical health, and physical activity, among other demographic, behavioral, and military characteristics. Specific questions on respiratory health included self-reported provider-diagnosed asthma, chronic bronchitis, emphysema, and persistent or recurrent cough and shortness of breath. Data on demographic and military characteristics, deployment in support of the operations in Iraq and Afghanistan, and deployment within a 5-mile radius of a documented burn pit from the three camp sites were obtained from DoD. For the respiratory outcomes analysis, the population included deployed personnel who completed the baseline questionnaire (administered June 2004–February 2006) and the first follow-up questionnaire cycle (administered June 2007–December 2008) of the Millennium Cohort Study. Newly reported outcomes were defined as the presence of the condition at follow-up without an indication of the condition at baseline, while the prevalence of self-reported respiratory symptoms was measured at both time points. Separate models were developed for each respiratory outcome. Multivariable logistic regression analyses were performed to compare the adjusted odds of association for respiratory outcomes relative to three metrics of exposure within a 5-mile radius of the documented burn pits: dichotomous deployment near the documented burn pits, cumulative days exposed to the burn pits, and exposure to the burn pits at three different base camp sites (Balad, Taji, or Speicher). Cumulative days exposed within a 5-mile radius of the documented burn pits were summed and categorized into quartiles, and persons in each quartile were compared with those with no documented exposure to these burn pit sites. The analyses were adjusted for sex, birth year, marital status, race/ethnicity, education, smoking status, physical activity, service branch, military rank, pay grade, and occupation. All covariates were measured at baseline, but smoking status was prospectively assessed using the 2004 and 2007 survey instruments, and physical activity was measured using the 2007 survey instrument.

Both Abraham et al. (2014) and Sharkey et al. (2015) used the same population as the AFHSC study (2010) but reported on analyses with an additional 12 months of follow-up (48 months total, starting April 2006) for respiratory outcomes. While both studies used the same cohort and data sources, there were slight methodologic differences between them, including the size of the nondeployed referent group (112,091 in Abraham et al. [2014] and 237,714 in Sharkey et al. [2015]) and the covariates used. None of the analyses were able to control for smoking or other important exposures related to respiratory disease, and both were limited by their exclusive use of military medical records (medical encounters outside of the military system were not included).

Sharkey et al. (2016) extended the analyses of this cohort by considering data from three additional sites, two of them located in the Southwest Asia theater. Study participants were U.S. Army or Air Force personnel who were deployed to Kabul (n = 5,670) and Bagram (n = 34,239) Air Force bases in Afghanistan—sites with similar, poor air quality—and Manas Air Force Base in Kyrgyzstan (n = 15,851)—a site with relatively better air quality. Any active-duty service member who spent 30 days or more deployed to one of these locations between January 1, 2002, and December 31, 2011, was eligible for inclusion in those exposure groups. These deployed personnel were compared with 40,470 stationed in Korea (a site with poor air quality) and with 122,687 service members who remained in the United States but who were fit to deploy. Demographic and location data from DoD's DMDC were extracted and combined with inpatient and outpatient medical encounter records maintained in the Defense Medical Surveillance System for use in the analyses. Deployed personnel were followed for up to 12 years from when they returned to the United States until the end of the study (December 31, 2013), while nondeployed service members were followed from entry into the study (April 15, 2006) through its end. Deployment location was used as a proxy for exposure as individual environmental exposures were not available. As is true with nearly all other studies that use deployment or base-specific location as a proxy of exposure, deployment duties, job classification, and specific individual behaviors would likely have a major impact on individual environmental exposures.

Other Studies of Post-9/11 Operations Veterans

Eight other epidemiologic studies of military personnel involved in post-9/11 operations in the Southwest Asia theater have addressed multiple respiratory health outcomes. Their study parameters are summarized below, while the results of these studies are presented where applicable in the outcomes sections of Chapter 4.

Abraham and Baird (2012) sought to evaluate the impact of ambient PM—specifically, $PM_{2.5}$ and PM_{10}[7]—on acute cardiorespiratory morbidity among U.S. military personnel deployed to Southwest Asia. The researchers conducted a case-crossover study, a type of case-only study in which each case serves as its own matched control, by linking ambient PM data collected by DoD between December 2005 and June 2007 with personnel, medical,

[7] $PM_{2.5}$ and PM_{10} refer to, respectively, particulate matter with a diameter less than 2.5 microns and particulate matter of size less than 10 microns.

and meteorological data (Engelbrecht and McDonald, 2009; Engelbrecht et al., 2008). They estimated base-specific associations and pooled those estimates using meta-analytic methods. The study population consisted of a case series of military personnel who had a medical encounter for a qualifying cardiovascular or respiratory event recorded in either Joint Medical Workstation or Transportation Command Regulating and Command and Control Evacuation System during the time period of environmental sampling and for whom deployment data at the time of the health event were known. The case status was defined as having any one of the qualifying outcomes in the medical record (ICD-9 390–459 "diseases of the circulatory system" or ICD-9 460–519 "diseases of the respiratory system"). Outcomes occurring within 7 days of the initial record were excluded from the analysis. Most qualifying encounters were for acute respiratory symptoms, but of the 343 encounters for COPD and allied conditions (ICD-9 490–496), 327 (95%) were for asthma (ICD-9 493). Standard stratified data analysis methods were used to analyze the case-crossover data. The stratifying (matching) variable was the individual subject experiencing an outcome event. Each risk set consisted of one individual as that individual "crossed over" between exposure levels in the referent and hazard time periods (and back again). The hazard period corresponding to each observed outcome event was matched with referent time periods within a 28-day time window centered on the event day. To minimize the influence of autocorrelation between hazard and referent periods, referent PM exposures were selected only from sampling days greater than 7 days on either side of the hazard day. Logistic regression was used to calculate the effects of PM exposure on respiratory diseases, and adjustments were made for meteorological parameters. The authors also conducted several sensitivity analyses, such as running models incorporating 2-day lagged exposures and running the models with PM data imputed for missing days using observed PM levels and meteorological data. These sensitivity analyses yielded qualitatively similar results to the primary analyses' results. This study benefits from a well-matched comparison group and from a primary sampling of the exposures of interest. As mentioned in Chapter 2, the sampling used in the DoD PM surveillance program has been criticized in previous reports (NRC, 2010) for using an inappropriate sampler, which may lead to exposure misclassification. Although there were flaws with the exposure measurement method, this is one of the few studies that objectively measured exposure. The authors did not adjust for confounders, but the case-crossover study design is less subject to bias from confounders that do not vary over short time periods. Residual confounding by time-varying factors is a potential source of bias in this study. The main source of bias is likely that the study was underpowered, given the small expected magnitude of the effect of PM exposure on the risk of respiratory disease in this population over such a short time period (2 years).

Abraham et al. (2012) linked deployment and medical history data of active-duty U.S. military personnel from DoD administrative databases to evaluate the association between post-deployment respiratory conditions and deployment to Iraq or Afghanistan. Using the number of deployments to categorize service members into single and multiple deployment groups, a 10% random sample of each group was selected, resulting in a cohort population of 44,919 single deployers and 14,695 multiple deployers to OEF/OIF through June 30, 2005. Medial encounters were based on primary ICD-9-CM diagnostic codes and classified into six categories: acute respiratory infections (ICD-9-CM 460–466), other diseases of the upper respiratory tract (ICD-9-CM 470–478), pneumonia and influenza (ICD-9-CM 480–487), asthma/COPD and allied conditions (ICD-9-CM 490–496), pneumoconiosis and other lung diseases due to external agents (ICD-9-CM 500–508), and other diseases of the respiratory system (ICD-9-CM 510–519). Primary diagnoses of "symptoms involving respiratory system and other chest symptoms" (ICD-9-CM 786) were also considered. All service members had at least 6 months of visits before and after deployment. Incidence rates of encounters were calculated and compared between single and multiple deployers in the pre- and post-deployment periods. To examine the independent effects of deployment status and cumulative time in theater on incident post-deployment obstructive pulmonary disease onset, they also conducted a nested case–control study. Cases (n = 532) of ICD-9-CM codes 490–496 post-deployment diagnosis of obstructive pulmonary disease and controls (n = 2,128) were selected from those who were free of respiratory diagnoses within 6 months before their deployment. Controls were matched on the year of case definition and the year of the last encounter during the study period as well as the total number of post-deployment medical encounters. In the nested case–control study, two proxy variables were created for exposure: number of deployments and cumulative time in theater, using the start and end dates of deployment records. Cumulative time in theater was calculated by summing the time for all the deployments before an obstructive pulmonary disease encounter for cases and before the last medical encounter for controls, and subsequently categorized into five levels (0–3, 4–6, 7–9, 10–12, and ≥13 months). Rates of encounters within selected primary diagnoses by deployment status for the pre- and post-deployment periods and by order of deployment were calculated. Conditional logistic regression analyses were used to examine the independent effects of number of deployments at diagnosis and cumulative time in theater up to diagnosis on post-deployment obstructive pulmonary disease encounter, controlling for potential confounders (gender, age, grade, occupation, time in theater, number of deployments, service branch, and tobacco-related diagnoses) in the model. This study had several limitations. Primary among them is a lack of smoking pattern data for the cohort. Because of the deployment and redeployment cycle, the follow-up period between deployments was likely too short for longer-term chronic obstructive disease conditions, such as emphysema, to develop. Finally, the study was further limited by a lack of specific deployment-related exposure assessments.

Baird et al. (2012) studied a unique exposure source: a fire at the Al-Mishraq sulfur plant near Mosul, Iraq, in 2003 that burned for nearly a month and that released dense clouds of sulfur dioxide into the atmosphere. The primary aim of this retrospective cohort study was to characterize the post-deployment respiratory health status of the U.S. Army personnel potentially exposed to emissions from that event and to compare the risk of plausible adverse health outcomes among this group with the risks in unexposed personnel. Health questionnaire data were based on completion of DoD mandatory standardized pre-deployment and 3-month post-deployment health assessments and documented medical encounters up to 4 years after the presumed exposure period. During the year before and the time after the index deployment, the authors used ICD-9-CM codes to identify clinical encounters related to diseases of the respiratory system overall (ICD-9-CM 460–519); diseases of the circulatory system (ICD-9-CM 390–459); and symptoms, signs, and ill-defined conditions (ICD-9-CM 780–799). Specific respiratory outcomes assessed included COPD, asthma, other chronic bronchitis, pneumoconiosis and other lung disease due to external agents, and symptoms involving the respiratory system (ICD-9-CM 786). Two were groups potentially exposed to the sulfur fire smoke plume—personnel involved in fighting the fire (n = 191) and personnel presumably downwind during the time of the fires (n = 6,341). These were compared with two unexposed groups: those that deployed to the area after the fire was extinguished (n = 2,284) and those deployed to other Southwest Asia locations contemporaneously with the time of the fire (n = 1,869). Two-thirds of the exposed groups were less than 29 years of age at the time of exposure, compared with 56% of the unexposed groups. The impact of exposure was assessed by calculating and comparing standardized morbidity ratios that were standardized for age, and by calculating incidence rates per 1,000 person-years within each exposure and comparison group in both the pre- and post-deployment time periods. This study has the advantage of evaluating a specific event with two exposure groups and two comparison groups. The study has several limitations, however. There was a lack of direct exposure assessment, so an inherent assumption made in all analyses is that the exposures were the same across each exposure group, which may lead to information bias. A threat of information bias is also inherent with self-reported symptoms and health concerns using pre- and post-deployment health assessments because responses may be influenced by different motivations for reporting or not reporting certain exposures and health concerns. Confounding is a major threat to validity in this study, as incidence rates were unadjusted, and the morbidity ratios were only standardized for age. Other uncharacterized differences in risk factors for adverse health outcomes, such as smoking behavior and other environmental or occupational exposures, may exist between the sulfur-fire-exposed and unexposed groups. The relatively short follow-up time (up to 4 years) does not permit the evaluation of associations between sulfur fire plume exposures and diseases with long latencies.

Krefft et al. (2017) conducted a pilot study to examine the role of lung clearance index as an early marker of lung injury in a sample of 24 healthy volunteers and 28 symptomatic veterans who had deployed to Southwest Asia in support of post-9/11. The symptomatic deployers had cough, chest tightness, wheezing, shortness of breath, or decreased exercise tolerance during or following OEF/OIF/OND deployment. Individuals who were found to have other explanations for their respiratory symptoms were excluded. Healthy controls who were at least 18 years of age, had no history of pre-existing lung disease, and reported no respiratory illness in the 4 weeks preceding enrollment and testing were also recruited. Both groups underwent lung clearance index testing to identify whether abnormalities were present in the peripheral airways of the lung. As part of their clinical evaluation, the veteran group completed body plethysmographic pulmonary function testing with pre- and post-bronchodilator spirometry, lung volumes, and diffusion capacity; cardiopulmonary exercise tolerance testing; and chest CT scans. Surgical lung biopsies were performed on 17 of the 28 veterans. Descriptive analyses were conducted, and the Fisher exact test was used to compare the demographic data between the deployers and the controls. Multiple linear regression models that adjusted for smoking, age, and BMI were used to compare differences in lung clearance index score between the deployers and healthy controls. This study aimed to describe the utility of lung clearance index to diagnose small airway abnormalities before they are readily apparent in clinical testing and without an invasive biopsy. This study is limited most by its small sample size, nonmatched controls, and absence of spirometry data in the healthy control group. The small sample of veterans is highly selective as they were all symptomatic and were seen at a single occupational lung disease clinic. Given that all of the members of the deployed group in this study were symptomatic and that they were compared with healthy controls, the study provides rather limited evidence to the committee's charge to understand the impact of deployment to Southwest Asia on the health of veterans. Additionally, the study was not designed to evaluate the impacts of deployment to theater on the health of veterans, and no adjustments were made for confounders such as smoking, obesity, or age in the assessments that were made.

Krefft et al. (2020) sought to describe deployment-related respiratory disease and the diagnostic utility of resting and exercise pulmonary function testing with a retrospective study of 127 military personnel, veterans, and civilian contractors who supported military operations in Southwest Asia who presented with new-onset respiratory symptoms between 2009 and 2017. The cohort was made up of patients who deployed to Southwest Asia between 2001 and 2019 and were self-referred or referred by treating physicians to a single occupational lung disease clinic for an evaluation of persistent respiratory symptoms that limited their ability to meet military physical fitness requirements. A comprehensive standardized questionnaire was used to collect detailed medical, occupational, and smoking histories and was completed by 107 of the 127 patients. For the other 20 patients, medical, occupational, and smoking histories were abstracted from the patients' electronic medical records. Of the 127 patients, 113 underwent pulmonary function testing, including pre- and post-bronchodilator spirometry, lung volumes determined by plethysmography, and carbon monoxide diffusion capacity measurement following American Thoracic Society standards. Chest CT scans were available for 118 of 127 symptomatic patients. Lung biopsies were performed in 52 patients (51 video-assisted thoracoscopic surgery, 1 transbronchial cryobiopsy). Deployment-related respiratory diseases were classified as proximal or distal or both. Distal lung disease was diagnosed when at least one of the following was present: emphysema under low- or high-power magnification, histopathologic findings of hyperinflation/emphysema, bronchiolitis, non-necrotizing granulomatous inflammation, small airways inflammation, peribronchiolar fibrosis, or granulomatous pneumonitis on surgical lung biopsy. Descriptive statistics and logistic regression were used to analyze lung function parameters associated with deployment-related distal lung disease. The biopsy reports were reviewed for several diagnoses. Descriptive statistical tests were conducted to analyze demographic factors, deployment, pulmonary function, and exercise testing. The researchers carried out Fisher's exact test for class variables, two-sample t-tests for continuous variables, and the Wilcoxon rank sum test for count or right-skewed continuous variables. This study provides a characterization of deployment-related lung disease in a cohort of veterans and military contractors with a history of deployment to Southwest Asia. The study is limited by having included only cases with respiratory disease and by not having included a control group.

Madar et al. (2017) retrospectively reviewed a series of biopsies of non-neoplastic lung disease that were evaluated at the Armed Forces Institute of Pathology or Joint Pathology Center from January 2005 through December 2012. Service members were grouped by the timing of the biopsy, before or after deployment to Southwest Asia. Of 391 individuals examined, 137 (35.0%) had deployed to Southwest Asia prior to the biopsy (termed the deployed group). Those under age 40 represented nearly 60% of the deployed personnel and 28.7% of the nondeployed personnel. Nondeployed personnel who underwent lung biopsy were more likely to be age 50 years or older. According to electronic medical records, 41% of the deployed and 56% of the nondeployed subjects were prior smokers; whether the individuals were smoking in theater or at the time of biopsy is not documented, and the records may underreport the service members' smoking history. Among the surgical biopsies, 79 occurred post-deployment and 137 occurred before deployment, and among the non-surgical biopsies 58 occurred post-deployment and 117 occurred before deployment. Histologic diagnoses were sorted into 38 categories, and the categories were collapsed into 10 major histologic groups: no specific pathologic diagnosis, smoking-related lung disease, idiopathic interstitial pneumonia, small airways disease, chronic inflammation (not otherwise specified), granulomatous disease, infection, eosinophilic pneumonia, pneumoconiosis, and other (which included, for example, pulmonary alveolar proteinosis and pleuritis). Multivariable binary logistic regressions were conducted to estimate the independent effect of deployment in predicting the probabilities of histologic diagnoses when the prevalence was amenable to statistical analysis. Logistic regression models controlled for age, gender, ethnicity, and tobacco use history. A separate series of multivariate binary logistic regressions also controlled for time in theater. All regressions included only those people for whom a single diagnosis was made. Pulmonary function testing data (available from associated medical records) were compared using a series of independent means t-tests. The specific results of this study are presented in the following respiratory outcomes sections of Chapter 4: Pulmonary Function Testing, Constrictive Bronchiolitis, Interstitial Lung Diseases (Sarcoidosis, Idiopathic Interstitial Pneumonias, Acute Eosinophilic Pneumonia, and Pulmonary Alveolar Proteinosis). Not all lung biopsies in the military are reviewed at the Joint Pathology Center, so there may be some degree of referral bias. The demographic characteristics of the deployed and nondeployed groups were statistically different with respect to age and tobacco use. Incomplete clinical data limited the ability to make associations with the presenting symptoms that prompted the biopsy. The inclusion of non-surgical samples may have enhanced the study's ability to diagnose some conditions, such as sarcoidosis, but it would have resulted in underestimates of other diagnoses, such as bronchiolitis and idiopathic interstitial lung diseases, that require surgical lung biopsy for diagnostic confirmation. Other conditions, such as eosinophilic pneumonia, do not typically require biopsy for diagnosis, and therefore this study design would not be expected to identify many such cases if they were present.

Pugh et al. (2016) conducted a retrospective cohort study to examine the prevalence of chronic lung disease and its relationship with military deployment using health care system data from 760,621 U.S. veterans deployed to combat operations in Iraq or Afghanistan who received care from VA between October 1, 2002, and September 30, 2011. Study investigators reviewed ICD-9-CM codes of inpatient and outpatient encounters for diseases of the respiratory system, which included asthma, COPD, and interstitial lung diseases. Smoking status was determined based on one of several indicators in the medical record, including ICD-9-CM codes for tobacco use/nicotine dependence, prescriptions for medications for the treatment of nicotine dependence, and individuals who received VA care in a smoking cessation clinic. Diagnoses of traumatic brain injury were collected and used in the analyses, as was whether an individual had two or more deployments. For each condition, the prevalence was calculated by year, with the number of unique OEF/OIF veterans who received VA care in that year being used as the denominator. Generalized estimating equations were used to determine if the log-odds of having a diagnosis of any of the respiratory outcomes increased from fiscal year 2003 to fiscal year 2011. Models were adjusted for demographic characteristics, multiple deployments, tobacco use, and traumatic brain injury to determine if the log-odds of diagnosis increased from 2003 to 2011. A total of 33,962 individuals had at least one diagnosis of the respiratory conditions of interest over the study period. The strengths of this study included the use of ICD-9-CM-coded diagnoses and a large study population. Although study investigators were able to assess the number of deployments, they were not able to assess the lengths of the deployments (to calculate total potential exposure time). Finally, temporal relationships between exposures and respiratory health outcomes could not be established, and the study population was limited to individuals who had received care within the VA health system.

Rohrbeck et al. (2016) conducted a small cohort study to look for associations between various health outcomes, which were based on ICD-9 codes assigned from post-deployment medical encounters, and known exposures to burn pits, which were based on deployment location. Using data from the Defense Medical Surveillance System, 200 service members were selected based on their participation in a previous environmental health assessment and known exposure to burn pits; of these 163 were Army personnel who had been assigned to Joint Base Balad, Iraq, and 37 were Air Force personnel who had been assigned to Bagram Airfield, Afghanistan. Each participant provided pre- and post-deployment serum specimens. Controls—200 randomly selected nondeployed service members from all branches from the Defense Medical Surveillance System—were matched to cases by time in service on the date on which the pre-deployment serum sample was collected. Data from medical encounters in military treatment facilities, both hospitalizations and outpatient visits, were used to capture information on signs, symptoms, and ill-defined conditions involving the respiratory system and other chest symptoms (ICD-9 786) regardless of diagnostic position. Chi-square statistics were used to compare the nondeployed with the deployed cohort as well as to compare service members who served at Balad with the Bagram cohort. Incident rate ratios were calculated to assess the risk for the various health outcomes among the nondeployed and deployed cohorts. Stratified survival analysis was used to examine deployment effect by location. In the multivariate regression analysis, models were adjusted for age, sex, race/ethnicity, occupation, deployment history, and history of illness prior to deployment, and the Bonferroni correction was used for multiple comparisons to reduce the chances of obtaining false-positive results; the significance level was set at $\alpha = 0.025$. This analysis had limited power for detecting differences in outcomes. Although burn pit exposure was documented, there is still individual variation in exposure that was not accounted for (deployment duties, job classification, and specific individual behaviors). Information on smoking was not available. The combined cohort of deployed service members was an odd choice because the two cohorts deployed 5 years apart, service members belonged to different branches, and the theaters were uniquely different. As with other studies that rely on the use of ICD-9 codes in medical encounter data, these are limited for most respiratory outcomes because most individuals are unlikely to seek medical attention unless the condition worsens or persists. This analysis was also limited by its representativeness, power for detecting differences in outcomes, and inability to control for smoking.

1990–1991 Gulf War Veterans

As noted in Chapter 1, the 1990–1991 Gulf War comprised two U.S. military operations—Operation Desert Shield and Operation Desert Storm—which took place between August 1990 and April 1991. In this section, descriptions of studies of U.S. veterans are presented first, followed by descriptions of epidemiologic studies conducted in cohorts of Australian, Canadian, and UK Gulf War veterans.

U.S. Gulf War Veterans

National Health Survey of Gulf War Era Veterans and Their Families and Follow-Up Studies PL 103-446 mandated that VA conduct a population-based study of U.S. Gulf War veterans. In response, VA has conducted a set of studies of health outcomes in Gulf War–era veterans that began with a longitudinal survey of 30,000 veterans known as the National Health Survey of Gulf War Veterans and Their Families (NHS).[8] Thus far, three survey waves have been conducted: wave 1 in 1993–1995 (Kang et al., 2000), with physical examinations in 1999–2001 (Eisen et al., 2005); wave 2 in 2003–2005 (Kang et al., 2009); and wave 3 in 2012–2013 (Dursa et al., 2016). Participants for waves 2 and 3 were recruited using participants selected for the wave 1 (baseline) population. Several derivative studies of the NHS and its successor research efforts are reviewed in Volumes 4 (IOM, 2006), 8 (IOM, 2010), and 10 (NASEM, 2016) of the *Gulf War and Health* series of National Academies reports. Four of these—the first paper to describe this effort and three other papers that address respiratory health outcomes—are summarized below. Chapter 4 also cites some additional NHS-related studies.

VA designed the NHS—originally described in Kang et al. (2000)—to be representative of the nearly 700,000 U.S. veterans sent to the Persian Gulf and 800,680 veterans who were not deployed but who were in the military between September 1990 and May 1991. In wave 1 of the survey, VA mailed questionnaires to a stratified random sample of 15,000 deployed and 15,000 nondeployed Gulf War veterans identified by DoD's DMDC. Women and those serving in the National Guard and reserves were oversampled, resulting in a study population that was approximately 20% women, 25% National Guard, and 33% reservists. The controls were stratified by gender, unit component, and branch of service to mirror the population of deployed veterans. The self-administered structured health questionnaire contained a 48-symptom inventory (somatic and psychological symptoms) and questions about chronic medical conditions, functional limitations, the use of medical services, and environmental exposures. Wave 1 also used telephone interview software in an attempt to capture those who did not respond to the mailed questionnaire. A total of 11,441 (75%) deployed and 9,476 (64%) nondeployed veterans participated in the study; 15,817 veterans responded to the questionnaire, and 5,100 responded to the telephone interview. Characteristics

[8] The National Health Survey of Gulf War Veterans and Their Families is also referred to as the Longitudinal Health Study of Gulf War Era Veterans in some VA publications (https://www.publichealth.va.gov/epidemiology/studies/gulf-war-longitudinal-study.asp [accessed June 8, 2020]).

of those who did not respond to the mailed survey were also examined. In addition, as part of wave 1, medical records were obtained for a random sample of 4,200 respondents to validate self-reports of clinic visits or hospitalizations within the previous year. Of the 2,233 veterans with at least one clinic visit, 43.2% provided medical record release consent; of the 310 with at least one hospitalization, 45.2% provided medical record release consent. Medical record reviews verified more than 90% of self-reported reasons for clinic visits or hospitalizations. The third phase was a comprehensive medical examination and laboratory testing of a random sample of 2,000 veterans drawn from the deployed and era groups. Three studies analyzed and reported on respiratory symptoms collected from wave 1 (Eisen et al., 2005; Kang et al., 2000; Karlinsky et al., 2004), and they are described below.

Kang et al. (2000) did not assess exposure–symptom relationships but rather noted the percentage of veterans who reported each of 23 environmental exposures and 9 vaccine or prophylactic exposures (such as to pyridostigmine bromide). The five most common environmental exposures—reported by more than 60% of survey participants—were diesel, kerosene, or other petrochemical fumes; local food other than that provided by the armed forces; chemical protective gear; smoke from oil-well fires; and burning trash or feces.

Karlinsky et al. (2004) examined pulmonary function and self-reported respiratory symptoms in 1,036 deployed and 1,103 nondeployed veterans who completed the clinical examination component of the NHS. The results of pulmonary function tests were classified into five categories: normal pulmonary function, nonreversible airway obstruction, reversible airway obstruction, restrictive lung physiology, and small-airway obstruction. The authors also reported on the pattern of pulmonary function test results in those exposed (n = 159) and those not exposed (n = 877) (according to DoD exposure estimates developed in 2002) to nerve agents resulting from the destruction of a munitions storage site at Khamisiyah, Iraq, in 1991.

Eisen et al. (2005) performed a cross-sectional analysis on health outcomes collected in a subset of 1,061 deployed and 1,128 nondeployed Gulf War veterans who completed the clinical examination component of the third phase of wave 1 of the NHS. The study population consisted of a stratified random sample of the 11,441 deployed and 9,476 nondeployed veterans who had responded to the mailed questionnaire or telephone interview described above. This study included a comprehensive medical examination and laboratory testing. Of the 1,996 eligible deployed veterans, 1,061 (53.1%) were examined, 680 (34.1%) declined, and 255 (12.8%) were not located. Of the 2,883 eligible nondeployed veterans, 1,128 (39.1%) were examined, 1,316 (45.7%) declined, and 439 (15.2%) were not located. Despite extensive recruitment efforts, the participation rate for this study was low—60.9% of deployed veterans and 46.2% of the nondeployed. Study participants were assigned a medical center closest to their residence where medical providers took histories and performed examinations; laboratory and pulmonary function tests were also performed. Twelve primary health outcome measures and physical functioning were examined using the 36-Item Short Form Health Survey. Outcome measures were chosen by the authors to cover the most common symptoms reported by veterans. Analyses adjusted for age, sex, race, years of education, cigarette smoking history, duty type (active versus reserves or National Guard), service branch (Army or Marines versus Navy or Air Force), and rank (enlisted versus officer). The two main limitations of this study were the fact that it was carried out 10 years after the 1990–1991 Gulf War, which precluded diagnoses that had already resolved, and its low participation rates, which introduced the possibility of participation bias.

Results of the third survey wave of the NHS were reported by Dursa et al. (2016). This survey consisted of the same 30,000 Gulf War–deployed and Gulf War–era veterans and the same administration methods as the two prior surveys—that is, via mail, website, or a computer-assisted telephone interview. A total of 14,252 veterans responded (8,104 deployed and 6,148 era veterans), for a response rate of 50% (57% deployed, 43% nondeployed). Respondents were more likely to have served in the Army compared with other branches, to have been deployed, to have been an officer, to have been older, and to have identified as white than were non-respondents. The wave 3 questionnaire was modified from the earlier versions, but it again collected information about the presence of various symptoms, including respiratory problems, functional status, activity limitations, health perceptions, chronic medical conditions (self-report of provider diagnoses), health care use, and potential confounders, such as the use of alcohol and cigarettes.

Other Studies of U.S. Gulf War Veterans Several other studies of Gulf War veterans have examined respiratory outcomes. Some of these examined cohorts that were selected based on their military occupation, such as the Seabees[9] (Gray et al., 2002), or state of home of record (Iowa Persian Gulf Study Group, 1997; Steele, 2000). Smith et al. (2006) conducted a large study of post-deployment hospitalization events of active-duty service members to examine respiratory conditions, including asthma, for service members deployed to Southwest Asia for peacekeeping missions post-Gulf War (n = 254,080) and service members deployed to Bosnia (1995–1998, n = 46,911) compared with Gulf War–deployed service members (n = 458,727). Bullman et al. (2005) explored the relationship between estimated exposure to chemical munitions destruction (including sarin gas) at Khamisiyah, Iraq, in 1991, with cause-specific mortality of Gulf War veterans through December 31, 2000.

In addition to these studies, five other epidemiologic studies of 1990–1991 Gulf War veterans are referenced in multiple locations in Chapter 4 (Hines et al., 2013; Hooper et al., 2008; Khalil et al., 2018; Maule et al., 2018; Zundel et al., 2019). Summaries of these follow.

Estimating inhalational exposures has been one of the more challenging aspects of health studies of those deployed to Southwest Asia. Hines et al. (2013) examined 37 1990–1991 Gulf War veterans who were enrolled in the VA Depleted Uranium Surveillance Program and had attended a biennial follow-up between April and June 2011 (the total cohort consisted of 80 veterans with known exposure to depleted uranium [DU]). Each veteran had sustained inhalational exposure to DU during friendly fire incidents in 1991. The purpose of this publication was to compare the likelihood of pulmonary health abnormalities in those with high body burdens of uranium (n = 12; >0.1 μg/g creatinine) versus those with low body burdens of uranium (n = 25; ≤0.1 μg/g creatinine). The authors hypothesized that service members with embedded DU fragments were more likely to have been closer to a blast source and to have undergone greater inhalational exposures to DU and blast particulate than those who had not had injuries from embedded DU. Service members with higher urine uranium concentrations were hypothesized to have reported greater frequencies of chest symptoms, have had more abnormal pulmonary function, and have had more abnormalities on chest CT than those with low urinary uranium concentrations. Study participants attended a 3-day, inpatient clinical assessment that included a detailed medical and exposure history, physical examination, laboratory studies, and a comprehensive assessment of pulmonary health and function via a respiratory symptom questionnaire and full pulmonary function tests, CT chest-imaging studies, and impulse oscillometry. Participants were also questioned regarding physician-prescribed steroids and smoking status. Participants with embedded uranium fragments underwent positron emission tomography accompanied by low-dose CT. Total uranium concentrations and the 235U/238U isotopic ratio in 24-hour urine samples were measured for all. While the use of an objective biomarker as a measure of exposure is a strength of this study, the findings are of limited relevance to the majority of those deployed, given that exposure to DU was and continues to be uncommon. Additionally, given the small sample size, there are concerns the study may be underpowered.

Hooper et al. (2008) examined the long-term hospitalization experience of regular active-duty U.S. Gulf War veterans (n = 211,642) still on active duty between 1994 and 2004 (presented at 3-year intervals) compared with veterans who had separated from military service (n = 321,806). Service rosters, demographic and military service characteristics, selected Gulf War exposure variables, and hospitalization data were collected from DMDC databases. Environmental exposure data, which included information on potential exposure to the Khamisiyah munitions depot demolition (March 10–12, 1991) and smoke from oil-well fires, came from the Naval Health Research Center and the U.S. Army Center for Health Promotion and Preventive Medicine. For multivariate modeling, a three-level Khamisiyah exposure variable (presumed not at risk, at risk of exposure but not exposed, and exposed) was applied. Other war-related exposures or experiences, including anthrax or botulinum immunization, in-theater hospitalization, and presence in theater during ground combat operations, were included and treated as dichotomous variables. To reduce possible effects of other deployments, service members who deployed between the end of the Gulf War and October 1, 1994 (the beginning of the period of observation) were excluded. Hospitalization data consisted of inpatient encounter records from military treatment facilities (including those that occurred in theater) and civilian facilities when costs were reimbursed by DoD that were coded using ICD-9-CM codes. Both primary and secondary diagnoses were included. Individuals could be counted in multiple diagnostic categories (presented by system or injury), but only once per category. Cox proportional hazard modeling was used to evaluate the independent predictors of all-cause hospitalization among those still on active duty and to estimate the cumulative

[9] The Seabees are service members who served with the U.S. Naval Mobile Construction Battalions.

probability of hospitalization, 1994–2004, by service branch. For the 10-year combined observation period, there were 43,346 hospitalizations for those who remained on active duty after 1994. Of those hospitalizations, 12.2% (n = 2,872) were coded as respiratory system. The most frequent categories were diseases of the musculoskeletal system (32.7%); diseases of the digestive system (23.4%); injury and poisoning (21.0%); and symptoms, signs, and ill-defined conditions (18.7%). For each diagnostic category, the top five primary diagnoses over the entire follow-up period were presented. Of the 4,031 hospitalizations for ill-defined conditions, 46.6% had respiratory system and other chest symptoms. Comparisons with the separated veteran group were not presented, nor were category hospitalizations by Gulf War exposures, which limited the informativeness of this study.

Khalil et al. (2018) was a descriptive analysis of the study design for the Gulf War Era Cohort and Biorepository, which was established by VA to be

> a nationally representative longitudinal cohort of U.S. veterans who served during the 1990–1991 Gulf War era … [combining] survey data, such as demographic, health behavior, and environmental exposure data; medical records; and a linked biorepository of blood specimens that can support a broad range of future research regarding health concerns unique to veterans of this era. (p. 2279)

The pilot phase of the effort started with a stratified recruitment panel of 90,000 veterans identified from DoD's DMDC and drawn from a total population of 4,966,117 veterans who served during August 1990–July 1991, without regard to deployment or combat status, health status, or whether the service member had enrolled in or used the Veterans Health Administration for health care. Of these, 10,042 met inclusion criteria (living with valid contact information and meeting residence location requirements), and an additional 168 self-nominated for inclusion. The pilot sample was constructed to frequency-match the geographic distribution of the recruitment panel across the four U.S. Census regions, reflecting geographic variation in the veteran population. The recruited veterans received a mail survey to complete along with consent forms granting permission for their VA and DoD records (including biospecimens) to be accessed for research purposes. Each participant gave a blood sample. The final enrollment consisted of 1,275 veterans who completed all study requirements, 900 (70.6%) of whom deployed to the Southwest Asia theater. Veterans who were female, nonwhite, served in the Army, or were active duty were all slightly overrepresented relative to the stratified recruitment panel. The most commonly reported exposure in those who had served in theater was "close proximity to smoke from oil-well fires" (60%); 39% reported five or more exposures, and just over 2% reported that they had not experienced any of the Gulf region exposures that they were queried about. Participants reported a median of 14 health symptoms that had been persistent or recurring over the last 6 months (range, 0–34 symptoms); 0.9% of participants reported experiencing all of the symptoms surveyed, and 2.8% reported experiencing none of the symptoms. Self-reported health outcomes of symptoms (in the past year) and health care provider–diagnosed conditions were reported stratified by users (n = 584) and nonusers (n = 679) of VA health care. Three respiratory symptoms were included as well as sleep apnea, COPD, tuberculosis, and lung cancer. Outcomes were not adjusted for confounding factors, and no comparisons between deployed and nondeployed veterans were made, but only between VA users and nonusers. Therefore, the findings are primarily descriptive in nature and are of limited utility for assessing the role of Gulf War deployment on respiratory symptoms.

Maule et al. (2018) conducted a meta-analysis of 21 studies published through 2017 on the prevalence of health diagnoses and symptoms representing more than 129,000 Gulf War–deployed and nondeployed era veterans to characterize the most frequently reported symptoms occurring among deployed versus nondeployed 1990–1991 Gulf War veterans. Pooled analyses were conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. For the meta-analysis of symptom prevalence in Gulf War–deployed and Gulf War–era veterans, separate random-effects binomial-normal models were used to estimate the combined log odds of a symptom and to calculate the pooled prevalence rate of individual symptoms. For the meta-analysis of odds ratios comparing symptom reporting in Gulf War–deployed veterans to Gulf War–era controls, a random effects binomial-normal model was used to estimate combined log odds ratios. In the model estimating log odds ratios, an offset term was included to take into account the different sample sizes of Gulf War–deployed and Gulf War–era veterans within a study. Qualitative and quantitative bias assessments were also performed. The authors stated that there was little evidence to support reporting bias (that is, selective reporting in studies of outcomes with positive findings) in contributing to the differences in prevalence. The bias assessment also demonstrated that Gulf War–deployed veterans continued to have higher odds of reporting all analyzed symptoms compared with Gulf War–era controls. Odds ratios were reported for each symptom along with I^2 statistics (a measure of the heterogeneity, or the percentage of variation across studies that is due to heterogeneity rather than chance). The included outcomes relevant to respiratory outcomes were respiratory symptoms, sinusitis, and asthma. For each of the 56 self-reported symptoms analyzed there was a higher combined prevalence in the Gulf War–deployed veterans than in the Gulf War–era veterans. The meta-analytic approach could not address concerns about either selection biases or information biases (due to self-reports of symptoms), concerns that were common to all of the studies included. Therefore, while this meta-analysis fairly summarizes reported findings on respiratory symptoms and provides assurance that reporting bias played little role, other important deficiencies in the published studies and their impacts on the findings were not addressed.

Zundel et al. (2019) compared survey results from a longitudinal cohort of 1990–1991 Gulf War veterans who returned from deployment in 1991 through Fort Devens, Massachusetts, with data from the National Health and Nutrition Examination Survey (NHANES; n = 2,949). The veterans cohort was established in 1991, and the 2013 survey was a follow-up of 448 participants (response rate 35%) that collected self-reports of doctor-diagnosed chronic conditions. These were compared with NHANES 2013–2014 data that were restricted to non-veterans and persons in the age range of the veteran survey respondents. A total of 401 male and 47 female Fort Devens participants responded to the survey and reported at least one chronic condition. Excess prevalence was calculated as the difference in prevalence estimates from the Fort Devens and the NHANES cohorts. Odds ratios and test-based confidence intervals were calculated from the prevalence estimates and standard errors that had been calculated for the two cohorts. To account for demographic differences between the cohorts, analyses were restricted to include white/Caucasian individuals with a high school education or above, and the analyses adjusted for these demographic differences by modifying the NHANES weights to match the age and education distribution, for men and women separately, of the Fort Devens cohort. The Fort Devens and NHANES cohorts differed significantly in age, sex, race, education, and current smoking status. For the Fort Devens exposure analyses, veterans who were exposed and unexposed did not differ on any of the demographic variables, but analyses for exposure were adjusted for gender and current smoking status. For the Fort Devens cohort, nine chronic medical conditions were compared by exposure/nonexposure to chemical or biologic warfare or pyridostigmine bromide pills. Compared with the NHANES sample from the general U.S. population, Gulf War veterans were at higher risk of chronic conditions. Exposure to chemical or biologic warfare or pyridostigmine bromide pills was associated with a statistically significant excess prevalence of several of the chronic conditions examined. This study likely suffers from information bias due to its use of self-reports of medical conditions and from selection bias because the sample was drawn from a group that is not representative of the overall population (white with education above high school) who had previously reported a chronic condition.

U.S. Studies with Modeled Exposure to Oil-Well Fire Smoke Three studies of U.S. service members or veterans specifically examined respiratory diagnoses or symptoms associated with modeled exposure to oil-well fires (Cowan et al., 2002; Lange et al., 2002; Smith et al., 2002).

Cowan et al. (2002) conducted a case–control study of 873 Gulf War veterans with a physician diagnosis of asthma versus 2,464 controls without asthma or other respiratory system diagnoses who were participants of the DoD Comprehensive Clinical Evaluation Program. Demographic information was obtained from the DoD Gulf War Registry, and oil-well fire smoke exposure was based on a National Oceanic and Atmospheric Administration (NOAA) atmospheric advection and diffusion model. Exposure was cumulatively modeled (low, intermediate, and high) and adjusted for sex, age, race, military rank, and smoking history.

Lange et al. (2002) used a cross-sectional study design to examine exposure to smoke from oil-well fires (self-reported and modeled) and asthma symptoms assessed via structured interviews conducted 5 years after the Gulf War for a subset of 1,560 Iowa veterans. Modeled exposures were developed using a geographic information system to integrate spatial and temporal records of smoke concentrations with troop movements ascertained from Global Positioning Systems records. Exposure was presented by quartiles. Odds ratios were adjusted for sex, age, race, military rank, smoking history, military service, and level of preparedness for war.

Smith et al. (2002) used DoD hospitalization data (ICD-9-CM codes) from August 1991–July 1999 and exposure models to examine associations between respiratory diseases, including asthma, chronic bronchitis, acute bronchitis, and respiratory cancers and different levels of modeled exposure to oil-well fires among service members. The results of the associations for each of these outcomes is presented under the applicable section in Chapter 4. The study population consisted of 405,142 active-duty service members who were deployed to the Gulf War theater of operations for 1 or more days during the period August 8, 1990–July 31, 1991, and who were still in the theater of operations during the time of the Kuwaiti oil-well fires but who did not remain in the region after the war. Demographic and deployment data were provided by DoD's DMDC. Exposure was estimated by using troop location data and estimated oil-smoke concentrations based on NOAA modeling that was used in other studies. Individuals were assigned to one of seven exposure groups, which combined duration and amount of exposure, ranging from no exposure to average daily exposure of >260 $\mu g/m^3$ for >50 days. Individuals with pre-existing conditions (hospitalizations for diagnoses of interest in the 3 years prior to the start of follow-up) were excluded from further analysis for that specific diagnosis. Cox's proportional hazards time-to-event modeling was used in the statistical analysis, and the time-to-event estimates were calculated by exposure level. Effect estimates were adjusted for demographic and military factors that were found to be statistically significant predictors of the outcomes in exploratory models (specific demographic and military characteristics not specified for each outcome), but no smoking data were available. There was no evidence of a trend of increasing risk of hospitalization for veterans exposed to oil-well fire smoke over all of the exposure groups. The adjusted risk ratios for post-war hospitalization for respiratory diseases (ICD-9-CM 460–519) showed a decreased risk of hospitalization for all six groups of exposed participants compared with the unexposed participants, and the decreased risk for the second highest exposure group (average daily exposure of 1–260 $\mu g/m^3$ for >50 days) was statistically significant (relative risk = 0.69, $p < 0.05$). Additional modeling for specific respiratory diagnoses and exposure to oil-well fire smoke collapsed exposure categories into two—exposed (n = 337,077) and nonexposed (n = 68,065). Tobacco use and exposure to fine desert dust, exhaust from diesel equipment, and other war-related exposures may have influenced some of the risk findings. Analyses were limited to morbidity severe enough to require admission to a DoD hospital for inpatient care, a major limitation for analysis of some of these respiratory outcomes, which rarely require hospitalization. In addition, personnel in direct combat roles, as a group, are more physically fit than support personnel and thus are less likely to be hospitalized post-deployment.

Australian Gulf War Veterans

The Australian Gulf War Veterans' Health Study—a national study of all Australian Gulf War veterans—was conducted in 2000–2002 (Sim et al., 2003), and the cohort has been followed since the initial study. A total of 14 derivative studies (Forbes et al., 2004; Gwini et al., 2015; Ikin et al., 2004, 2005, 2015; Kelsall et al., 2004a,b, 2005, 2006, 2007, 2009, 2014; McKenzie et al., 2004; Sim et al., 2015) have been described in volumes of the *Gulf War and Health* series of reports. Of the derivative studies, few (Gwini et al., 2016; Kelsall et al., 2004b; Sim et al., 2015) have presented outcomes on respiratory symptoms. Kelsall et al. (2004b) used data collected during the 2000–2002 study, Sim et al. (2015) used data from the follow-up assessment conducted in 2011–2013, and Gwini et al. (2016) examined new onset of self-reported conditions using data collected from both the initial and follow-up assessments.

In the initial study of the Australian Gulf War veterans, all 1,871 Australian veterans deployed to the Gulf War region from August 2, 1990, to September 4, 1991, were included; naval personnel made up 86.5% of this cohort (Sim et al., 2003). The control group consisted of 2,924 nondeployed Australian Defence Force personnel matched by service type, sex, age, and military status. Participation rates were 81% (n = 1,456) for the deployed and 57% (n = 1,588) for the control group. A mailed 58-item questionnaire was distributed in 2000–2002 (10 years after the Gulf War), which included the 12-Item Short Form Health Survey, General Health Questionnaire-12, and questions regarding physical and psychological health, military service history, and exposures during deployment. The questionnaire asked about problems or conditions that had been diagnosed or treated by a medical doctor and the year in which the condition was first diagnosed. In addition, participants were asked to attend one of 10 Health Services Australia medical clinics to undergo a comprehensive health assessment, a full physical examination, blood work, and fitness tests. Spirometric tests were performed, and a respiratory questionnaire was administered as part of this assessment. Sim et al. (2003) reported information on some respiratory health outcomes, but these were more thoroughly addressed by Kelsall et al. (2004b).

Kelsall et al. (2004b) examined the respiratory health status of Australian veterans using the Sim et al. (2003) data, focusing on the effects of exposure to oil fire smoke and dust storms. The subjects were the same as those in the original study: a deployed cohort comprising 1,456 participants who were compared with 1,588 randomly sampled military personnel who served during the same time period but who were not sent to the theater. The comparison group was frequency matched to the deployed group by service type, age (within 3-year age bands), and rank (officer/non-officer) for Army participants or aircrew/non-aircrew status for Air Force participants. While data were collected for female veterans, there were too few to allow analyses to be conducted, so the results were restricted to male subjects. The study's strengths include its use of a comparison group that was similar to the exposed (deployed) subjects with regard to characteristics, such as age and smoking status, that are predictive of health outcomes, and the gathering of some data through a medical assessment and physical examination. Its weaknesses include the high percentage of naval personnel in the cohort—which make the attribution of health problems to in-theater airborne exposures problematic—and the use of self-reported exposure and health data collected 10 years after deployment to the 1990–1991 conflict. The investigators also note that participation bias and recall bias could not be ruled out as at least partial explanations for some of the findings.

Sim et al. (2015), as noted above, reported the results of the Australian Gulf War Veterans' Follow Up Health Study, which was conducted in 2011–2013. This study assessed the entire Australian Gulf War cohort 10 years after the 2000–2002 baseline investigation and 20 years after the war. All participants in the original study were eligible to take part; 715 Gulf War veterans and 675 comparison group veterans responded to recruitment efforts (a 50% participation rate). Respiratory health data were available on 697 Gulf War veterans and 659 comparisons. The follow-up study collected much of the same information as the original study, but it also inquired about additional outcomes, including pain, sleep disturbance, injury, musculoskeletal disorders, demoralization, and measures of well-being (quality of life, life satisfaction, life events, financial distress, suicidal ideation, and community participation). The follow-up also extended exposure assessment efforts from those used in the first, or baseline, study. The data were collected by mailed questionnaire, telephone interview, collection of the Australia Department of Veterans' Affairs' health data, and claims history from the Australia Medicare, Pharmaceutical Benefits Scheme, and Repatriation Pharmaceutical Benefits Scheme. Other databases included national mortality and cancer registries and information from the baseline study. Respiratory health was assessed at both baseline and follow-up, but the scope of respiratory health data collected and the mode of data collection changed for some factors, which limited the ability to assess change over time for some of the outcomes. The follow-up study collected information on respiratory symptoms and medical conditions, including asthma, using a brief list of outcomes that were assessed via self-report questionnaire. The questions on respiratory symptoms and conditions included at follow-up were pared down or modified from a larger set that were administered by a nurse in the baseline study. Spirometry or other lung function tests were not included at follow-up. The follow-up study included an assessment of respiratory health medications dispensed to participants under the Pharmaceutical Benefits Scheme or Repatriation Pharmaceutical Benefits Scheme, which were data sources not included at baseline. Estimates were adjusted for age group, service branch, and rank estimated as of August 1990, and any atopy at baseline and current smoking status (never, former, current smoker).

Canadian Gulf War Veterans

Goss Gilroy Inc. was contracted by the Canadian Department of National Defence to carry out an epidemiologic survey of Canadians who had served in the Gulf War to determine their health status (Goss Gilroy Inc., 1998; Statistics Canada, 2005). The survey was mailed to 9,961 Canadian Forces personnel: the entire cohort of Canadian Gulf War veterans who had been deployed to the Gulf War (n = 4,262) and a comparison group of personnel who had deployed elsewhere (n = 5,699) during the same period. The overall response rate was higher among Gulf War veterans (n = 3,113; response rate 73.0%) than among the comparison veterans deployed elsewhere (n = 3,439; response rate 60.3%). Generally, deployed veterans had higher rates of self-reported chronic conditions and symptoms of a variety of clinical outcomes than controls. Respiratory diseases were included in the outcomes of interest.

United Kingdom Gulf War Veterans

Two studies of the health of UK military veterans who served during the Gulf War addressed respiratory outcomes. Simmons et al. (2004) used data collected as part of a mail survey of UK Gulf War veterans. While the survey was designed largely to assess reproductive outcomes among the veterans, it also contained open-ended questions about the veterans' current health and about changes in their health since 1990, with the answers categorized, including asthma and respiratory problems not otherwise specified. The exposed cohort consisted of all UK Gulf War veterans, and the unexposed cohort consisted of a random sample of nondeployed UK military personnel from the same period. Although the number of surveys returned in the study was large (25,084 by Gulf War veterans and 19,003 by era Gulf War veterans), the participation rate was low (47.3% and 37.5% of male and female Gulf War veterans, respectively, and 57.3% and 45.6% of male and female nondeployed veterans). Estimates were adjusted for age at time of survey, service and rank at time of the Gulf War, serving status at time of survey, alcohol consumption, and smoking.

Unwin et al. (1999) conducted a cross-sectional postal survey from 1997 to 1998 to compare the health profiles of veterans and military service members from the United Kingdom (n = 8,195; overall response rate 65.1%). The study population was randomly selected, and the sample was stratified into three cohorts: deployed male and female Gulf War veterans and military service personnel (n = 2,961) who served in the Gulf region between September 1, 1990, and June 30, 1991 (response rate = 70.4%); deployed military personnel who had served in Bosnia (n = 2,620) between April 1, 1992, and February 6, 1997 (response rate 61.9%); and veterans and military personnel who were in the armed forces on January 1, 1991 (n = 2,614) but were not deployed to the Gulf War (response rate 62.9%). Odds ratios were calculated, and the proportions of symptoms, disorders, and exposures were compared between the Gulf cohort and the two comparison cohorts. Study investigators controlled for potential confounders including sociodemographic (age, marital status, education, employment), military (rank, still serving or discharged), and lifestyle (smoking, alcohol consumption) factors. The strengths of this study included its use of two different military control groups that came from a large, randomly selected population-based study population and the fact that it accounted for pre-existing health status and cigarette smoking. Among the limitations was its reliance on unverified self-reported medical symptoms and conditions; however, the committee believed that differential non-response or recall bias was unlikely, based on the results of subanalyses presented by study investigators.

REFERENCES

Abraham, J. H., and C. P. Baird. 2012. A case-crossover study of ambient particulate matter and cardiovascular and respiratory medical encounters among U.S. military personnel deployed to Southwest Asia. *Journal of Occupational and Environmental Medicine* 54(6):733–739.

Abraham, J. H., S. F. DeBakey, L. Reid, J. Zhou, and C. P. Baird. 2012. Does Deployment to Iraq and Afghanistan Affect Respiratory Health of US Military Personnel? *Journal of Occupational and Environmental Medicine* 54(6):740–745.

Abraham, J. H., A. Eick-Cost, L. L. Clark, Z. Hu, C. P. Baird, R. DeFraites, S. T. Tobler, E. E. Richards, J. M. Sharkey, R. J. Lipnick, and S. L. Ludwig. 2014. A retrospective cohort study of military deployment and postdeployment medical encounters for respiratory conditions. *Military Medicine* 179(5):540–546.

AFHSC (Armed Forces Health Surveillance Center), Naval Health Research Center, and U.S. Army Public Health Command (Provisional). 2010. *Epidemiological studies of health outcomes among troops deployed to burn pit sites*. Silver Spring, MD: Department of Defense. https://www.vetshq.com/wp-content/blogs.dir/files/sites/11/2013/10/Epidemiological-Studies-of-Health-Outcomes-Among-Troops-Deployed-to-Burn-Pit-Sites.pdf (accessed June 15, 2020).

Baird, C. P., S. DeBakey, L. Reid, V. D. Hauschild, B. Petruccelli, and J. H. Abraham. 2012. Respiratory health status of US Army personnel potentially exposed to smoke from 2003 Al-Mishraq Sulfur Plant fire. *Journal of Occupational and Environmental Medicine* 54(6):717–723.

Barth, S. K., E. K. Dursa, M. R. Peterson, and A. Schneiderman. 2014. Prevalence of respiratory diseases among veterans of Operation Enduring Freedom and Operation Iraqi Freedom: Results from the National Health Study for a New Generation of U.S. Veterans. *Military Medicine* 179(3):241–245.

Barth, S. K., E. K. Dursa, R. Bossarte, and A. Schneiderman. 2016. Lifetime prevalence of respiratory diseases and exposures among veterans of Operation Enduring Freedom and Operation Iraqi Freedom veterans: Results from the National Health Study for a New Generation of U.S. Veterans. *Journal of Occupational and Environmental Medicine* 58(12):1175–1180.

Blackwell, T. 2019. *Lung pathology in patients with post-deployment constrictive bronchiolitis*. Vanderbilt University Medical Center. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Brown, R. 2019. *Respiratory health effects, airborne hazard exposures in Southwest Asia Theater of Operations (Desert Shield/Storm)*. Vietnam Veterans of America. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 4, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Bullman T. A., C. M. Mahan, H. K. Kang, and W. F. Page. 2005. Mortality in U.S. Army Gulf War veterans exposed to 1991 Khamisiyah chemical munitions destruction. *American Journal of Public Health* 95(8):1382–1388.

Butzko, R. P., A. M. Sotolongo, D. A. Helmer, J. C. Klein-Adams, O. Y. Osinubi, A. R. Berman, R. Ortiz-Pacheco, and M. J. Falvo. 2019. Forced oscillation technique in veterans with preserved spirometry and chronic respiratory symptoms. *Respiratory Physiology & Neurobiology* 260:8–16.

Chesbrough, K. B., M. A. K. Ryan, P. Amoroso, E. J. Boyko, G. D. Gackstetter, T. I. Hooper, J. R. Riddle, G. C. Gray, and the Millennium Cohort Study Group. 2002. A 21-year prospective cohort study of 140,000 military personnel. *Military Medicine* 167(6):483–488.

Cowan, D. N., J. L. Lange, J. Heller, J. Kirkpatrick, and S. DeBakey. 2002. A case–control study of asthma among U.S. Army Gulf War veterans and modeled exposure to oil well fire smoke. *Military Medicine* 167(9):777–782.

Díaz Santana, M. V., S. Eber, S. Barth, Y. Cypel, E. Dursa, and A. Schneiderman. 2017. Health-related quality of life among U.S. veterans of Operations Enduring Freedom and Operation Iraqi Freedom—Results from a population-based study. *Military Medicine* 182(11/12):e1885–e1891.

Dursa, E. K., S. K. Barth, A. I. Schneiderman, and R. M. Bossarte. 2016. Physical and mental health status of Gulf War and Gulf era veterans. *Journal of Occupational and Environmental Medicine* 58(1):41–46.

Eber, S., S. Barth, H. Kang, C. Mahan, E. Dursa, and A. Schneiderman. 2013. The National Health Study for a New Generation of United States Veterans: Methods for a large-scale study on the health of recent veterans. *Military Medicine* 178(9):966–969.

Eisen, S. A., H. K. Kang, F. M. Murphy, M. S. Blanchard, D. J. Reda, W. G. Henderson, R. Toomey, L. W. Jackson, R. Alpern, et al. 2005. Gulf War veterans' health: Medical evaluation of a U.S. cohort. *Annals of Internal Medicine* 142(11):881–890.

Engelbrecht, J. P., and E. V. McDonald. 2009. Characterizing mineral dusts and other aerosols from the Middle East—Part 1: Ambient sampling. *Inhalation Toxicology* 21:297–326.

Engelbrecht, J. P., E. V. McDonald, J. A. Gillies, and A. W. Gertler. 2008. *Department of Defense Enhanced Particulate Matter Surveillance Program (EPMSP). Final report*. Desert Research Institute, Reno, NV. February 2008 [online]. https://pdfs.semanticscholar.org/18af/a824db71d54eb0242659b5b224c71e32aaba.pdf (accessed May 10, 2020).

Falvo, M. J. 2017. *Effects of deployment exposures on cardiopulmonary and autonomic function (AirHzds)*. https://clinicaltrials.gov/ct2/show/NCT01754922 (accessed May 10, 2020).

Falvo, M. J. 2019. *Effects of deployment exposures on cardiopulmonary and autonomic function*. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Falvo, M. J., J. H. Abraham, O. Y. Osinubi, J. Klein, A. M. Sotolongo, D. Ndirangu, L. A. Patrick-DeLuca, and D. A. Helmer. 2016a. Bronchodilator responsiveness and airflow limitation are associated with deployment length in Iraq and Afghanistan Veterans. *Journal of Occupational and Environment Medicine* 58(4):325–328.

Falvo, M. J., D. A. Helmer, J. C. Klein, O. Y. Osinubi, D. Ndirangu, L. A. Patrick-DeLuca, and A. M. Sotolongo. 2016b. Isolated diffusing capacity reduction is a common clinical presentation in deployed Iraq and Afghanistan veterans with deployment-related environmental exposures. *The Clinical Respiratory Journal* 12:795–798.

Forbes, A. B., D. P. McKenzie, A. J. Mackinnon, H. L. Kelsall, A. C. McFarlane, J. F Ikin, D. C. Glass, and M. R. Sim. 2004. The health of Australian veterans of the 1991 Gulf War: Factor analysis of self-reported symptoms. *Journal of Occupational and Environmental Medicine* 61(12):1014–1020.

Funk, W. E. 2019. *Emerging biomarker approaches and technologies for exposure assessment*. Northwestern University Feinberg School of Medicine. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 4, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Garshick, E. 2019. *Service and health among deployed veterans (SHADE)—Update: VA cooperative study #595: Pulmonary health and deployment to Southwest Asia and Afghanistan*. VA Boston Healthcare System. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Garshick, E., J. H. Abraham, C. P. Baird, P. Ciminera, G. P. Downey, M. J. Falvo, J. E. Hart, D. A. Jackson, M. Jerrett, et al. 2019. Respiratory health after military service in Southwest Asia and Afghanistan—an official American Thoracic Society workshop report. *Annals of the American Thoracic Society* 16(8):e1–e16.

Goss Gilroy Inc. 1998. *Health study of Canadian forces personnel involved in the 1991 conflict in the Persian Gulf*, Vol 1. Ottawa, Canada: Goss Gilroy Inc. and Department of National Defence.

Gray, G. C., R. J. Reed, K. S. Kaiser, T. C. Smith, and V. M. Gastanaga. 2002. Self-reported symptoms and medical conditions among 11,868 Gulf War-era veterans: The Seabee Health Study. *American Journal of Epidemiology* 155(11):1033–1044.

Gwini, S. M., A. B. Forbes, H. L. Kelsall, J. F. Ikin, and M. R. Sim. 2015. Increased symptom reporting persists in 1990–1991 Gulf War veterans 20 years post deployment. *American Journal of Industrial Medicine* 58(12):1246–1254.

Gwini, S. M., H. L. Kelsall, J. F. Ikin, M. R. Sim, A. C. McFarlane, and A. B. Forbes. 2016. New onset of chronic diseases and changes in lifestyle risk factors among Gulf War veterans. *Journal of Occupational and Environmental Medicine* 58(8):770–777.

Hardie, A. 2019. *Respiratory health research: Impact on veterans*. Veterans for Common Sense. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 4, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Helmer, D. 2019. *Update and perspective from the Airborne Hazards and Burn Pits Center of Excellence (AHBPCE)*. Michael E. DeBakey VA Medical Center. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Hill, A. B. 1965. The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine* 58(5):295–300.

Hines, S. E., P. Gucer, S. Kligerman, R. Breyer, J. Centeno, J. Gaitens, M. Oliver, S. Engelhardt, K. Squibb, and M. McDiarmid. 2013. Pulmonary health effects in Gulf War I service members exposed to depleted uranium. *Journal of Occupational and Environmental Medicine* 55(8):937–944.

Hoffman, E. A. 2019. *CT and MRI serving to provide lung structure-function relationships for the phenotyping of lung disease*. University of Iowa Carver College of Medicine. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 4, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Hooper, T. I., S. F. Debakey, K. S. Bells, K. L. Cox, and G. D. Gackstetter. 2008. The Joint Medical Workstation (JMeWS) database in 2003: Intradeployment health encounters of military personnel supporting Operation Enduring Freedom and Iraqi Freedom. *Military Medicine* 173(2):119–128.

Ikin, J. F., M. R. Sim, M. C. Creamer, A. B. Forbes, D. P. McKenzie, H. L. Kelsall, D. C. Glass, A. C. McFarlane, M. J. Abramson, P. Ittak, et al. 2004. War-related psychological stressors and risk of psychological disorders in Australian veterans of the 1991 Gulf War. *British Journal of Psychiatry* 185(2):116–126.

Ikin, J. F., D. P. McKenzie, M. C. Creamer, A. C. McFarlane, H. L. Kelsall, D. C. Glass, A. B. Forbes, K. W. A. Horsley, W. K. Harrex, and M. R. Sim. 2005. War zone stress without direct combat: The Australian naval experience of the Gulf War. *Journal of Traumatic Stress* 18(3):193–204.

Ikin, J. F., D. P McKenzie, S. M. Gwini, H. L. Kelsall, M. Creamer, A. C. McFarlane, D. M. Clarke, B. Wright, and M. Sim. 2015. Major depression and depressive symptoms in Australian Gulf War veterans 20 years after the Gulf War. *Journal of Affective Disorders* 189:77–84.

IOM (Institute of Medicine). 1999. *Gulf War veterans: Measuring health*. Washington, DC: National Academy Press.

IOM. 2006. *Gulf War and health: Volume 4: Health effects of serving in the Gulf War.* Washington, DC: The National Academies Press.

IOM. 2010. *Gulf War and health: Volume 8: Update of health effects of serving in the Gulf War*. Washington, DC: The National Academies Press.

IOM. 2011. *Long-term health consequences of exposure to burn pits in Iraq and Afghanistan*. Washington, DC: The National Academies Press.

Iowa Persian Gulf Study Group. 1997. Self-reported illness and health status among Gulf War veterans. *Journal of the American Medical Association* 277(3):238–245.

Jani, N., M. Falvo, A. Sotolongo, O. Osinubi, C. L. Tseng, M. Rowneki, M. Montopoli, S. Morley, V. Mitchell, and D. Helmer. 2017. Self-reports of constrictive bronchiolitis among service members participating in the Veterans Administration and Department of Defense Airborne Hazards and Open Burn Pit Registry. *Chest* 152(4 Suppl):A822.

Kang, H. K., C. M. Mahan, K. Y. Lee, C. A. Magee, and F. M. Murphy. 2000. Illnesses among United States veterans of the Gulf War: A population-based survey of 30,000 veterans. *Journal of Occupational and Environmental Medicine* 42(5):491–501.

Kang, H. K., B. Li, C. M. Mahan, S. A. Eisen, and C. C. Engel. 2009. Health of U.S. veterans of 1991 Gulf War: A follow-up survey in 10 years. *Journal of Occupational and Environmental Medicine* 51(4):401–410.

Karlinsky, J. B., M. Blanchard, R. Alpern, S. A. Eisen, H. Kang, F. M. Murphy, and D. J. Reda. 2004. Late prevalence of respiratory symptoms and pulmonary function abnormalities in Gulf War I veterans. *JAMA Internal Medicine* 164(22):2488–2491.

Kelsall, H. L., M. J. Sim, A. B. Forbes, D. C. Glass, D. P. McKenzie, J. F. Ikin, M. J. Abramson, L. Blizzard, and P. Ittak. 2004a. Symptoms and medical conditions in Australian veterans of the 1991 Gulf War: Relation to immunisations and other Gulf War exposures. *Journal of Occupational and Environmental Medicine* 61(12):1006–1013.

Kelsall, H. L., M. R. Sim, A. B. Forbes, D. P. McKenzie, D. C. Glass, J. F. Ikin, P. Ittak, and M. J. Abramson. 2004b. Respiratory health status of Australian veterans of the 1991 Gulf War and the effects of exposure to oil fire smoke and dust storms. *Thorax* 59(10):897–903.

Kelsall, H., R. Macdonell, M. Sim, A. Forbes, D. McKenzie, D. Glass, J. Ikin, and P. Ittak. 2005. Neurological status of Australian veterans of the 1991 Gulf War and the effect of medical and chemical exposures. *International Journal of Epidemiology* 34(4):810–819.

Kelsall, H., M. Sim, D. McKenzie, A. Forbes, K. Leder, D. Glass, J. Ikin, and A. McFarlane. 2006. Medically evaluated psychological and physical health of Australian Gulf War veterans with chronic fatigue. *Journal of Psychosomatic Research* 60(6):575–584.

Kelsall, H. L., M. R. Sim, J. F. Ikin, A. B. Forbes, D. P. McKenzie, D. C. Glass, and P. Ittak. 2007. Reproductive health of male Australian veterans of the 1991 Gulf War. *BMC Public Health* 7:79.

Kelsall, H. L., D. P. McKenzie, M. R. Sim, K. Leder, A. B. Forbes, and T. Dwyer. 2009. Physical, psychological, and functional comorbidities of multisymptom illness in Australian male veterans of the 1991 Gulf War. *American Journal of Epidemiology* 170(8):1048–1056.

Kelsall, H. L., D. P. McKenzie, A. B. Forbes, M. H. Roberts, D. M. Urquhart, and M. R. Sim. 2014. Pain-related musculoskeletal disorders, psychological comorbidity, and the relationship with physical and mental well-being in Gulf War veterans. *Pain* 155(4):685–692.

Khalil, L., R. B. McNeil, K. J. Sims, K. A. Felder, E. R. Hauser, K. M. Goldstein, C. I. Voils, N. G. Klimas, M. T. Brophy, C. M. Thomas, et al. 2018. The Gulf War Era Cohort and Biorepository: A longitudinal research resource of veterans of the 1990–1991 Gulf War Era. *American Journal of Epidemiology* 187(11):2279–2291.

Klimas, N. 2019. *Military veteran biorepositories*. Miami VA Medical Center. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Krefft, S. D., M. Strand, J. Smith, C. Stroup, R. Meehan, and C. Rose. 2017. Utility of lung clearance index testing as a noninvasive marker of deployment-related lung disease. *Journal of Occupational and Environmental Medicine* 59(8):707–711.

Krefft, S. D., J. Wolff, L. Zell-Baran, M. Strand, E. B. Gottschall, R. Meehan, and C. S. Rose. 2020. Respiratory diseases in post-9/11 military personnel following Southwest Asia deployment. *Journal of Occupational and Environmental Medicine* 62(5):337–343.

Lange, J. L., D. A. Schwartz, B. N. Doebbeling, J. M. Heller, and P. S. Thorne. 2002. Exposures to the Kuwait oil fires and their association with asthma and bronchitis among Gulf War veterans. *Environmental Health Perspectives* 110(11):1141–1146.

Lindheimer, J. B., D. B. Cook, J. C. Klein-Adams, W. Qian, H. Z. Hill, G. Lange, D. S. Ndirangu, G. R. Wylie, and M. J. Falvo. 2019. Veterans with Gulf War illness exhibit distinct respiratory patterns during maximal cardiopulmonary exercise. *PLOS ONE* 14(11):1–14.

Madar, C. S., M. R. Lewin-Smith, T. J. Franks, R. A. Harley, J. S. Klaric, and M. J. Morris. 2017. Histological diagnoses of military personnel undergoing lung biopsy after deployment to Southwest Asia. *Lung* 195(4):507–515.

Maule, A. L., P. A. Janulewicz, K. A. Sullivan, M. H. Krengel, M. K. Yee, M. McClean, and R. F. White. 2018. Meta-analysis of self-reported health symptoms in 1990–1991 Gulf War and Gulf War-era veterans. *BMJ Open* 8:e016086.

Mauzy, C. 2019. *Toxicity evaluation and biomarker identification in rats exposed to burn pit emissions and respirable sand from Afghanistan*. Air Force Research Laboratory. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 4, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

McKenzie, D. P., J. F. Ikin, A. C. McFarlane, M. Creamer, A. B. Forbes, H. L. Kelsall, D. C. Glass, P. Ittak, and M. R. Sim. 2004. Psychological health of Australian Veterans of the 1991 Gulf War: An assessment using the SF-12, GHQ-12 and PCL-S. *Psychological Medicine* 34(8):1419–1430.

Morris, M. J. 2019a. *STAMPEDE studies of post-deployment respiratory symptoms*. Brooke Army Medical Center. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Morris, M. J. 2019b. *Pre post deployment spirometry*. Brooke Army Medical Center. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Morris, M. J., R. T. Oleszewski, J. B. Sterner, and P. F. Allan. 2013. Vocal cord dysfunction related to combat deployment. *Military Medicine* 178(11):1208–1212.

Morris, M. J., D. W. Dodson, P. F. Lucero, G. D. Haislip, R. A. Gallup, K. L. Nicholson, and L. L. Zacher. 2014. Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE). *American Journal of Respiratory and Critical Care Medicine* 190(1):77–84.

Morris, M. J., A. J. Skabelund, F. A. Rawlins, R. A. Gallup, J. K. Aden, and A. B. Holley. 2019. Study of Active Duty Military Personnel for Environmental Deployment Exposures: Pre- and Post-Deployment Spirometry (STAMPEDE II). *Respiratory Care* 64(5):536–544.

Morris, M. J., R. J. Walter, E. T. McCann, J. H. Sherner, C. G. Murillo, B. S. Barber, J. C. Hunninghake, and A. B. Holley. 2020. Clinical evaluation of deployed military personnel with chronic respiratory symptoms—Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE) III. *Chest* 157(6):1559–1567.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2016. *Gulf War and health: Volume 10: Update of health effects of serving in the Gulf War, 2016*. Washington, DC: The National Academies Press.

NASEM. 2017. *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry*. Washington, DC: The National Academies Press.

NASEM. 2020. *Assessment of long-term health effects of antimalarial drugs when used for prophylaxis*. Washington, DC: The National Academies Press.

NRC (National Research Council). 2010. *Review of the Department of Defense Enhanced Particulate Matter Surveillance Program report*. Washington, DC: The National Academies Press.

Patterson, S. 2019. *Exposure assessment in a military environment: Perspectives from the field*. Johns Hopkins University Applied Physics Laboratory. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 4, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Porter, B., K. Long, R. P. Rull, and E. K. Dursa. 2020. Prevalence of chronic multisymptom illness/Gulf War illness over time among Millennium Cohort participants, 2001 to 2016. *Journal of Occupational and Environmental Medicine* 62(1):4–10.

Pugh, M. J., C. A. Jaramillo, K. Leung, P. Faverio, N. Fleming, E. Mortensen, M. E. Amuan, C. Wang, B. Eapen, M. Restrepo, and M. J. Morris. 2016. Increasing prevalence of chronic lung disease in veterans of the wars in Iraq and Afghanistan. *Military Medicine* 181(5):476–481.

Reibman, J. 2019. *Respiratory health outcomes in community members exposed to environmental toxins: Lessons learned from the WTC disaster*. World Trade Center Environmental Health Center. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Rivera, A. C., T. M. Powell, E. J. Boyko, R. U. Lee, D. J. Faix, D. D. Luxton, and R. P. Rull. 2018. New-onset asthma and combat deployment: Findings from the Millennium Cohort Study. *American Journal of Epidemiology* 187(10):2136–2144.

Rohrbeck, P., Z. Hu, and T. M. Mallon. 2016. Assessing health outcomes after environmental exposures associated with open pit burning in deployed U.S. service members. *Journal of Occupational and Environmental Medicine* 58(85):S104–S110.

Rull, R. 2019. *The Millennium Cohort Study: Respiratory health research*. Naval Health Research Center. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Schneiderman, A. 2019. *National Health Study for a New Generation of U.S. Veterans and Comparative Health Assessment Interview (CHAI) research study*. VA Post Deployment Health Services. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Schneiderman, A., F. Akhtar, J. Blosnich, Y. Cypel, V. Davey, M. Dichter, E. Dursa, D. R. Garfin, C. Hoffmire, E. Ishii, S. Maguen, S. Smith, and D. Vogt. 2020. *Comparative Health Assessment Interview research study*. Department of Veterans Affairs. https://www.publichealth.va.gov/epidemiology/studies/CHAI-study.asp (accessed May 10, 2020).

Sharkey, J. M., C. Baird, A. Eick-Cost, L. Clark, Z. Hu, S. Ludwig, and J. Abraham. 2015. Review of epidemiological analyses of respiratory health outcomes after military deployment to burn pit locations with respect to feasibility and design issues highlighted by the Institute of Medicine. In C. P. Baird and D. K. Harkins (eds.), *Airborne hazards related to deployment*. Fort Sam Houston, TX: Borden Institute, U.S. Army Medical Department Center and School. Pp. 291–304.

Sharkey, J. M., J. H. Abraham, L. L. Clark, P. Rohrbeck, S. L. Ludwig, Z. Hu, and C. P. Baird. 2016. Postdeployment respiratory health care encounters following deployment to Kabul, Afghanistan: A retrospective cohort study. *Military Medicine* 181(3):265–271.

Shrier, I., and R. W. Platt. 2008. Reducing bias through directed acyclic graphs. *BMC Medicine Respiratory Methodology* 8(1):70.

Sim, M., M. Abramson, A. Forbes, D. Glass, J. Ikin, P. Ittak, H. Kelsall, K. Leder, D. McKenzie, J. McNeil, M. Creamer, and L. Fritschi. 2003. *Australian Gulf War Veterans' Health Study*. Canberra, Australia: Department of Veterans' Affairs. https://www.dva.gov.au/sites/default/files/files/consultation%20and%20grants/healthstudies/gulfwar/gulfwarvolone.pdf (accessed June 16, 2020).

Sim, M., D. Clarke, B. Forbes, D. Glass, S. Gwini, J. Ikin, H. Kelsall, D. McKenzie, B. Wright, A. McFarlane, M. Creamer, and K. Horsley. 2015. *Australian Gulf War Veterans' Follow Up Health Study—Technical report 2015*. Canberra, Australia: Department of Veterans' Affairs. https://www.dva.gov.au/sites/default/files/files/consultation%20and%20grants/healthstudies/gulfwar/follow_up2015/aus_gulf_war_follow_up_tech_report2015.pdf (accessed April 1, 2019).

Simmons, R., N. Maconochie, and P. Doyle. 2004. Self-reported ill health in male UK Gulf War veterans: A retrospective cohort study. *BMC Public Health* 4(1):27.

Smith, B., T. C. Smith, M. A. K. Ryan, and G. C. Gray. 2006. A comparison of the postdeployment hospitalization experience of U.S. military personnel following service in the 1991 Gulf War, Southwest Asia after the Gulf War, and Bosnia. *Journal of Occupational Environmental Hygiene* 3(12):660–670.

Smith, B., L. K. Chu, T. C. Smith, P. J. Amoroso, E. J. Boyko, T. I. Hooper, G. D. Gackstetter, and M. A. K. Ryan. 2008. Challenges of self-reported medical conditions and medical records among members of a large military cohort. *BMC Medicine Respiratory Methodology* 8(37):1–10.

Smith, B., C. A. Wong, T. C. Smith, E. J. Boyko, G. D. Gackstetter, and M. A. K. Ryan. 2009. Newly reported respiratory symptoms and conditions among military personnel deployed to Iraq and Afghanistan: A prospective population-based study. *American Journal of Epidemiology* 170(11):1433–1442.

Smith, B., C. A. Wong, E. J. Boyko, C. J. Philips, G. D. Gackstetter, M. A. K. Ryan, and T. C. Smith. 2012. The effects of exposure to documented open-air burn pits on respiratory health among deployers of the Millennium Cohort Study. *Journal of Occupational Environmental Medicine* 54(6):708–716.

Smith, T. C., J. M. Heller, T. I. Hooper, G. D. Gackstetter, and G. C. Gray. 2002. Are Gulf War veterans experiencing illness due to exposure to smoke from Kuwaiti oil well fires? Examination of Department of Defense hospitalization data. *American Journal of Epidemiology* 155(10):908–917.

Statistics Canada. 2005. *The Canadian Persian Gulf Cohort Study: Detailed report*. Prepared by Statistics Canada for the Gulf War Veterans Cohort Study Advisory Committee. https://www.veterans.gc.ca/pdf/about-us/research-directorate/gulf-war-linkage-project.pdf (accessed May 15, 2020).

Steele, L. 2000. Prevalence and patterns of Gulf War illness in Kansas veterans: Association of symptoms with characteristics of person, place, and time of military service. *American Journal of Epidemiology* 152(10):992–1002.

Sullivan, K. 2019. *Military veteran biorepositories*. Boston University School of Public Health. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Therkorn, J. 2019. *Exposure assessment in a military environment: Tools and methods*. Johns Hopkins University Applied Physics Laboratory. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 4, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Unwin, C., N. Blatchley, W. Coker, S. Ferry, M. Hotopf, L. Hull, K. Ismail, I. Palmer, A. David, and S. Wessely. 1999. Health of UK servicemen who served in Persian Gulf War. *Lancet* 353:169–178.

Uppal, K. 2019. *Application of high-resolution metabolomics, data science, and integrative omics to evaluate health effects of environmental exposures*. Emory University School of Medicine. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

VA (Department of Veterans Affairs). 2019. *Gulf War service*. https://www.publichealth.va.gov/exposures/gulfwar/military-service.asp (accessed May 10, 2020).

VA. 2020. *War Related Illness and Injury Study Center*. https://www.warrelatedillness.va.gov (accessed May 10, 2020).

Waters, K. 2019. *Biomarker strategies for exposure and response*. Pacific Northwest National Laboratory. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 4, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Wu, R. R. *Gulf War era cohort and biorespository project (CSP 585)*. Durham VA Cooperative Studies Program Epidemiology Center. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www8.nationalacademies.org/pa/projectview.aspx?key=HMD-BPH-18-09; under "Events," "Oct 3, 2019."

Zundel, C. G., M. H. Krengel, T. Heeren, M. K. Yee, C. M. Grasso, P. A. Janulewicz Lloyd, S. S. Coughlin, and K. Sullivan. 2019. Rates of chronic medical conditions in 1991 Gulf War veterans compared to the general population. *International Journal of Environmental Research and Public Health* 16(6):949.

4

Evaluation of Respiratory Outcomes

Veterans who were deployed to the Southwest Asia Theater of Military Operations, in support of either the 1990–1991 Gulf War or post-9/11 conflicts, have consistently reported having poorer health and quality of life than veterans who served in the military during these conflicts but who were not deployed or were deployed elsewhere. This increase in adverse health effects has been seen not only in U.S. veterans but also in veterans of the coalition forces, including Australia, Canada, Denmark, and the United Kingdom. Although other reports (notably the *Gulf War and Health* series) have reviewed all health outcomes generally grouped by body system, this chapter examines the epidemiologic studies that focused on symptoms, conditions, and diseases of the respiratory tract and their relationship with exposure to airborne hazards from serving in Southwest Asia.

The spectrum of respiratory outcomes of interest is presented in order of nonspecific to more specific and moves through the respiratory tract from the nasal passages to the lungs. It begins with respiratory symptoms, including cough, wheeze, and shortness of breath, which are followed by upper airway conditions, including sinusitis and rhinitis, vocal cord dysfunction, and sleep apnea. A discussion of pulmonary function tests and the epidemiologic studies that used these objective measures is then presented because many of the conditions of the lower airway—the next section—reference those measures. Included in lower airway conditions and diseases are asthma; chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema; constrictive bronchiolitis; interstitial lung disease, which includes diagnoses of hypersensitivity pneumonitis, sarcoidosis, acute eosinophilic pneumonia, and pulmonary alveolar proteinosis; and infectious diseases of the lower airway. The available epidemiologic evidence on respiratory cancers is then described. The final outcome included in this chapter is mortality from respiratory diseases.

Each respiratory condition section starts with an overview of the condition, its symptoms, its diagnostic criteria and pathology where applicable, and its prevalence in the general U.S. population. That is followed by a summary of findings on that outcome from epidemiologic studies that were considered in previous National Academies assessments of respiratory health and military service in Southwest Asia. Those studies were not reassessed by the current committee; instead the committee relied on the assessments and inferences of those previous committees regarding those studies. Summaries and assessments of newly identified epidemiologic studies[1] are then presented,

[1] Appendix C presents a table overview of the 57 newly reviewed epidemiologic studies that summarizes the study population, conflicts served (1990–1991 Gulf War or post-9/11), and respiratory outcomes assessed in each. Studies that used cohorts as specifically mentioned in the Statement of Task are noted.

ordered by conflict (post-9/11[2] first and 1990–1991 Gulf War second) and by country of origin; studies of U.S. military personnel are presented first, followed by studies of coalition forces. Within the post-9/11 literature, the studies are summarized with those from cohorts listed in the committee's Statement of Task presented first, when applicable: Millennium Cohort Study, Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE), National Health Study for a New Generation of U.S. Veterans (NewGen), Comparative Health Assessment Interview (CHAI) Study, Pulmonary Health and Deployment to Iraq and Afghanistan Objective Study, Effects of Deployment Exposures on Cardiopulmonary and Autonomic Function Study, and research being conducted by the Department of Veterans Affairs' War Related Illness and Injury Study Center (WRIISC) Airborne Hazards Center of Excellence. Then other studies of military personnel and veterans are summarized. Information on the committee's process and criteria for identifying, reviewing, and assessing the literature as well as a description of the categories of association the committee used may be found in Chapter 3. Several of the studies reported results pertaining to multiple respiratory outcomes of interest. To minimize repetition, those studies are described in detail in Chapter 3, and only the relevant results pertaining to the outcome of interest are summarized in each section. The 32 studies that are summarized in Chapter 3 are Abraham and Baird, 2012; Abraham et al., 2014; AFHSC, 2010; Baird et al., 2012; Barth et al., 2014; Bullman et al., 2005; Dursa et al., 2016b; Eisen et al., 2005; Hines et al., 2013; Hooper et al., 2008; Kang et al., 2000; Karlinsky et al., 2004; Kelsall et al., 2004; Khalil et al., 2018; Krefft et al., 2017, 2020; Madar et al., 2017; Maule et al., 2018; Morris et al., 2014, 2019, 2020; NASEM, 2017; Pugh et al., 2016; Rohrbeck et al., 2016; Sharkey et al., 2015, 2016; Sim et al., 2015; Smith et al., 2002, 2008, 2009, 2012; and Zundel et al., 2019.

Each condition section ends with a synthesis of the findings and inferences that can be made from the epidemiologic literature on that condition, which is followed by a conclusion concerning the strength of the association between exposure to airborne hazards as encountered in the Southwest Asia theater and the condition of interest. Where the data permit, a conclusion is specific to the strength of the evidence by conflict cohort (1990–1991 Gulf War and post-9/11).

The committee relied on human epidemiologic studies to draw its conclusions about the strength of evidence regarding associations between deployment to Southwest Asia and respiratory health conditions observed in military personnel and veterans. Descriptive studies that present frequencies without modeling risk or odds and case series that lack a comparison group are included for completeness, especially for rare outcomes where there is a dearth of epidemiologic evidence. Often deployment is used as a surrogate of exposure, and a common comparison group is nondeployed individuals who served in the armed forces during the same time period. However, deployed service members experience different exposures for different durations, which may result in misclassification of exposure that would likely lead to underestimating associations. Inasmuch as military personnel must meet physical-health criteria when they enter the military and during the time they are on active duty, particularly when deployed, the group's health status is usually better than that of their nondeployed counterparts or of the general population of the same age and sex. Further complicating the assessment of veterans' health is that the diagnostic criteria or definitions for health conditions may be revised to reflect the evolving understanding of these conditions brought on by scientific and medical advances. These types of changes are normal in medical science, and it is likely that the diagnostic criteria for these conditions will further change in the future as knowledge about them grows. As future bodies review and compare studies using the old criteria and new diagnostic criteria, there may be differences in the incidence or prevalence of a condition that may result from the use of the revised criteria.

RESPIRATORY SYMPTOMS

Respiratory symptoms are relatively common and nonspecific. Several symptom complexes sometimes occur without definitive underlying diagnoses, such as chronic persistent cough, dyspnea, and wheezing. Broadly speaking, chronic persistent cough is a cough that lasts longer than 8 weeks but typically disappears once an underlying problem is treated. Chronic cough is associated with sleep disruption and can leave patients feeling exhausted.

[2] As discussed in Chapter 1, the primary post-9/11 U.S. military operations in the Southwest Asia theater were Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND).

Severe cases of chronic cough can cause vomiting, lightheadedness, and rib fractures. Conditions typically associated with chronic cough include the following, either alone or in combination: post-nasal drip, asthma, gastroesophageal reflux disease, lung infections, and COPD. The use of various drugs, including drugs for treating high blood pressure, may also result in chronic cough (Mayo Clinic, 2019a). Additionally, chronic cough can have a psychogenic origin. Occupational and environmental risk factors include outdoor air pollution and allergens and also indoor irritant and allergenic agents, such as cigarette smoke, cooking fumes, animals, dust mites, fungi, and cockroaches (Tarlo, 2006). The population prevalence of chronic cough in the United States is estimated to be between 10% and 15% of the adult population (Song et al., 2015).

Dyspnea, or shortness of breath, is a sensation of difficulty breathing, breathlessness, or even suffocation. Chronic dyspnea is often associated with chronic respiratory diseases, including asthma, COPD, and interstitial lung diseases, such as pulmonary fibrosis (Mayo Clinic, 2019b). As is the case with chronic cough, dyspnea also has psychogenic causes. The prevalence of chronic dyspnea is highly variable, depending on the etiology (Rawat et al., 2019).

Wheeze is a high-pitched whistling sound made with breathing that occurs most commonly on expiration, although it can also be heard on inspiration. While typically associated with asthma or, less commonly COPD, it is a nonspecific finding that can be reported with several conditions, including congestive heart failure. In the studies reviewed, wheeze was based largely on self-report, although the use of *International Classification of Diseases* (ICD) coding to detect symptoms may also have included wheeze detected on physical examination. The value of self-reported wheeze is diminished by the variability in what patients understand to be wheeze; although this is true to some extent of all self-reported symptoms, it is especially acute with wheeze. For example, upper airway sounds will often be described by patients as wheeze.

Respiratory symptoms are arguably the most commonly studied health outcomes in association with deployment in the Southwest Asia Theater of Military Operations. This may be because they were often the only set of outcomes associated with any number of possible exposures; the fact that they are often observed in the absence of any other detectable respiratory health conditions; and, in many instances, they are among the earliest signs of health outcomes to be exhibited following an adverse respiratory exposure.

There are nevertheless significant challenges in interpreting findings of studies of respiratory symptoms, some of which are related to the nature of symptoms themselves as outcomes and others of which are specific to military deployment. These challenges need to be kept in mind when assessing studies that present information on symptoms. First, information on symptoms is typically collected through self-report. As such, symptoms are notoriously susceptible to information bias. In the military deployment setting, differential misclassification of the outcome can occur if those who have respiratory symptoms are more likely to recall inhalational exposures than those who are asymptomatic, or alternatively, if those who experienced inhalational exposures are more likely to report symptoms for any given degree of exposure. Second, and related to the first challenge, symptoms are subjective. Third, it can be difficult to be confident that symptoms did not predate exposure, such as an exposure during deployment, making it challenging to attribute reports of symptoms to deployment-related exposures.

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports

In general, previous *Gulf War and Health* committees grouped all non-cancerous respiratory conditions, including symptoms to specific diagnoses, together when summarizing the available literature. Over the course of the series, 15 studies included symptom outcomes. Those committees categorized studies as primary or secondary studies. In the current assessment, studies are grouped into those reviewed in previous reports and newer studies that have not been previously reviewed. Newer studies are then further categorized into those conducted using populations of U.S. military personnel and those using populations from other Gulf War coalition force countries. These are then classified into those investigating effects of deployment in general and those investigating specific exposures, such as burn pit exposures.

Symptoms were ascertained primarily by self-report, and most of these studies found that deployed veterans report higher levels of respiratory symptoms than nondeployed veterans regardless of country of origin. This trend continues even when studies were conducted several years after deployment. Each study suffers from various methodologic weaknesses. The results related to respiratory symptoms are summarized below, but the uniformity of findings is striking, especially given that the same studies found Gulf War deployment status to be statistically significantly associated with self-reports of respiratory symptoms among cohorts of U.S., UK, and Australian veterans. The prior Gulf War and Health committees made conclusions based on grouping all respiratory symptoms and conditions and did not make separate conclusions for specific respiratory outcomes (Volumes 4, 8, and 10). The Volume 4 committee concluded

> Respiratory symptoms are strongly associated with Gulf War deployment when using comparison groups of non-deployed veterans in most studies addressing this question. However, studies with objective pulmonary function measures find no association between respiratory illnesses with Gulf War deployment across the four cohorts in which this has been investigated. (IOM, 2006, p. 9)

The Volume 6 (IOM, 2008) committee was tasked with assessing the long-term health effects of deployment-related stress, and as such included respiratory outcomes. Based on several epidemiologic studies, including those that examined posttraumatic stress disorder and respiratory disease, that committee concluded that there was inadequate/insufficient evidence to determine whether an association exists between deployment to a war zone and chronic respiratory effects. The Volume 8 committee found that "self-reported symptoms and self-reported diagnoses related to respiratory disease have inconsistently but frequently shown an excess among Gulf War veterans" (IOM, 2010, p. 149). However, that committee also found that there appeared to be no increase in respiratory disease among Gulf War veterans when examined with objective measures of disease, pulmonary function studies, or mortality studies. Based on those findings, the Volume 8 committee concluded that there was insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and respiratory disease. That committee also concluded that there was limited/suggestive evidence of no association between deployment to the Gulf War and decreased lung function in the first 10 years after the war. Based on three newly identified studies of respiratory conditions and data submitted by the Department of Veterans Affairs (VA), the Volume 10 committee concurred with the Volume 8 committee and concluded that there is insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and respiratory disease. However, in a change from Volumes 4 and 8, the Volume 10 committee also concluded that there was limited/suggestive evidence of no association between deployment to the Gulf War and decreased lung function.

The committees of Volumes 2 (IOM, 2003a) and 9 (IOM, 2014) made conclusions specific to respiratory symptoms (grouped) based on associations with specific exposures, including insecticides, organic solvents, and mixtures (Volume 2) and blasts (Volume 9). The Volume 2 committee found that the available literature consisted primarily of cross-sectional studies on lung function that did not examine long-term, persistent outcomes after cessation of exposure, and many studies did not control for confounding by smoking and other common causes of lung disease. Therefore, the Volume 2 committee concluded that there was

- inadequate/insufficient evidence to determine whether an association exists between exposure to the insecticides that they were tasked to examine and persistent respiratory symptoms or impairment after cessation of exposure;
- limited/suggestive evidence of an association between high-level exposure to mixtures of organic solvents and reactive airways dysfunction syndrome, which would be evident with exposure and could persist for months or years; and
- inadequate/insufficient evidence to determine whether an association exists between exposure to the specific organic solvents examined or solvent mixtures and persistent respiratory symptoms or impairment after cessation of exposure.

The Volume 9 committee examined the evidence that exposure to explosive blasts may have on long-term effects on pulmonary function, respiratory symptoms, and exercise limitation as well as long-term effects after acute blast lung injury. Of the approximately 45 published peer-reviewed studies on long-term respiratory health effects of blast exposure considered, all were considered to be methodologically lacking. Acute injuries to the respiratory tract are quite common after blasts, but despite the obvious acute injuries and the high plausibility of long-term sequelae, the Volume 9 committee found that there was a dearth of data on the long-term pulmonary outcomes of exposure to blast, and that the possibility of other long-term pulmonary consequences of blast exposure, such as the effect of explosion-related dust exposure, and of other exposures, such as smoking, had not been adequately examined. Therefore, the Volume 9 committee concluded that there was inadequate/insufficient evidence of an association between exposure to blast and long-term effects on pulmonary function, respiratory symptoms, exercise limitation, and long-term effects after acute blast lung injury.

1990–1991 Gulf War Veterans

The National Health Survey of Gulf War Era Veterans and Their Families (NHS), described in Chapter 3, is a population-based survey of U.S. Gulf War veterans that was conducted to estimate the prevalence of symptoms and other health outcomes in Gulf War veterans (n = 15,000) versus Gulf War–era veterans (n = 15,000) who were not deployed to the Persian Gulf (Kang et al., 2000). Questions regarding respiratory symptoms asked about coughing, shortness of breath, wheezing, and tightness in chest, with the severity of each also indicated (mild, severe, and total). Population prevalence rates were calculated using statistical analysis techniques to account for stratified random sampling of unequal probabilities of selecting various strata. Coughing was reported by 24% of deployed Gulf War veterans compared with 14% of nondeployed veterans (rate difference [RD] = 10, 95% confidence interval [CI] 9.9–10.1); and shortness of breath by 24% of deployed veterans compared with 11% of nondeployed veterans (RD = 13, 95%CI 12.9–13.1). Wheezing (22% vs 11%; RD = 11, 95%CI 10.9–11.1) and tightness in chest (21% vs 11%; RD = 10, 95%CI 9.9–10.1) were also reported nearly twice as frequently by deployed than by nondeployed veterans. Rate differences of the total frequencies were statistically significant ($p \leq 0.05$) for all four outcomes. Smoking was not controlled for in the analyses; the authors note that a significantly higher proportion of Gulf War veterans than Gulf War–era veterans were smokers (34.7% vs 29.9%).

Karlinsky et al. (2004) collected data on pulmonary histories (including self-reported cough, sputum production, and shortness of breath when climbing stairs) and objective measurements of pulmonary function from 1,036 deployed and 1,103 nondeployed veterans who completed the clinical examination component of the third phase of the NHS. Examinations were performed 10 years after the 1990–1991 Gulf War. Deployed veterans were statistically significantly more likely than era veterans to self-report history of smoking (odds ratio [OR] = 1.31, 95%CI 1.03–1.67) and, separately, wheezing (OR = 1.67, 95%CI 1.06–2.62), but there was no difference between the groups for cough (OR = 1.12, 95%CI 0.80–1.57). Estimates for wheezing and cough were not adjusted for smoking status. Sputum production data were collected, but results were not reported.

Eisen et al. (2005) performed a cross-sectional analysis on health outcomes collected in a subset of 1,061 deployed and 1,128 nondeployed Gulf War veterans (the same population used by Karlinsky et al., 2004) who completed the clinical examination component of the third phase of the NHS. The investigators examined several outcomes, including "obstructive lung disease," which was defined as "a history of lung disease (asthma, bronchitis, or emphysema) or pulmonary symptoms (wheezing, dyspnea on exertion, or persistent coughing with phlegm) and either the use of bronchodilators or at least 15% improvement in FEV_1[3] after a short-acting bronchodilator" (Eisen et al., 2005, p. 884). No difference in these outcomes was found between deployed and nondeployed veterans (OR = 0.91, 95%CI 0.52–1.59); analyses were adjusted for age, sex, race, years of education, cigarette smoking, component (active versus reserves or National Guard), service branch, and rank. No findings on specific respiratory symptoms were reported.

Several other studies that reported on respiratory symptoms were conducted using specific subsets of U.S. 1990–1991 Gulf War veterans, identified by branch of service, military occupation, base location, or home state of residence.

The "Iowa study" was a cross-sectional survey of a representative sample of 4,886 military personnel from all service branches who were randomly selected from those who had listed Iowa as their home of record at the time of enlistment (Iowa Persian Gulf Study Group, 1997). Trained examiners using standardized questions, instruments, and scales interviewed the subjects. It was the first major population-based study of U.S. Gulf War veterans to group sets of symptoms into categories suggestive of known syndromes or disorders, such as fibromyalgia or

[3] The amount of air that can be forcibly exhaled in 1 second after taking in the deepest breath possible.

depression. This work led to future research on what would become known as Gulf War illness. Doebbeling et al. (2000) conducted a factor analysis to identify patterns of symptoms and also reported higher frequency of both congested mucus or phlegm (10% difference, 95%CI 8–12) and bothered by a cough (10% difference; 95%CI 8–12) between deployed and nondeployed veterans to the Persian Gulf.

Proctor et al. (1998) examined nearly 300 service members who represented a stratified random sample of 2,949 troops from Fort Devens and 928 troops from New Orleans; both groups consisted of active-duty, reserve, and National Guard troops. The comparison group was Germany-deployed veterans from an air ambulance company (n = 48). The study described self-reported exposures to a variety of agents and included measures on the Expanded Combat Exposure Scale regarding exposure to chemical- and biologic-warfare agents. Relevant respiratory exposures included pesticides, chemical- and biologic-warfare agents, oil fire smoke, vehicle exhaust, smoke from tent heaters, and smoke from burning human waste. In comparison with veterans deployed to Germany during the Gulf War era, stratified random samples of both Gulf War cohorts (Fort Devens and New Orleans) had an increased prevalence of 51 out of 52 items on a health-symptom checklist, including pulmonary symptoms of "difficulty breathing or shortness of breath," "common cold or flu," and "rapid breathing." ORs weighted for sampling design and participation base and adjusted for age, sex, and education (but not smoking, which was collected) were elevated for pulmonary symptoms for both deployed groups compared with Germany-deployed veterans but were not statistically significant.

Petruccelli et al. (1999) conducted a study of self-administered questionnaires from 1,599 U.S. soldiers from the 11th Armored Cavalry Regiment after their return from a 3-month mission in 1991 in Kuwait. Symptoms occurring before, during, and after the mission were collected, and each symptom was accompanied by a four-level frequency scale (never, occasionally, most days, and every day). Smoking status and changes in frequency were also captured; 45% of respondents were regular smokers or had been smokers at some time, 25% reported smoking more in Kuwait, and 12% reported smoking less or quitting. Compared with baseline (while the unit was based in Germany), respiratory symptoms reported more frequently for the Kuwait period were upper respiratory tract irritation, shortness of breath, and cough. Of the relatively few troops whose responses on wheezing changed, there were more than twice as many wheezing frequently while in Kuwait as there were during the post-return period. The proportion of soldiers recalling a recurrent cough in Kuwait was nearly twice as high among smokers (28.0%) as among nonsmokers (15.5%), but smoking status was not reported to correlate with other symptoms. Comparisons of soldiers with a self-reported history of allergies or asthma with those without these conditions showed soldiers with the conditions reported a higher incidence of shortness of breath (17.6% vs 8.6%) and cough (27.8% vs 18.8%) associated with the Kuwait period. Shortness of breath and fatigue were lower than baseline after soldiers returned to Germany. Cough, however, was substantially more frequent within a month after the Kuwait experience compared with what respondents considered normal for themselves. Shortness of breath and cough were both more likely to be reported for soldiers who reported spending more than 5 hours per day outdoors, felt that the oil-well fires were more severe than expected, had a different job than at their home base, reported flying insects to have been a significant problem, thought pollution was the worst part of deployment, noted heat exhaustion as problematic, and were injured in an ammunition dump explosion. Other factors were statistically significantly associated with new-onset or exacerbations of shortness of breath or cough separately. The proportion of respondents with symptoms occurring every day or most days increased with decreasing distance to fires; the strongest correlation with distance was demonstrated for cough.

Gray et al. (1999) included cough and shortness of breath in their examination of several self-reported conditions and symptoms among 527 deployed and 970 nondeployed active-duty Seabees (U.S. Navy construction battalions). Odds of having both cough (OR = 1.8, 95%CI 1.2–2.8) and shortness of breath (OR = 4.0, 95%CI 2.2–7.3) lasting at least 1 month were statistically significantly increased for deployed Seabees relative to nondeployed Seabees. When symptoms were compared by exposure categories among the deployed veterans, elevated ORs ($p < 0.05$) for cough were found for veterans exposed to airborne hazards of smoke from oil-well fires, airplane fuel burned in tent heaters, and petroleum solutions sprayed over large areas as well as for those who used pyridostigmine bromide and ciprofloxacin. ORs for shortness of breath were statistically significantly increased for veterans exposed to airborne hazards of smoke from oil-well fires and petroleum solutions sprayed over large areas.

Gray et al. (2002) expanded the deployed and nondeployed cohorts that were first reported in Gray et al. (1999) to include all Seabees who had been on active duty during the time of the Gulf War regardless of whether they remained on active duty, were in the reserve, or had separated from service (n = 11,868 participants, 67.4% participation rate). Participants were divided into three exposure groups: 3,831 who had been deployed to the Gulf War, 4,933 who had been deployed elsewhere, and 3,104 who had not been deployed. Those who had been deployed to the Gulf theater had statistically significantly higher odds of ever smoking compared with nondeployed Seabees (OR = 3.09, 95%CI 2.79–3.42) and of current smoking compared with both Seabees deployed elsewhere (OR = 1.20, 95%CI 1.09–1.31) and nondeployed Seabees (OR = 2.68, 95%CI 2.37–3.04). When asked about shortness of breath, continual cough, and several other medical problems experienced in the past 12 months, Gulf theater–deployed Seabees reported higher frequencies of all 33 outcomes. Following adjustment for age, gender, active-duty versus reserve status, race/ethnicity, current smoking, and current alcohol drinking, ORs were statistically significantly elevated for shortness of breath for Gulf theater–deployed Seabees compared with both Seabees deployed elsewhere (OR = 3.14, 95%CI 2.68–3.68) and nondeployed Seabees (OR = 3.62, 95%CI 3.01–4.51). The odds of continual cough were also statistically significantly higher for Gulf theater–deployed Seabees compared with both Seabees deployed elsewhere (OR = 3.03, 95%CI 2.48–3.71) and nondeployed Seabees (OR = 2.70, 95%CI 2.11–3.44).

Using lists of eligible veterans from the Department of Defense (DoD), Steele (2000) conducted a population-based survey of veterans who listed Kansas as their home state of record (1,548 deployed and 482 nondeployed) and examined factors that may be related to Gulf War illness. The survey asked about 16 specific medical or psychiatric conditions, 37 symptoms, locations during the Gulf War (including whether the veterans were notified about the Khamisiyah demolitions), and vaccinations. Comparing deployed veterans with the nondeployed veterans after adjustment for sex, age, income, and education level, ORs were elevated for difficulty breathing or catching breath (OR = 4.09, 95%CI 2.49–6.17), persistent cough without a cold (OR = 2.20, 95%CI 1.49–3.26), wheezing in chest (OR = 2.51, 95%CI 1.57–4.01), and moderate or multiple respiratory symptoms (OR = 3.37, 95%CI 2.19–5.18).

Other Coalition Forces Veterans Using results from the Australian Gulf War Veterans' Health Study conducted in 2000–2002, Kelsall et al. (2004) examined respiratory health outcomes in 1,456 deployed veterans and 1,588 randomly sampled military personnel who served during the same time period but who were not sent to the Gulf theater. As part of the medical assessment and physical examination, spirometric tests were performed and a respiratory questionnaire was administered. Respiratory symptoms collected included wheeze, cough, sputum, and dyspnea experience in the previous 12 months, with additional more precise circumstances (e.g., wheeze only, wheeze when no cold, and wheeze with breathlessness). Deployed veterans reported all respiratory symptoms more frequently than did the comparison group in analyses that adjusted for age, height, weight, smoking, atopy, education, marital status, service, and rank for all symptoms except morning cough, day or nighttime cough, morning sputum, and nocturnal dyspnea. Table 4-1 summarizes these results.

Sim et al. (2015) reported the results of the Australian Gulf War Veterans' Follow Up Health Study, which was conducted in 2011–2013. Respiratory health was assessed at both baseline and follow-up, but the scope of respiratory health data collected and the mode of data collection changed for some factors, which limited the ability to assess change over time for some of the outcomes. The follow-up study collected self-reported information on respiratory symptoms and medical conditions, including wheeze, cough, and sputum. Lung function tests were not included at follow-up. Gulf War veterans were statistically significantly more likely than the comparison group to report all measured symptoms of wheeze, cough, and sputum. Estimates were adjusted for age group, service branch, and rank estimated as of August 1990, and any atopy at baseline and current smoking status (never, former, current smoker). Wheeze was reported as overall in the last 12 months (risk ratio [RR] = 1.44, 95%CI 1.15–1.80) and as subcategories of wheeze with breathlessness (RR = 1.34, 95%CI 1.02–1.75) and wheeze present but not a cold (RR = 1.23, 95%CI 1.03–1.47). Three outcomes of cough were also presented, and again Gulf War veterans reported statistically significantly higher prevalence compared with the era veterans after estimates were adjusted: woken by nocturnal cough in the last 12 months (RR = 1.37, 95%CI 1.11–1.69), morning cough (RR = 1.67, 95%CI 1.26–2.23), and day- or nighttime cough (RR = 1.36, 95%CI 1.09–1.70). Questions on sputum were constrained to experience during winter, and the reported occurrences were found to be statistically significantly higher in

TABLE 4-1 Adjusted Odds Ratio (OR) and 95% Confidence Interval (95%CI) for Self-Reported Respiratory Symptoms in the Previous 12 Months in Australian Military Personnel Deployed to the 1990–1991 Gulf War Theater Compared with Nondeployed Era Veterans

Respiratory Symptom	OR*	95%CI
Wheeze only	1.4	1.2–1.7
Wheeze when no cold	1.6	1.3–2.0
Wheeze with breathlessness	1.8	1.3–2.3
Nocturnal chest tightness	1.4	1.1–1.9
Nocturnal cough	1.4	1.1–1.7
Morning cough	1.2	0.9–1.5
Day- or nighttime cough	1.3	1.0–1.6
Morning sputum	1.2	1.0–1.5
Spontaneous dyspnea	1.6	1.1–2.2
Post-exertional dyspnea	1.3	1.1–1.6
Nocturnal dyspnea	1.5	1.0–2.2

* OR is adjusted for age, height, smoking, weight, atopy, education, marital status, service, and rank.
SOURCE: Kelsall et al., 2004.

Gulf War veterans than in the era veterans after estimates were adjusted: morning sputum in winter (RR = 1.38, 95%CI 1.10–1.74), day- or nighttime sputum in winter (RR = 1.31, 95%CI 1.06–1.63), and, as a subcategory of the day- or nighttime sputum, sputum most days for 3 months in two successive years (RR = 1.31, 95%CI 1.04–1.65).

Post-9/11 Veterans

As first described and assessed in *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan* (IOM, 2011) and detailed in Chapter 3, the Armed Forces Health Surveillance Center (AFHSC, 2010) examined medical encounters using ICD-9 codes of Army and Air Force personnel 36 months after deployment to bases/camps with and without burn pits compared with personnel who were deployed to the Republic of Korea or who remained in the United States. Personnel who served within 3 miles of burn pits were considered exposed and were compared with personnel at bases without burn pits and those in the United States who had not deployed. When signs, symptoms, and ill-defined conditions involving the respiratory system and other chest symptoms (ICD-9 786) were examined using Poisson models, the incidence rate ratios (IRRs) were statistically significantly lower for troops deployed to Camp Buehring (no burn pit) (IRR = 0.79, 95%CI 0.67–0.94) and Korea (IRR = 0.91, 95%CI 0.89–0.94) than for the nondeployed U.S. cohort; no other statistically significant associations for the other locations with or without burn pits were found.

Additional analyses of respiratory health outcomes among troops deployed to areas with known burn pits were conducted by linking data AFHSC data with the Millennium Cohort Study. Multivariable logistic regression analyses were performed to evaluate associations between respiratory outcomes and three metrics of exposure within a 5-mile radius of the documented burn pits: dichotomous deployment near the documented burn pits, cumulative days exposed to the burn pits, and exposure to the burn pits at three different bases or camps in Iraq (Balad, Taji, or Speicher). Cumulative days exposed within a 5-mile radius of the documented burn pits were summed and categorized into quartiles, and service members within each of those quartiles were compared with those with no documented exposure to these burn pit sites. Analyses were adjusted for sex, birth year, marital status, race/ethnicity, education, smoking status, physical activity, service branch, military rank, pay grade, and occupation. For the analyses of respiratory symptoms, effect estimates were also adjusted for respiratory symptom prevalence at baseline (from the Millennium Cohort Study questionnaire). All covariates were measured at baseline, but smoking status was prospectively assessed using the follow-up questionnaire, as was physical activity. Comparing service members deployed within a 5-mile radius of a burn pit with those deployed outside of that radius, no statistically significant differences were seen for the respiratory symptoms of persistent or recurring cough or shortness of breath (OR = 1.04, 95%CI 0.95–1.14). After adjustment no statistically significant associations were found between cumulative days exposed within 5-miles of the documented burn pits and self-reported respiratory symptoms for any of the four quartiles or between respiratory symptoms and specific base/camp sites ($p = 0.51$) compared with those deployed outside of the 5-mile radius (AFHSC, 2010).

The committee responsible for the 2017 National Academies report *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry* carried out an analysis of the initial months of data gathered from respondents to the registry questionnaire as part of its Statement of Task (NASEM, 2017). Based on data that were derived from the first 13 months of completed self-administered questionnaires (n = 46,404), representing approximately 1.0% of 1990–1991 Gulf War veterans and 1.7% of post-9/11 veterans that met the registry's eligibility criteria, respiratory symptoms were queried using a checklist of symptoms. Those symptoms were cough for more than 3 weeks; sputum or phlegm production for more than 3 weeks; wheezing or whistling in the chest; shortness of breath or breathlessness; decreased ability to exercise; hay fever or other respiratory allergy; sore throat, hoarseness, or change in voice; chest pain, chest discomfort, or chest tightness; and chronic sinus infection or sinusitis. Analyses that reported "any respiratory symptoms" used any affirmative response to the checklist and did not break down reported results by specific symptoms, such as cough or wheeze. Most participants (74.4%) indicated at least one respiratory symptom during or after deployment. Analyses found increasing ORs of reporting "any respiratory symptom" with increasing self-reported exposure to burn pit emissions. Models were adjusted for sex, age, education level, body mass index (BMI), smoking status, unit component, rank, service branch, and occupation.

Update of the Scientific Literature on Respiratory Symptoms

Newer studies evaluating associations between deployment in the Southwest Asia Theater of Military Operations and respiratory symptoms include studies of both post-9/11 veterans and 1990–1991 Gulf War veterans. The studies differ in the exposure evaluated and outcome ascertainment. Several studies of post-9/11 veterans (Abraham et al., 2012; Baird et al., 2012; Krefft et al., 2017; Morris et al., 2014, 2019, 2020; Saers et al., 2017; Smith et al., 2009, 2012; Taylor and Ross, 2019) and two in 1990–1991 Gulf War veterans (Khalil et al., 2018; Maule et al., 2018) assessed exposure based on deployment to Southwest Asia. Some studies evaluated specific in-theater exposures, including deployment to areas with burn pits (Abraham et al., 2014; Rohrbeck et al., 2016; Sharkey et al., 2015, 2016; Smith et al., 2012), blast exposure (Jani et al., 2017a), and depleted uranium exposure in 1990–1991 Gulf War veterans (Hines et al., 2013).

Three studies (Butzko et al., 2019; Klein-Adams, 2019; Morris et al., 2013) were also identified that reported on the frequency of different respiratory symptoms in their respective study populations. Two of these studies (Butzko et al., 2019; Klein-Adams, 2019) used populations of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans referred to VA's specialty clinic, WRIISC Airborne Hazards and Burn Pits Center of Excellence, which is one of the research initiatives specified in the Statement of Task. However, because there were no comparison groups included in these three studies, they cannot be used to help inform the association between respiratory symptoms and deployment to Southwest Asia.

Post-9/11 Veterans

Smith et al. (2009) examined newly reported respiratory symptoms (defined as persistent or recurring cough or shortness of breath) and other respiratory conditions among 46,077 Millennium Cohort Study participants who completed baseline (2001–2003) and follow-up (2004–2006) questionnaires. Respiratory symptoms were analyzed by deployment status (deployed versus nondeployed) and by cumulative time deployed (quartiles of days ranging from 0 days [nondeployed, referent group] to >270 days), while stratifying by service branch and controlling for military and demographic characteristics and smoking behavior. Multivariable logistic regression was used to compare the adjusted odds of the newly reported respiratory symptoms for deployed (n = 9,210) versus nondeployed (n = 29,783) participants. New-onset respiratory symptoms were more frequent in the deployed group than in the nondeployed group (14% vs 10%, respectively). Among the deployed group, new-onset cough was reported by 937 personnel, and shortness of breath was reported by 606 personnel, whereas among the 3,038 nondeployed with new-onset respiratory symptoms, 2,051 reported cough and 1,464 reported shortness of breath. Deployed participants who reported new-onset respiratory symptoms were more likely to be male, to have been born in 1970 or later, to have never married, and to be consistent smokers than nondeployed personnel who reported respiratory symptoms. Smoking status did not significantly modify the relationship between deployment and newly reported respiratory symptoms ($p = 0.23$). Service branch was found to be a statistically significant effect modifier of deployment and newly reported respiratory symptoms ($p < 0.0001$). Deployment was associated with respiratory symptoms in both Army (OR = 1.73, 95%CI 1.57– 1.91) and Marine Corps (OR = 1.49, 95%CI 1.06–2.08) personnel, but no difference in respiratory symptoms was found for Navy/Coast Guard or Air Force personnel. Deployment length was linearly associated with increased symptom reporting in Army personnel ($p < 0.0001$). Respiratory symptoms were further examined by modeling cough and shortness of breath separately, and the findings were reported to remain consistent, with statistically significantly elevated odds of cough among Army (OR = 1.74, 95%CI 1.56–1.94) and Marine Corps (OR = 1.76, 95%CI 1.22–2.54) personnel and statistically significantly elevated odds of shortness of breath among Army personnel only (OR = 1.64, 95%CI 1.45–1.86). Additional models were used to assess associations between new-onset respiratory symptoms and cumulative deployment duration, adjusted for the same covariates as in the deployed-versus-nondeployed models. Among Army personnel there was an exposure–response relationship between deployment length and increasing adjusted odds of respiratory symptoms ($p < 0.0001$) compared with no days of deployment. For Air Force and Marine personnel, there was no observed exposure–response relationship, and personnel in only one quartile of deployment exposure were found to have statistically significantly increased odds of developing respiratory symptoms compared with those in that same service branch who did not deploy. Although new-onset respiratory symptoms were associated with deployment compared with no deployment, the inconsistency in odds with cumulative exposure time suggests that specific exposures rather than deployment in general are determinants of post-deployment respiratory symptoms. In an analysis of deployed cohort members with self-reported information on deployment location (n = 9,861), 3,474 reported deployment to Iraq exclusively, 373 reported deployment to Afghanistan exclusively, 3,232 reported deploying to both Iraq and Afghanistan or to other locations in support of those military efforts, 486 reported sea-based deployments, 937 reported deployment to other locations, and 1,359 had been deployed to an unknown location. Of these six deployment locations, deployment exclusively to Iraq represented the highest proportion of newly reported respiratory symptoms (18%), followed by deployments exclusively to Afghanistan and to unknown locations (both 14%), deployments to Iraq and Afghanistan or to other countries in support of those efforts (12%), sea-based deployments (9%), and deployments to other locations (8%). Among the examined locations, statistically significant increased adjusted odds of respiratory symptoms were associated with deployment to Iraq exclusively (OR = 2.16, 95%CI 1.52–3.07), deployment to Afghanistan exclusively (OR = 1.87, 95%CI 1.17–2.99), deployment to unknown locations (OR = 1.77, 95%CI 1.22–2.59), and deployment to Iraq and Afghanistan or other countries in support of those operations (OR = 1.68, 95%CI 1.18–2.40). No difference in odds was observed between other deployment locations and respiratory symptoms. This study has a number of strengths, including its large population-based design, use of prospectively collected data on the same individuals, and control of multiple demographic, military, and lifestyle confounders in modeling associations.

Smith et al. (2012) investigated the effects of exposure to documented open-air burn pits within 2, 3, or 5 miles on self-reported respiratory symptoms of persistent or recurring cough or shortness of breath and other respiratory outcomes among Millennium Cohort Study Army and Air Force participants who were deployed to Iraq or Afghanistan after January 1, 2003, and who completed the baseline questionnaire and one of the follow-up assessment cycles through 2008. After individuals with missing data were excluded, 22,297 participants who had deployed were included in the analyses of respiratory symptoms; of these 3,585 had deployed to locations with documented burn pits. Similar proportions of newly reported respiratory symptoms in 2007 were found for those exposed and nonexposed within 3 miles of a burn pit (21.3% vs 20.6%, respectively). Those personnel who were deployed in proximity to documented burn pits were more likely to be younger, less educated, aerobically active, active duty, and to serve in the Army than those deployed to locations outside the 3-mile radius of a documented burn pit. Three proxy exposure metrics were modeled, and analyses were adjusted for demographic and military characteristics, smoking status, and physical activity. When exposed participants were compared with participants who were deployed to other locations in Iraq and Afghanistan, no statistically significant associations in newly diagnosed self-reported respiratory symptoms were found (OR = 1.03, 95%CI 0.94–1.13). However, when self-reported respiratory symptoms as documented on the 2004–2006 reassessment were compared with those documented on the 2007–2008 assessment, those individuals deployed within a 3-mile radius had statistically significantly and substantially increased odds of continuing to report respiratory symptoms (OR = 4.85, 95%CI 4.49–5.25). No differences were found when service members deployed at each of the three sites with documented burn pits (Joint Base Balad, Camp Taji, or Camp Speicher) were compared with those deployed to areas outside of the 3-mile burn pit exposure radius. Air Force personnel deployed within a 2-mile radius of the burn pit at Joint Base Balad were found to have statistically significantly increased odds for respiratory symptoms (OR = 1.24, 95%CI 1.01–1.52) compared with those deployed to other locations. When investigating the effect of cumulative days exposed within a 3-mile radius of the burn pits, increasing number of days near the burn pits was not associated with the adjusted odds of new self-reported respiratory symptoms ($p = 0.94$). When examining the risk of respiratory symptoms within a 5-mile radius of the burn pit sites and outside of that radius, no differences were found for cumulative deployment length or camp location.

Morris et al. (2014) conducted a study, termed Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE I), of 50 active-duty U.S. military personnel recruited within 6 months after they had returned from deployment to Iraq or Afghanistan, all of whom had reported new-onset pulmonary symptoms. Participants completed a deployment questionnaire and underwent a physical exam as well as pulmonary function testing and several other tests and imaging. Largely, frequencies of respiratory symptoms of dyspnea, wheeze, cough, and sputum pre-deployment, during deployment, and post-deployment were reported. The mean frequency of each of the four symptoms continuously increased from pre-deployment to during deployment to post-deployment, although there was no statistical assessment of differences throughout these periods. The most frequent symptom at all three time points was dyspnea. Conclusions that can be drawn from this study are limited by the small number of cases examined at one medical center, the likelihood of referral bias, and the study design that lacked a comparison group, so measures of association could not be estimated.

Using data collected as part of STAMPEDE II, Morris et al. (2019) reported on respiratory health outcomes and the changes in lung function of Army soldiers recruited from Fort Hood, Texas, between 2011 and 2014 before ($n = 1,693$) and after ($n = 843$) deployment to Southwest Asia. Participants completed a baseline questionnaire on their respiratory health and underwent examinations that included chest radiography, spirometry, and impulse oscillometry; the questionnaire with additional questions on exposures was administered post-deployment, and each of the lung function tests was also repeated post-deployment. The respiratory symptoms collected by questionnaire were dyspnea, cough, wheezing, sputum production, and exercise intolerance, and for each symptom the frequency of occurrence from never to daily was also collected. The mean frequencies of all symptoms were highest during deployment and lowest pre-deployment. The post-deployment frequency of all symptoms was higher than pre-deployment levels but lower than during deployment levels. The highest mean frequency score (approximately 0.95, classified as mild—occurring less than twice weekly) was for cough during deployment. No clinically or statistically significant increase was found in symptoms during deployment compared with reported pre-deployment levels. Mean symptom scores related to airborne exposures experienced during deployment were quantified as less than mild for cough (0.26 ± 0.43), wheeze (0.08 ± 0.27), dyspnea (0.15 ± 0.35), decreased exercise tolerance (0.10 ± 0.30), and sputum production (0.09 ± 0.28). Logistic regression analysis was applied for spirometric obstruction, with significant results detected only for increasing age, although ORs were elevated for deployed soldiers who self-reported asthma or were obese, smokers, or male. Based on post-deployment symptoms, spirometric results were statistically significantly different only for wheeze between normal versus obstruction groups (mean ± standard deviation of 1.21 ± 0.55 vs 1.41 ± 0.79, $p = 0.03$, respectively). Smoking behavior changes relative to deployment were not considered when evaluating symptom frequency even though these data were collected pre- and post-deployment. Although respiratory symptoms were found to be elevated during deployment compared with pre- and post-deployment, even the highest levels were considered mild. The pattern of increased symptom prevalence during deployment compared with post-deployment was different from the pattern observed in the first STAMPEDE study, in which the prevalence of respiratory symptoms post-deployment was higher than during deployment, although only 50 active-duty personnel were included in the earlier investigation (Morris et al., 2014).

Morris et al. (2020) reported on the results of STAMPEDE III, an investigation of clinical lung diseases in 380 military personnel who had deployed to Southwest Asia and reported having chronic respiratory symptoms temporally related to deployment. The post-deployment symptoms were reported to last 4.6 ± 3.6 years. At the time of examination, exertional dyspnea was reported by 75.1% of participants, and decreased exercise tolerance was reported by 72.6% of participants; other symptoms were common but less frequently reported—cough (55.2%), wheeze (42.1%), and sputum production (33.3%). Exertional dyspnea and decreased exercise had mean occurrences of slightly more than twice weekly. Sputum was reported least often. The frequency of self-reported symptoms before, during, and post-deployment all showed statistically significant increases ($p < 0.001$). Frequencies were reported to be highest post-deployment, followed by during deployment, and lowest for before deployment. While data were available, no adjustment or stratification was made for smoking status or specific reported exposures and respiratory symptoms.

Abraham et al. (2012) conducted a cohort and nested case–control study to evaluate the relationship between deployment and respiratory system diseases (ICD-9 460–519) in U.S. military personnel. The cohort, which was created from DoD administrative and medical data, included 44,919 single deployers and 14,695 multiple deployers deployed to OEF/OIF through June 30, 2005. All service members had at least 6 months of data pertaining to visits before and after deployment. The researchers did not find evidence of an increase in respiratory symptoms based on deployment. The rate of respiratory symptom encounters (ICD-9-CM 786) among single deployers (53.8 encounters per 1,000 person-years; 95%CI 50.7–56.8) was higher than among multiple deployers (37.0 encounters per 1,000 person-years; 95%CI 32.6–41.4) in the pre-deployment period. Respiratory symptom rates for both single and multiple deployers increased after deployment. A nested case–control analysis was undertaken to examine the independent effects of deployment status and cumulative time in theater on incident post-deployment obstructive pulmonary disease onset, but primary diagnoses of respiratory symptoms were not included in the case definition. This study had several limitations, such as a lack of measurement of smoking and a lack of specific deployment-related exposure assessments.

Krefft et al. (2017) conducted a pilot study to examine the role of lung clearance index as an early marker of lung injury in a sample of 24 healthy volunteers and 28 symptomatic veterans who had deployed to Southwest Asia in support of post-9/11 operations. The symptomatic deployers had cough, chest tightness, wheezing, shortness of breath, or decreased exercise tolerance during or following deployment. Individuals who were found to have other explanations for their respiratory symptoms were excluded. The healthy controls were at least 18 years of age, had no history of pre-existing lung disease, and reported no respiratory illness in the 4 weeks preceding enrollment and testing. Both groups underwent lung clearance index testing to identify whether abnormalities were present in the peripheral airways of the lung. As part of their clinical evaluation, the veteran group completed testing of pre- and post-bronchodilator spirometry, lung volumes, and diffusing capacity; cardiopulmonary exercise tolerance testing; and chest computed tomography (CT) scans. Surgical lung biopsies were performed on 17 of the 28 veterans. Of the 28 veterans with respiratory symptoms, 17 were found to have definite and 11 were found to have probable deployment-related lung disease. The authors suggested that among veterans who deployed to Southwest Asia and have respiratory symptoms, deployment-related disease may be common. However, the small sample of veterans is highly selective as they were all symptomatic and were seen at an occupational lung disease clinic. Additionally, the study was not designed to evaluate the impacts of deployment to theater on the health of veterans, and no adjustments were made for confounders such as smoking, obesity, or age in the assessments that were made.

Several other studies were identified that focused on specific types of exposures experienced during deployment to the Southwest Asia theater. Of these, the effects of exposure to burn pits have been the most commonly studied (Abraham et al., 2014; Rohrbeck et al., 2016; Sharkey et al., 2015, 2016). Other exposures included fires at a sulfur plant in Iraq (Baird et al., 2012) and blasts (Jani et al., 2017a). In addition to studies of those cohorts that the committee was specifically charged with reviewing, several studies were published using the AFHSC collaborative study, and one study examined outcomes using VA's Gulf War Era Cohort and Biorepository.

Abraham et al. (2014) built on the AFHSC (2010) analysis by adding an additional 12 months of follow-up (for a total of 48 months) of personnel deployed to four Southwest Asia theater sites with and without burn pits, along with those deployed to Korea and a comparison population of service members who stayed in the United States. Both studies are described in additional detail in Chapter 3. Compared with the rates for nondeployed personnel, the rate of medical encounters for respiratory symptoms among personnel deployed to the four in-theater sites was elevated, adjusted for age, gender, race, and military rank (IRR = 1.25, 95%CI 1.20–1.30). Information on smoking was not factored into the analyses. Rates for personnel deployed to bases with burn pits (IRR = 1.24, 95%CI 1.19–1.29) and without burn pits (IRR = 1.28, 95%CI 1.20–1.37) were also statistically significantly elevated for respiratory symptoms (as well as for Joint Base Balad, Camp Taji, and Camp Arifjan, individually). Compared with the rates for personnel stationed in Korea, the rates of medical encounters for respiratory symptoms were no different for personnel stationed with exposure to burn pits. In the locations without burn pits, respiratory symptoms at Camp Arifjan were statistically significantly elevated (IRR = 1.12, 95%CI 1.03–1.20), but respiratory symptoms at Camp Buehring were statistically significantly reduced (IRR = 0.83, 95%CI 0.70–0.98). As compared with military personnel deployed at bases without burn pits (Arifjan and Buehring), there was no difference in rates of respiratory symptoms among those deployed in areas with burn pits (Balad and Taji) (IRR = 0.95, 95%CI 0.88–1.03).

The analyses by Sharkey et al. (2015) also used the same deployed and nondeployed populations as the AFHSC (2010) analysis but used a larger U.S.-based reference population and included an additional 12 months of data. Poisson models were adjusted for age, pay grade, sex, race, and service branch in this retrospective cohort study. As was found in the AFHSC (2010) analysis, the risks of respiratory symptoms for personnel deployed to four Southwest Asia bases and Korea were all similar to, or statistically significantly lower than, the risks for personnel who remained in the United States. IRRs were reported for the bases, but no comparisons between bases with and bases without burn pits were made. At 48 months follow-up, adjusted IRRs for "signs, symptoms, ill-defined conditions–respiratory symptoms and other chest symptoms" (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] 786) remained lower for troops deployed to Camp Buehring, Kuwait—which did not have burn pits—than for the nondeployed U.S. reference cohort (IRR = 0.80, 95%CI 0.68–0.94). The same lower risk was observed for troops deployed to Korea compared with the nondeployed at 36 months (IRR = 0.91, 95%CI 0.89–0.94) and 48 months (IRR = 0.93, 95%CI 0.91–0.96). IRRs for personnel deployed to two other bases with burn pits (Joint Base Balad and Camp Taji, Iraq) and one without burn pits (Camp Arifjan, Kuwait) were no different than the nondeployed U.S. reference cohort.

Sharkey et al. (2016) extended the analysis of the data first analyzed by the AFHSC (2010) by adding additional Army or Air Force personnel who were deployed to Kabul (n = 5,670) and Bagram (n = 34,239) Air Force bases in Afghanistan—sites with similar, poor air quality—and Manas Air Force Base in Kyrgyzstan (n = 15,851)—a site with relatively better air quality, and extended the follow-up period of active-duty personnel to 12 years. Cases of symptoms, signs, and ill-defined conditions involving the respiratory system were defined as service members with a single inpatient or outpatient health care encounter coded ICD-9-CM 786 in any diagnostic position. IRRs were calculated and adjusted for age, sex, race, military rank, and prior medical encounters for symptoms, signs, and ill-defined conditions involving the respiratory system. Incidence rates for respiratory symptoms in the Kabul cohort were statistically significantly higher than the rates for personnel from all the other locations except the Manas group. IRRs were highest for Kabul-deployed personnel compared with nondeployed U.S.-stationed personnel (IRR = 1.52, 95%CI 1.43–1.62). Information on smoking was only available for Air Force personnel, and the authors report no evidence of confounding as RRs were similar with and without adjustment for smoking status. The use of ICD-9-CM codes implies severity of respiratory symptoms, and most individuals who have symptoms of cough or shortness of breath are unlikely to seek medical attention unless the conditions worsen or persist.

Rohrbeck et al. (2016) conducted a small study of 200 service members with known exposure to burn pits and 200 matched nondeployed service members, all selected from the Defense Medical Surveillance System, to examine differences in post-deployment respiratory health outcomes. Data from medical encounters, both hospitalizations and outpatient visits, in military treatment facilities were used to capture information on signs, symptoms, and ill-defined conditions involving respiratory system and other chest symptoms (ICD-9 786) regardless of diagnostic position. A total of 33 counts of respiratory symptoms were found in both the deployed cohort (with the majority for those deployed at Joint Base Balad [n = 30] versus Bagram Airfield [n = 3]) and among the nondeployed controls. Incidence rates (IRs) per 1,000 person-years were similar between the deployed cohort (IR = 69.5, 95%CI 45.8–93.2) and the nondeployed cohort (IR = 68.8, 95%CI 45.3–92.3). Using Cox proportional hazards regression, relative risks were adjusted for age, sex, race/ethnicity, occupation, deployment history, and history of illness prior to deployment and the Bonferroni correction was applied. The risk of respiratory symptoms was found to be decreased for those deployed to Joint Base Balad compared with the nondeployed (RR = 0.41, 95%CI 0.15–1.13), which may be due, in part, to a healthy warrior (deployer) effect. Although burn pit exposure was documented, there was no information on deployment duties, job classification, or specific individual behaviors, including smoking.

Baird et al. (2012) examined the post-deployment respiratory health status of U.S. Army personnel potentially exposed to emissions from the fire at the Al-Mishraq sulfur plant near Mosul, Iraq, in 2003. Two were groups potentially exposed to the sulfur fire smoke plume—personnel involved in fighting the fire (n = 191) and personnel presumably downwind during the time of the fires (n = 6,341). These were compared with two unexposed groups: those that deployed to the area after the fire was extinguished (n = 2,284) and those deployed to other Southwest Asia locations contemporaneously with the time of the fire (n = 1,869). About one-quarter of presumed exposed personnel reported a change in health for the worse during deployment; health concerns were reported by 39% of the firefighters and 23% of the personnel downwind of the fires. Furthermore, 24% of firefighters self-reported cough, and 31% reported difficulty breathing. In the downwind group, 16% reported cough, and 14% reported shortness of breath. Overall, the frequency of encounters for respiratory signs, symptoms, and ill-defined conditions (ICD-9-CM 786) increased post-deployment, relative to the pre-deployment period for all four groups, but was statistically significant among the downwind group only. The age-adjusted standardized morbidity ratio for signs, symptoms, and ill-defined conditions involving the respiratory system and chest (ICD-9-CM 786) was not statistically significantly different from 1.0 when firefighters were compared with the contemporaneously deployed group (morbidity ratio = 1.05, 95%CI 0.61–1.61) but was statistically significantly decreased when firefighters were compared with the group deployed to the area before or after the fire (morbidity ratio = 0.57, 95%CI 0.33–0.88). Regarding the potentially exposed personnel who were deployed downwind of the fires, the standardized morbidity ratio for signs, symptoms, and ill-defined conditions involving the respiratory system and chest was slightly elevated when compared with the contemporaneously deployed group (morbidity ratio = 1.08, 95%CI 1.0–1.17) and statistically significantly decreased compared with the group deployed to the area before or after the fire (morbidity ratio = 0.58, 95%CI 0.54–0.63). Because the authors were concerned that differential misclassification bias would be introduced if the accuracy and completeness of post-deployment survey data was not independent of exposure to the sulfur fire in this population, comparisons of outcomes between the exposed and the unexposed group were not made. Confounding due to potential uncharacterized differences in risk factors, such as smoking behavior and other environmental or occupational exposures, between the sulfur fire exposed and unexposed groups cannot be ruled out.

Blast exposures were another common exposure of post-9/11 deployments. Jani et al. (2017a) used the responses of 42,558 service members and veterans who had participated in the Airborne Hazards and Open Burn Pit Registry between 2014 and 2015 to assess the association between self-reported blast exposure and self-reported current dyspnea or decreased ability to exercise. Blast exposure was reported by 74% of respondents overall—79% of those with current symptoms and 66% of those without current symptoms. Current dyspnea was reported by 61% of respondents. Following adjustment for self-reported age; sex; branch of service; BMI; smoking status; exposure to burn pit smoke; nonmilitary occupational exposure to dust, gas, smoke, chemical vapors, or fumes; and time since deployment, the odds of dyspnea or decreased ability to exercise were increased (OR = 1.66, 95%CI 1.5–1.7) among the group with blast exposure as compared with military personnel without blast exposure. This finding is limited by the self-selected voluntary nature and the reliance on self-reported exposures and outcomes of the registry data.

Other Coalition Forces Veterans Two studies of foreign military service personnel were identified. In the first (Taylor and Ross, 2019) British service personnel stationed in Kabul, Afghanistan, a highly polluted city, from December 2016–August 2017 completed a respiratory health questionnaire that collected information on nasal congestion, shortness of breath, wheeze, cough, and sputum. Comparisons were made between service members stationed at a base in Kabul and those stationed on the outskirts of Kabul as well as between service members deployed over winter and over summer. The prevalence of symptoms of nasal congestion, shortness of breath, wheeze, and cough were higher among those stationed in the center of Kabul than in the outskirts, and these symptoms were reported to be higher in the winter season (ranging from approximately 50% to 80% in central

Kabul, depending on the symptom, and from 50% to 65% in the Kabul outskirts), which had higher air pollution concentrations than the spring (ranging from approximately 40% to 55% in central Kabul and from 15% to 45% in the Kabul outskirts). The higher prevalence of symptoms reported by those stationed in central Kabul, regardless of the season, than in those stationed in the city outskirts suggests that urban air pollution could have played a role in the differences in the frequency of symptoms that were reported.

Saers et al. (2017) examined the prevalence of self-reported respiratory symptoms (wheeze, wheeze with breathlessness, wheeze without a cold, nocturnal chest tightness, nocturnal breathlessness, and nocturnal cough) in the previous 12 months in a random sample of 1,032 Swedish military personnel from selected units (response rate 50%). Military personnel were either currently or previously stationed in Kosovo (in the period 2005–2008) or Afghanistan (2008–2009) and were matched on age, gender, smoking habits, BMI, and education level using a ratio of 1:1 to a general population sample of people who had participated in the Global Asthma and Allergy European Network study. The prevalence of all symptoms except nocturnal chest tightness and nocturnal breathlessness was statistically significantly increased ($p < 0.05$) in the military personnel compared with the matched sample from the general population. The most common of the reported symptoms for the military versus the comparison group was nocturnal cough (26.6% vs 17.2%), and the least frequent symptom was nocturnal breathlessness (4.2% vs 4.1%). Analyses with logistic regression also showed statistically significantly increased odds of wheeze, wheeze with breathlessness, wheeze when not having a cold, and nocturnal cough in the military population compared with the general population. No difference in the prevalence of respiratory symptoms was found for military personnel who were stationed in Afghanistan ($n = 682$) versus Kosovo ($n = 393$). Within the group stationed in Afghanistan, an increasing number of months spent deployed was associated with increased odds of wheeze ($p = 0.002$), wheeze with breathlessness ($p = 0.001$), and nocturnal cough ($p = 0.046$). Military personnel who reported having been exposed to sandstorms had a higher prevalence of nocturnal coughing than those who were not exposed (29.6% vs 16.2%, $p = 0.002$). Duties that required regular transportation in vehicles versus duties that were more stationary were associated with a higher prevalence of wheeze (18.1% vs 11.4%, $p = 0.046$), wheeze with breathlessness (11.8% vs 5.1%, $p = 0.02$), and nocturnal chest tightness (10.2% vs 3.8%, $p = 0.01$). The finding of no difference in symptom prevalence between those stationed in Afghanistan and Kosovo calls into question the role of Southwest Asia deployment as a cause of the differences in prevalence relative to the general population.

1990–1991 Gulf War Veterans

Khalil et al. (2018) described the study design for the Gulf War Era Cohort and Biorepository, which was established by VA to be a nationally representative longitudinal cohort of U.S. veterans who served during the 1990–1991 Gulf War era. The pilot phase of the effort enrolled 1,275 veterans who completed all study requirements and were frequency-matched to the geographic distribution of the recruitment panel across U.S. Census regions; 900 (70.6%) of the veterans deployed to the Southwest Asia theater. Self-reported health outcomes of symptoms (in the past year) and health care provider–diagnosed conditions were stratified by users ($n = 584$) and nonusers ($n = 679$) of VA health care. Three respiratory symptoms were included, and for each the VA users reported higher frequencies than nonusers in the past 6 months: difficulty breathing or shortness of breath (43.5% vs 24.7%), frequent coughing without also having a cold (37.3% vs 23.3%), and wheezing (28.8% vs 16.3%). While the reported proportions of veterans with symptoms seem high, there was no formal assessment of differences in the frequency of symptoms between VA users and nonusers. Furthermore, there were no comparisons between deployed and nondeployed veterans and, hence, these results do not inform questions about the role of Gulf War deployment on increased risks of respiratory symptoms.

Hines et al. (2013) examined 37 1990–1991 Gulf War veterans who were enrolled in the VA Depleted Uranium Surveillance Program and had attended a biennial follow-up in 2011 to compare the likelihood of pulmonary health abnormalities in those with high body burdens of uranium ($n = 12$; >0.1 μg/g creatinine) versus those with low body burdens of uranium ($n = 25$; ≤ 0.1 μg/g creatinine). Using 24-hour creatinine-corrected urinary uranium as a validated marker of exposure, no statistically significant differences in the prevalence of any respiratory symptom—frequent cough, coughing up phlegm, shortness of breath, or wheezing—were observed in those with high versus low urinary uranium. Because smokers often report respiratory symptoms, the frequency of symptoms was also compared between ever smokers and never smokers; the only symptom more frequently reported in ever smokers versus never smokers was frequent cough (p = 0.05). While the findings from this study made use of a rigorous exposure assessment through analysis of uranium in urinary samples, the findings are not particularly pertinent to this assessment, given that exposure to depleted uranium was uncommon.

Maule et al. (2018) conducted a meta-analysis of 21 studies published through 2017 on the prevalence of health symptoms, including respiratory symptoms, with those 21 studies representing more than 129,000 1990–1991 Gulf War–deployed and nondeployed era veterans. In pooled analyses, a higher combined prevalence of respiratory symptoms was found for deployed than for era veterans: coughing (19.2% vs 9.1%), wheezing (17.5% vs 8.6%), and shortness of breath (14.9% vs 5.1%). The bias assessment also demonstrated that Gulf War–deployed veterans continued to have higher odds of reporting all analyzed symptoms than Gulf War–era controls. ORs were reported for each symptom along with I^2 statistics (a measure of the heterogeneity, or the percentage of variation across studies that is due to heterogeneity rather than chance). Although the odds of all respiratory symptoms were statistically significantly increased for Gulf War veterans compared with era veterans—shortness of breath (OR = 2.81, 95%CI 2.35–3.35; 6 studies), coughing (OR = 2.02, 95%CI 1.72–2.38; 11 studies), and wheezing (OR = 1.92, 95%CI 1.66–2.22; 5 studies)—the heterogeneity was considerable (>0.7) for all outcomes. The meta-analytic approach could not address concerns about either selection biases or information biases (due to self-reports of symptoms), which were common to all the included studies. However, the committee found that the methods used in this meta-analysis fairly summarize reported findings on respiratory symptoms, and the bias assessment provides assurance that reporting bias played little role. Moreover, the committee also notes that some other important deficiencies in the published studies, such as individual design and population selection, and their impacts on the findings were not addressed.

Synthesis

Previous reports in the *Gulf War and Health* series have concluded that "studies of Gulf War veterans based on self-reported symptoms and self-reported diagnoses have frequently, but inconsistently, shown an excess of respiratory conditions" (NASEM, 2016, p. 151). This conclusion was confirmed by the results of a recent meta-analysis of 21 studies of 1990–1991 Gulf War veterans that used self-reported respiratory symptoms (Maule et al., 2018).

Respiratory symptoms are generally presented as a group and may include cough, wheeze, dyspnea or shortness of breath, sputum or phlegm, exercise intolerance, and other nonspecific symptoms or symptoms that appear under specific conditions, such as "morning cough." In the assessment of the first 13 months of Airborne Hazards and Open Burn Pit Registry data, at least one respiratory symptom of 13 possible symptoms was reported by 74.4% of participants.

The committee identified and evaluated 16 studies that evaluated associations between respiratory symptoms among post-9/11 veterans and 3 studies among 1990–1991 Gulf War veterans and deployment in the Southwest Asia Theater of Military Operations. The studies differ in how exposure was evaluated (e.g., deployment versus specific in-theater exposures) and in the heterogeneity of the respiratory symptoms assessed. Findings from these more recent studies are largely in line with those reported previously, with mixed evidence about associations between deployment and respiratory symptoms. In contrast to use of deployment to the Southwest Asia Theater of Military Operations as a metric for exposure, there were too few studies about specific exposures (e.g., burn pit exposure, blast exposure, or exposure to depleted uranium) upon which to base an assessment.

Among the research cohorts that were included in the committee's Statement of Task, two studies from the Millennium Cohort Study and three studies from STAMPEDE evaluated respiratory symptoms in their respective populations. Among Millennium Cohort Study participants with follow-up through 2006, differences were detected by service branch, respiratory symptom, and exposure metric. For example, following adjustment for smoking and other risk factors, Smith et al. (2009) found positive associations between deployment and new-onset respiratory symptoms only for Army and Marine Corps personnel. When modeled separately, positive associations for cough were found for both Army and Marine Corps personnel, whereas odds of shortness of breath were elevated only among Army personnel. Furthermore, an increasing exposure–response relationship was found between duration of deployment and new-onset respiratory symptoms for Army personnel, but not for the other service branches.

In another analysis of the Millennium Cohort Study with the same follow-up as Smith et al. (2009), but restricted to Army and Air Force personnel who had deployed to locations with burn pits, Smith et al. (2012) reported no significant associations in newly diagnosed self-reported respiratory symptoms between those deployed to areas within 5 miles or 3 miles of burn pits compared with personnel deployed outside of the burn pit buffer zones; nor were there differences by base site. In addition, no significant associations were found when evaluating cumulative days exposed, deployment to a specific burn pit site, or deployment within a 2-mile radius of a burn pit, except for the latter metric, where U.S. Air Force personnel deployed to Joint Base Balad were found to have increased odds for respiratory symptoms relative to those deployed to other locations.

Three studies of STAMPEDE (Morris et al., 2014, 2019, 2020) examined respiratory symptoms. In the first analysis of 50 active-duty U.S. military personnel recruited within 6 months after they had returned from deployment to Iraq or Afghanistan (Morris et al., 2014), there is evidence of service personnel reporting increased frequency of dyspnea, wheeze, cough, and sputum continuously from pre-deployment to during deployment and post-deployment, with dyspnea being more frequently reported than the other respiratory symptoms. In a larger study of changes in respiratory health outcomes with data that were collected before and after deployment to Southwest Asia—STAMPEDE II—the proportion of service personnel reporting cough, dyspnea, and wheeze was higher post-deployment and during deployment than pre-deployment, with slightly lower frequencies post-deployment than during deployment (Morris et al., 2019). Although information on smoking was collected both pre- and post-deployment, it appears not to have been used in modeling differences. Because smoking rates typically increase during deployment, the lack of accounting for changes in cigarette smoking habits somewhat limits confidence in the conclusions that can be drawn from this otherwise strong study. A third study—STAMPEDE III—of 380 military personnel who had deployed to the Southwest Asia theater and reported having chronic respiratory symptoms similarly found that the frequency of self-reported symptoms pre-, during, and post-deployment all showed statistically significant increases ($p < 0.001$) (Morris et al., 2020). Although information on smoking was collected in STAMPEDE both pre- and post-deployment, it appears not to have been used in these studies in making comparisons in changes in symptom frequency over time. Because smoking rates typically increase during deployment (Meadows et al., 2018), the lack of accounting for cigarette smoking habits limits the conclusions that can be drawn from this otherwise strong study.

Of the three studies of 1990–1991 Gulf War veterans reviewed, the most informative was the meta-analysis of 21 studies on prevalence of health symptoms, including respiratory symptoms, representing more than 129,000 1990–1991 Gulf War–deployed and nondeployed era veterans (Maule et al., 2018). In pooled analyses higher prevalence of coughing, wheezing, and shortness of breath was found for deployed than era veterans, and the odds of all three respiratory symptoms were statistically significantly increased for Gulf War veterans compared with era veterans, although the heterogeneity was considerable. While the findings from Hines et al. (2013) made use of a rigorous exposure assessment through analysis of uranium in urinary samples, the findings are not particularly pertinent, given that exposure to depleted uranium was uncommon.

Overall, the studies reviewed by the committee were subject to many of the same limitations as previously reviewed studies (lack of specific or objective exposure information or stratification of personnel by military occupations, lack of adjustment for potential confounding factors such as smoking). However, at least one study reported similar findings in models with and without cigarette smoking (Sharkey et al., 2016); therefore, there is a need to confirm the role of smoking as a potential confounder in future investigations given that the lack of control for smoking is often identified as a weakness in studies of military health. Some studies used ICD-9 codes—specifically 786 for signs, symptoms, and ill-defined conditions of the respiratory system—contained in medical encounter databases to attempt to overcome the subjective nature of symptom reporting. Use of this ICD-9 code also has some limitations, including that medical encounters outside of the administrative database population are not captured (such as visits that occur outside of DoD facilities), medical encounters capture only the more severe of the symptom spectrum, and outcome misclassification based on ICD coding is inevitable. However, the documentation of symptoms using ICD-9 codes and the ability to estimate incidence rates are important strengths.

Given the findings from all the reviewed studies, the available evidence suggests an association between service in the Southwest Asia theater and respiratory symptoms. Nonetheless, many of these studies have the potential for information bias, and some of them are also subject to potential selection bias due to the self-selection of participants into the studies, if those with symptoms and in-theater exposures are more likely to participate. The greatest concern for bias due to confounding relates to those studies in which there was no control for cigarette smoking.

Conclusions

Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is limited or suggestive evidence of an association between airborne hazards exposures in the Southwest Asia theater and subsequent development of respiratory symptoms.

UPPER AIRWAY DISORDERS

The upper airway serves several critical functions. It is the first respiratory mucosa to encounter inhaled particulate matter (PM), gases, and fumes; it warms and humidifies inhaled air and filters large particles, including many common allergens; and it is the primary adsorptive surface for water-soluble gases, such as formaldehyde. It also removes substantial quantities of less soluble gases, such as ozone. Obstruction of the nasal passages may result in a change from nasal to oral breathing, especially with exertion. Oral breathing bypasses the filtering functions of the nose, increasing the hazard to the lower airways and the lungs (Bascom and Raford, 1994).

Rhinitis and Sinusitis

Rhinitis may be a consequence of mucosal irritation (irritant rhinitis) or immunological response (allergic rhinitis). Both seasonal and perennial antigens may cause allergic rhinitis, with the dominant antigens varying by region. Although recent research has focused primarily on the home as an important source of exposure to antigens such as house dust mites, cockroaches, and rodents, the workplace (e.g., office buildings) is also an important potential source of these antigens. There is some evidence, as has been demonstrated in relation to immunoglobin E (IgE)-mediated asthma, that exposure to environmental irritants such as ozone may enhance the likelihood of allergic rhinitis (Higgins and Reh, 2012); likewise, nasal instillation of diesel exhaust particles can increase in vivo IgE and cytokine production at the human upper respiratory mucosa, exacerbating allergic inflammation (Díaz-Sanchez et al., 1999). Allergic rhinitis typically presents with sneezing, rhinorrhea, and nasal congestion and may accompany occupational asthma. Symptoms may be immediate (occurring soon after exposure) or delayed (late-onset symptoms 8–24 hours after exposure). Upper respiratory sensitizers, including protein allergens (e.g., flour dust or laboratory animals) and low-molecular-weight chemicals (e.g., isocyanates), have been documented to cause work-related allergic rhinitis (Bascom and Raford, 1994). Around 19.9 million adults in the United States are diagnosed with allergic rhinitis per year, representing an annual incidence of around 8.1% of the adult population[4] (CDC, 2017).

Irritant rhinitis is defined as rhinitis symptoms induced by dusts, chemicals, or fumes that are noxious to tissues. The mechanism is generally considered to be an activation of the sensory irritant receptors. The symptoms are similar to those of allergic rhinitis and may be due to exposures to chemicals such as formaldehyde and environmental tobacco smoke. The list of chemical agents known to cause irritant rhinitis is lengthy and most often dose dependent. The optimal treatment is avoidance (Bascom and Raford, 1994). In the United States, there are approximately 30 million people with irritant rhinitis (Scarupa and Kaliner, 2009).

Sinusitis is an inflammation in the sinuses. The frontal, ethmoid, maxillary, and sphenoid sinuses are paired cavities, lined with mucosa, in the anterior portion of the skull. Symptoms and signs suggesting acute sinusitis include purulent nasal discharge, facial pain or tenderness, nasal congestion, fever, and cough. Chronic sinusitis often presents with protracted nasal congestion, nasal discharge, and facial pain. Sinusitis is often preceded by a viral upper respiratory infection. Local edema, allergic rhinitis, and nasal polyps may obstruct the sinus ostium, leading to acute or chronic disease. Exposure to tobacco smoke, air pollutants, and several chemicals has been

[4] Table A-2a. See https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_A-2.pdf (accessed July 3, 2020).

shown to cause or exacerbate sinus disease. Around 30.8 million adults in the United States have been diagnosed with chronic sinusitis, representing a prevalence of around 12.5% of the adult population[5] (CDC, 2017).

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports

Volumes 4, 8, and 10 of the *Gulf War and Health* series have discussed respiratory symptoms as a group, which has included rhinitis and sinusitis when present. No conclusion was made specific to rhinitis or sinusitis. No studies reviewed in these previous volumes reported on outcomes of rhinitis, and only one study (Kang et al., 2000) reviewed in Volume 4, included sinusitis as a distinct health outcome. Kang et al. (2000) used information collected as part of VA's NHS survey, a population-based retrospective cohort design, to estimate the prevalence of symptoms and other health outcomes in Gulf War veterans (n = 15,000) compared with era veterans (n = 15,000). Population prevalence rates were calculated using statistical analysis techniques to account for stratified random sampling of unequal probabilities of selecting various strata. Compared with nondeployed era veterans, Gulf War–deployed veterans had a significantly higher symptom prevalence of sinusitis experienced in the 12 months before the survey: 38.6% for deployed versus 28.1% for the nondeployed (RD = 10.47, 95%CI 10.32–10.62). Estimates were not adjusted for smoking or other factors.

As first described in the Respiratory Symptoms section, using results from the Australian Gulf War Veterans' Health Study conducted in 2000–2002, Kelsall et al. (2004) investigated whether Australian Gulf War veterans had a higher-than-expected prevalence of recent symptoms and medical conditions that were first diagnosed in the period following the 1990–1991 Gulf War, and whether effects were associated with exposures and experiences that occurred during deployment. Self-reported "sinus problems" that were first diagnosed in 1991 or later were more frequent in Gulf War veterans than in the era veterans (11% vs 7%, respectively), and the difference was statistically significant after adjustment for service type, rank, age, education, and marital status (OR = 1.5, 95%CI 1.1–2.0). When sinus problems that were first diagnosed in 1991 or later were rated as "possible or probable" based on an assessment by a research team doctor, they were again more frequent in Gulf War veterans than in the era veterans (10% vs 7%, respectively), and the difference was again statistically significant after adjustment for service type, rank, age, education, and marital status (OR = 1.5, 95%CI 1.1–2.0).

Sim et al. (2015) reported on the results of the Australian Gulf War Veterans' Follow Up Health Study, which was conducted in 2011–2013. Gulf War veterans were statistically significantly more likely than the comparison group to report doctor-diagnosed sinus problems (RR = 1.51, 95%CI 1.07–2.15), adjusted for age group, service branch, and rank estimated as of August 1990, for any atopy at baseline, and for current smoking status (never, former, current smoker).

The 2011 report on the long-term health consequences of burn pit exposure in Iraq and Afghanistan included studies of surrogate populations (firefighters, incinerator workers, communities near incinerators) who were exposed to chemicals known to be associated with burn pit emissions and primarily relied on *Gulf War and Health: Volume 8* (IOM, 2010) for conclusions on the association between exposure and health outcomes in service members and veterans, except when new studies were identified. As in the *Gulf War and Health* series reports, conclusions on the association between exposure to burn pit emissions and respiratory symptoms, conditions, and diseases were presented as a group, and no studies of rhinitis or sinusitis were identified in service members or veterans (IOM, 2011).

Update of the Scientific Literature on Sinusitis and Rhinitis

Thirteen studies were identified that examined the occurrence of post-deployment rhinitis or sinusitis or both. However, five of the studies (Butzko et al., 2019; Dursa et al., 2016a; Korzeniewski and Brzozowksi, 2011; Korzeniewski et al., 2013; Sanders et al., 2005)—one of which was conducted by WRIISC investigators (Butzko et al., 2019)—did not include appropriate comparison groups or only provided descriptive statistics, and thus could not provide information to contribute to inferences that can be made regarding deployment to Southwest Asia and

[5] Table A-2a. See https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_A-2.pdf (accessed July 3, 2020).

sinusitis and rhinitis. For example, Dursa et al. (2016a) used data collected from the NewGen survey to examine the health outcomes of OEF/OIF veterans who use VA health care services and those who do not; however, although the models were adjusted for deployment to OEF/OIF, the inferences that can be made on the association between deployment to Southwest Asia and sinusitis are too limited to be considered informative.

Post-9/11 Veterans Two of the studies (Barth et al., 2014, 2016a) used data collected from VA's NewGen survey (detailed in Chapter 3) to examine the population prevalence of three self-reported doctor-diagnosed respiratory conditions (asthma, bronchitis, and sinusitis) in veterans who had deployed to Southwest Asia and those who had not. Barth et al. (2014) examined the association between deployment to Southwest Asia and self-reported doctor-diagnosed sinusitis among 13,162 deployed and 7,401 nondeployed veterans. Unweighted and weighted prevalences of sinusitis were calculated and stratified by time of diagnosis (before or after 2001), and logistic regression was used to calculate adjusted ORs for deployment status and sinusitis. Models were adjusted for birth year, sex, service branch, unit component, race/ethnicity, education, and smoking status. Separate models were constructed for diagnosis before 2001 and during or after 2001. For respiratory conditions diagnosed before 2001, the weighted prevalence for sinusitis was higher in the nondeployed group than in the deployed group (7.8% vs 4.9%). Among those with respiratory disease diagnosed prior to 2001, the weighted prevalence of sinusitis was higher in the deployed than in the nondeployed group (6.9% vs 5.6%). Among those with respiratory disease diagnosed during or after 2001, the deployed group had statistically significantly greater odds of sinusitis compared with nondeployed veterans (OR = 1.30, 95%CI 1.13–1.49). The observed effect of deployment was statistically significantly decreased among veterans with sinusitis diagnosed prior to 2001 (OR = 0.72, 95%CI 0.63–0.82).

Barth et al. (2016a) again used the NewGen data to expand on the analysis by Barth et al. (2014) to examine the prevalence of respiratory diseases and their association with self-reported respiratory exposures during military service for OEF/OIF deployed and nondeployed veterans. Logistic regression analyses were used to calculate weighted, adjusted odds of respiratory disease stratified by deployment status and controlled for sex, birth year, race/ethnicity, education, smoking status, unit component, service branch, and number of OEF/OIF deployments. Of the 3,190 veterans who self-reported doctor-diagnosed sinusitis, 15.1% (weighted) had no deployments, and 15.5% (weighted) had three or more deployments. Sinusitis was most frequent among women (22.6% weighted), those who served in the Air Force (17.6% weighted), those who had an advanced degree (22.0% weighted), and those who identified as former smokers (21.7%). Stratified by deployment status, 13% (weighted) of veterans with sinusitis were deployed to OEF/OIF, and 14.9% (weighted) of veterans with sinusitis were nondeployed. Whereas among all deployed veterans 95% (weighted) reported at least one respiratory exposure, only 13.1% (weighted) of the deployed with a diagnosis of sinusitis reported any respiratory exposure. Among deployed veterans, statistically significant increased odds of sinusitis were observed for all specific exposures and for both the high-exposure and low-exposure categories; the highest odds for sinusitis were for those categorized as high exposure (OR = 2.11, 95%CI 1.58–2.81) and for those who reported exposure to dust and sand specifically (OR = 1.80, 95%CI 1.44–2.23). For nondeployed veterans, statistically significant increased odds of sinusitis were also observed for all specific exposures and for both the high-exposure and low-exposure categories; the highest odds for sinusitis were again for those who were categorized as high exposure (OR = 2.54, 95%CI 2.00–3.21), and among specific exposures, industrial pollution had the highest odds (OR = 1.81, 95%CI 1.52–2.15). These results show that exposures were associated with the development of sinusitis in both deployed and nondeployed groups. A strength of this analysis is that it attempted to characterize the types of exposure associated with clinical respiratory outcomes.

Smith et al. (2008) used self-reported clinician-diagnosed health data from regular, active-duty participants from the first panel (2001–2003) of the Millennium Cohort Study (n = 37,798) to compare the agreement of 38 medical conditions—including sinusitis—with that obtained from electronic medical records based on ICD-9-CM codes. Any diagnostic code for these 38 conditions in any portion of the medical record indicated agreement with a self-reported medical condition of interest. Positive and negative agreement was used to compare self-reported data with those from electronic medical records. Prevalence of sinusitis (considered to be more likely to be acute or transient) was 14.8% (95%CI 14.5–15.1) for self-reported and 13.9% (95%CI 13.5–14.2) for the electronic medical record; 8.8% were exclusively recorded in the electronic medical record. The positive agreement between self-report and electronic medical record was 35.7%, and negative agreement (the condition was not reported either by self-report or found in the medical record) was 89.2%. Sinusitis was examined by length of service in years, and the prevalence and agreement values varied with increasing length of service. In most cases, both prevalence and positive agreement increased with longer time in service. For example, the prevalence of sinusitis based on self-report increased from 8.7% among those with 0–5 years of service to 20.6% among those with ≥16 years of service. The prevalence of sinusitis based on electronic medical records increased from 12.8% among those with 0–5 years of service to 15.0% among those with 11–15 years of service but decreased to 14.2% for those with ≥16 years of service. For individuals with up to 10 years of service, the self-reported prevalence of sinusitis was lower than what was recorded in the electronic medical records.

Baird et al. (2012) examined the post-deployment respiratory health status of U.S. Army personnel potentially exposed to emissions from the fire at the Al-Mishraq sulfur plant near Mosul, Iraq, in 2003. Two groups were potentially exposed to the sulfur fire smoke plume—personnel involved in fighting the fire (n = 191) and personnel presumably downwind during the time of the fire (n = 6,341). These were compared with two unexposed groups: those that deployed to the area after the fire was extinguished (n = 2,284), and those deployed to other Southwest Asia locations contemporaneously with the time of the fire (n = 1,869). Rhinitis was assessed by comparing the percentage of those that reported runny nose (34% of firefighters and 28% in the downwind group); however, statistical testing of these differences was not conducted, limiting the informativeness of this study regarding an association between deployment and rhinitis.

Other Coalition Forces Veterans Taylor and Ross (2019) conducted a study of UK service personnel who completed a respiratory questionnaire and who were stationed in Kabul, Afghanistan, a highly polluted city, in 2016–2017. The self-reported prevalence of nasal congestion was higher for personnel stationed in a compound in the center of Kabul than for those stationed in the outskirts of Kabul (96% vs 52%, respectively), suggesting that urban air pollution could have been responsible for the higher rates of symptoms. This study is limited in that it did not conduct statistical analyses of these differences or adjust for confounders and that it relied on self-reported symptoms.

1990–1991 Gulf War Veterans Hooper et al. (2008) used DoD administrative data to examine the long-term hospitalization experiences, based on ICD-9-CM codes, of regular active-duty U.S. Gulf War veterans (n = 211,642) still on active duty between 1994 and 2004 (presented at 3-year intervals) versus veterans who had separated from military service (n = 321,806). For the 10-year combined observation period, there were 43,346 hospitalizations for those who remained on active duty after 1994. Of those hospitalizations, 12.2% (n = 2,872) were coded as being related to the respiratory system. For each diagnostic category, the top five primary diagnoses over the entire follow-up period were presented. Chronic sinusitis ranked fifth, at 8.9% (n = 255) of inpatient hospitalizations for respiratory diseases. Of the 4,031 veterans hospitalized for ill-defined conditions, 46.6% had respiratory system and other chest symptoms. Comparisons with the separated veteran group were not presented, nor were there comparisons of hospitalizations by specific Gulf War exposures, making this primarily a descriptive study and limiting its informativeness.

One study that used an objective measure of exposure to examine a variety of respiratory symptoms (including sinus trouble and frequent runny nose) was a study of those accidentally exposed to depleted uranium; the exposure was estimated objectively using an exposure biomarker (Hines et al., 2013). A subset (n = 37) of 1990–1991 Gulf War veterans who were enrolled in the VA Depleted Uranium Surveillance Program and had attended a biennial follow-up in 2011 were examined to compare the likelihood of pulmonary health abnormalities in those with high body burdens of uranium (n = 12; >0.1 µg/g creatinine) versus those with low body burdens of uranium (n = 25; ≤0.1 µg/g creatinine). Using 24-hour creatinine-corrected urinary uranium as a validated marker of exposure, no statistically significant differences in the prevalence of sinus trouble or frequent runny nose were observed in those with high versus low urinary uranium. Because smokers often report respiratory symptoms, the frequency of symptoms was also compared between ever smokers and never smokers; frequent runny nose and sinus trouble were not reported more frequently by ever smokers than by never smokers. While the findings from this study made use of a rigorous exposure assessment through analysis of uranium in urinary samples, the findings are not particularly pertinent to this assessment given that exposure to depleted uranium was uncommon.

Maule et al. (2018) conducted a meta-analysis on the prevalence of health symptoms, including sinus congestion, using 21 studies published through 2017, representing more than 129,000 1990–1991 Gulf War–deployed and nondeployed era veterans. In pooled analyses a higher combined prevalence of sinus congestion was found for deployed than for era veterans (40.4% vs 24.9%, respectively). ORs were reported for each symptom along with I^2 statistics. Although the odds of sinus congestion were statistically significantly increased for Gulf War veterans compared with era veterans (OR = 1.63, 95%CI 1.46–1.81; nine studies), the heterogeneity was considerable ($I^2 = 0.75$). The meta-analytic approach could not address concerns about either selection biases or information biases (due to self-reports of symptoms), which were common to all of the included studies. However, the committee found that the methods used in this meta-analysis fairly summarize reported findings on symptoms of sinus congestion, and the bias assessment provides assurance that reporting bias played little role. Moreover, the committee also notes that some other important deficiencies in the published studies, such as individual design and population selection and their impacts on the findings, were not addressed.

Synthesis

Volumes 4, 8, and 10 of the *Gulf War and Health* series addressed respiratory symptoms as a group and included rhinitis and sinusitis when present. None of these volumes reported a conclusion that was specific to rhinitis or sinusitis. The 2011 National Academies report on the long-term health consequences of burn pit exposure also presented respiratory symptoms, conditions, and diseases as a group, but it did not identify any studies of rhinitis or sinusitis in service members or veterans (IOM, 2011).

This report summarizes eight new studies that examined the occurrence of post-deployment sinusitis; five were conducted using populations of post-9/11 personnel, and three studies used 1990–1991 Gulf War veterans. Although symptom reports of sinusitis for deployed veterans were generally found to be increased, the inferences that can be drawn from these results are limited due to poor exposure characterization, namely using deployment as a surrogate for exposures encountered in theater; using data based only on self-report and recall; and presenting conclusions regarding deployment without taking into account details such as the number of deployments, the total days of deployment, or deployment to areas other than Southwest Asia. Furthermore, only some of the studies reviewed by the committee controlled for confounders, and those that did, did so incompletely, leading to uncertainty about whether a deployment-related effect was being observed.

Conclusions

Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and subsequent development of rhinitis or sinusitis.

Vocal Cord Dysfunction

Vocal cord dysfunction is characterized by paradoxical closure of the vocal cords during inspiration and sometimes exhalation. Signs and symptoms of vocal cord dysfunction resemble those of laryngeal edema, vocal cord paralysis, and frequently asthma. It is a functional disorder that serves as an important mimicker of asthma. Wheezing or stridor and acute shortness of breath are typical and are often dramatic, with the appearance of acute respiratory failure. Vocal cord dysfunction is most likely due to laryngeal hyper-responsiveness, with increased sensitivity of the laryngeal sensory receptors and heightened response of the glottic closure and cough reflexes to a number of triggers. Exercise and psychological factors have been identified as triggers. Exposure to irritants, including chemicals such as chlorine, ammonia, perfume, and other odors in the workplace, have been linked with vocal cord dysfunction. The diagnosis of vocal cord dysfunction is made during a direct visualization of the vocal cords during an attack. Inspiratory, anterior vocal cord closure with a posterior glottic chink is seen (Dunn et al., 2015). There is no precise information on the prevalence of vocal cord dysfunction in adults due to a lack of formal surveillance of the disease and inconsistencies in the disease definition in the epidemiologic literature (Kenn and Hess, 2008).

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports

Previous reports in the *Gulf War and Health* series or other reports related to burn pit exposures (IOM, 2011) have not addressed whether deployment to Southwest Asia is related to vocal cord dysfunction.

Update of the Scientific Literature on Vocal Cord Dysfunction

The committee's literature search identified four studies that evaluated vocal cord dysfunction. Two studies (Krefft et al., 2020; Morris et al., 2014)—one of which was conducted by the STAMPEDE investigators (Morris et al., 2014)—did not include a comparison group and so did not provide information that could contribute to inferences that can be made regarding deployment to Southwest Asia and vocal cord dysfunction. Morris et al. (2013) conducted a retrospective review that identified 48 U.S. military personnel evaluated at a level 3 evacuation medical center (Landstuhl, Germany) for vocal cord dysfunction; however, this retrospective case series is of limited relevance for the committee's purposes because there was no comparison group and no data collected on exposures experienced during deployment.

Dion et al. (2013) evaluated the differences in vocal cord function and dysphonia between deployed and nondeployed U.S. Army soldiers in a cross-sectional medical records study using DoD military health system databases, which contain medical records for all DoD members and their families who receive care in the military health system. A retrospective search of the database was restricted to soldiers on active duty between January 1, 2008, and March 1, 2012. Diagnoses of dysphonia were identified using ICD-9 codes for various forms of dysphonia grouped into four categories, and individuals with any of the listed diagnosis codes before the study period were excluded. Deployment status was considered only during the study period (therefore, people who deployed before 2008 but not during the study period were counted in the nondeployed group). A total of 1,309,015 soldiers met the inclusion criteria, and of those, 4,921 soldiers had received a diagnosis of dysphonia; 1,895 had been deployed and 3,026 were nondeployed during the study period, resulting in a crude risk ratio of 1.13. Chi-squared analysis was used to determine statistical differences in the deployed versus nondeployed population of soldiers with dysphonia ($p < 0.001$). A convenience sample of 292 soldiers was selected for further evaluation of known factors linked to dysphonia; it included all subjects from the Army-wide population who were enrolled in centers covered by the Brooke Army Medical Center institutional review board. Demographic, military, and additional health information (including diagnosis, reflux status, tobacco use, and alcohol use) were collected using the electronic medical records for each individual in the convenience sample. Multinomial logistic regression was used in a combined model for variables found on chi-squared analysis to be independent to determine associations and relevant ORs. Risk factors and exposures common to patients with dysphonia were not statistically different between deployed and nondeployed soldiers. Additionally, the type of dysphonia diagnosis was not significantly different between deployed and nondeployed soldiers. None of the reviewed parameters accounted for the difference in dysphonia rate between deployed and nondeployed soldiers, suggesting that occupational exposures of deployed soldiers account for the increase in the diagnoses of dysphonia.

Synthesis

Previous National Academies reports in the *Gulf War and Health* series and other related reports have not addressed vocal cord dysfunction. Only one identified study (Dion et al., 2013) specifically examined the association between vocal cord dysfunction and dysphonia with deployment to Southwest Asia. Although there was a statistical difference in dysphonia between deployed and nondeployed soldiers, the inferences that can be made are limited.

Conclusions

Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and the subsequent development of vocal cord dysfunction.

Sleep Apnea

Sleep apnea is a disorder in which breathing repeatedly stops and starts while sleeping. There are three main types of sleep apnea: obstructive sleep apnea, central sleep apnea, and complex sleep apnea. Obstructive sleep apnea, the most common type, occurs when the muscles in the upper airway relax during sleep and is commonly associated with obesity or other conditions that increase the amount of tissue in the neck around the airway. It is characterized by loud snoring and daytime sleepiness. Central sleep apnea occurs when the brain does not send proper signals to the muscles that control breathing. Complex sleep apnea syndrome, also referred to as treatment-emergent central sleep apnea, is defined by having both obstructive and central sleep apnea (Mayo Clinic, 2020).

The prevalence of obstructive sleep apnea is not well characterized. One study, using in-laboratory polysomnography, estimated that the prevalence of obstructive sleep apnea in 602 middle-aged adults between 30 and 60 years of age was 9% for women and 24% for men (Young et al., 1993). There are some estimates of prevalence of sleep apnea among Southwest Asia theater veterans. Using data from the 2005–2014 National Survey on Drug Use and Health, Jackson et al. (2017) estimated that the prevalence of sleep apnea was more than 8% in 2014. They also pointed to an evaluation of OEF/OIF/OND veterans that found that 69.2% of 159 veterans screened were at high risk for obstructive sleep apnea.

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports

Previous committees have noted that personnel deployed to Southwest Asia have reported more sleep problems or disturbances than nondeployed veterans (Bossarte, 2014; Cherry et al., 2001; Doebbeling et al., 2000; Goss Gilroy Inc., 1998; Gray et al., 1999, 2002; Ishoy et al., 1999; Kang et al., 2000; Nisenbaum et al., 2004; Proctor et al., 1998; Sim et al., 2015; Simmons et al., 2004; Steele, 2000; Unwin et al., 1999). Sleep apnea as a distinct outcome was only assessed by Sim et al. (2015) using data collected from the Australian Gulf War Veterans' Follow Up Health Study conducted in 2011–2013. Sleep apnea (self-reported as being diagnosed with or treated for by a medical doctor) was reported by 70 (10.2%) of the Gulf War–deployed veterans and 63 (9.7%) of the non-deployed comparison group. The difference between the groups did not reach statistical significance (RR = 1.04, 95%CI 0.75–1.45) when adjusted for age group, service branch, and rank estimated as of August 1990, any atopy at baseline, and current smoking status (never, former, current smoker).

An analysis conducted by the AFHSC (2010) examined ICD-9-coded medical encounters at military facilities by Army and Air Force personnel within 36 months of April 2006 after deployment between 2005 and 2007 to Joint Base Balad or Camp Taji (with burn pits), Camp Buehring or Camp Arifjan (without burn pits), or the Republic of Korea (urban air pollution and PM exposure). Sleep apnea was examined using Poisson models, with analyses adjusted for sex, birth year, marital status, race/ethnicity, education, smoking status, physical activity, service branch, military rank, pay grade, and occupation. IRRs for sleep apnea were statistically significantly lower for personnel deployed to Joint Base Balad (IRR = 0.81, 95%CI 0.73–0.89), Camp Buehring (IRR = 0.63, 95%CI 0.40–0.99), and Korea (IRR = 0.87, 95%CI 0.81–0.93) compared with the nondeployed U.S. cohort; IRRs were no different for those deployed to Camp Arifjan (IRR = 1.08; 95%CI 0.92–1.26) or Camp Taji (IRR = 0.89; 95%CI 0.68–1.16).

Update of the Scientific Literature on Sleep Apnea

The committee identified 10 previously unreviewed studies that examined sleep apnea in Southwest Asia theater veterans. Four of the studies (Butzko et al., 2019; Dursa et al., 2016a; Morris et al., 2014, 2020) did not use appropriate comparison groups and thus did not provide information that could contribute to inferences that can be made regarding deployment to Southwest Asia and sleep apnea; these included two studies by STAMPEDE investigators (Morris et al., 2014, 2020) and one study involving veterans who had been referred to VA's WRIISC specialty clinic (Butzko et al., 2019).

Post-9/11 Veterans Smith et al. (2008) used self-reported clinician-diagnosed health data from regular, active-duty participants from the first panel (2001–2003) of the Millennium Cohort Study (n = 37,798) to compare the agreement of 38 medical conditions, which included sleep apnea, with that obtained from electronic medical records based on ICD-9-CM codes. Any diagnostic code for these 38 conditions in any portion of the medical record indicated agreement with a self-reported medical condition of interest. Positive and negative agreement was used to compare self-reported data with that from electronic medical records. The prevalence of sleep apnea was 2.7% (95%CI 2.6–2.9) for self-report and 1.5% (95%CI 1.4–1.6) for the electronic medical records; 0.5% were exclusively recorded in the electronic medical record. The positive agreement between self-report and electronic medical record sleep apnea was 45.1%, and the negative agreement (the condition was not reported either by self-report or found in the medical record) was 98.8%.

Díaz Santana et al. (2017) used data collected from the NewGen survey to examine the prevalence of 19 self-reported, physician-diagnosed mental and physical health outcomes, including sleep apnea, between deployed (n = 12,705) and nondeployed (n = 7,124) veterans. Sampling weights were applied to account for nonresponse and temporal misclassification of deployment status in the sampling frame to enhance the accuracy and precision of the estimates. Weighted mean physical and mental component summary scores were calculated by demographic and military characteristics. Multivariable logistic regression analysis was performed, and weighted, adjusted ORs were presented for each of the 19 self-reported medical conditions and deployment status. Models were adjusted for gender, birth year, service branch, unit component, race/ethnicity, education, and VA health care user status. The weighted prevalence of sleep apnea was 10.3% for the deployed and 9.7% for the nondeployed; no difference in sleep apnea was observed between deployed veterans and nondeployed veterans (OR = 1.02, 95%CI 0.91–1.14).

Rohrbeck et al. (2016) conducted a cohort study that compared U.S. service members deployed to Iraq (2006–2008, n = 163) and Afghanistan (2011–2012, n = 37) with matched nondeployed service members (n = 200) to examine the association between exposure to burn pits and the occurrence of ICD-coded respiratory outcomes, including sleep apnea, after returning from deployment. Data from medical encounters, both hospitalizations and outpatient visits, in military treatment facilities were used to capture information on sleep apnea. A 3% increase in the incidence of sleep apnea was reported in the Iraq cohort compared with the nondeployed cohort, although this was not statistically significant due to the study being underpowered. Using Cox Proportional Hazards regression, relative risks were adjusted for age, sex, race/ethnicity, occupation, deployment history, and history of illness prior to deployment, and the Bonferroni correction was applied. No difference was found for developing sleep apnea in the deployed cohort compared with the nondeployed cohort (RR = 0.54, 95%CI 0.05–5.78). This analysis had several limitations, including its representativeness, its power for detecting differences in outcomes, its lack of individual exposure assessment, and its inability to control for smoking, which limits its contribution to the evidence base.

1990–1991 Gulf War Veterans Khalil et al. (2018) described the study design for the Gulf War Era Cohort and Biorepository and preliminary results from the pilot phase of the effort, which had enrolled 1,275 veterans. Self-reported health outcomes of symptoms (in the past year) and health care provider–diagnosed conditions were reported stratified by users (n = 584) and nonusers (n = 679) of VA health care. Respiratory disease was not reported as a category, but sleep apnea was presented under other conditions by 39.2% of users and 21.2% of nonusers. While the reported proportions of veterans with sleep apnea seem high, there was no formal assessment of differences in the frequency of symptoms between VA users and nonusers. Furthermore, there were no comparisons between deployed and nondeployed veterans and, hence, these results do not inform questions about the role of Gulf War deployment on increased risk of sleep apnea.

Peacock et al. (1997) conducted a clinical assessment of 1990–1991 Gulf War veterans who participated in DoD's Comprehensive Clinical Evaluation Program and who were seen at Brooke Army Medical Center to examine the prevalence of sleep apnea and hypopnea. After the veterans completed an initial survey that included information on symptoms, environmental exposures, vaccination history, and areas of deployment during the war, clinicians performed an interview and examination. Of the 192 veterans, 46 had histories suggestive of a sleep disorder and were referred for further evaluation to the pulmonary division for nocturnal polysomnography. Of the 46 who underwent further evaluation, 15 veterans met the criteria for sleep apnea or hypopnea, which was defined as a respiratory disturbance index greater than 15 in an individual who is experiencing symptoms. The authors report that a majority of those who met the criteria had symptoms of fatigue and memory loss. The study did not present comparisons with veterans who were not referred for additional testing or with another group; confounding factors, such as age and weight, were collected and presented along with the results of the assessments only for those 15 individuals who met the criteria for sleep apnea or hypopnea, which severely limits the informativeness of this study.

Other Coalition Forces Veterans Gwini et al. (2016) examined new onset of self-reported conditions in deployed Gulf War veterans using data collected from wave 1 and wave 2 of the Australian Gulf War Veterans' Health Study. Veterans in wave 1, conducted in 2000–2002 (10 years after the Gulf War), were given a questionnaire that collected information on general health, physical and psychological health, military service history, and exposures during deployment and were also given a comprehensive health assessment, a full physical examination, blood work, and fitness tests; 81% (n = 1,456) of the deployed participated. Wave 2 was conducted in 2011–2013 and had a 50% participation rate. The follow-up study collected much of the same information as the original study, but it also inquired about additional outcomes. Participants were grouped into low (n = 272), moderate (n = 328), and high (n = 80) symptom reporting groups at wave 1 and assessed at wave 2 for selected symptoms and disease diagnosis to determine the new onset or incidence of particular conditions. Those who reported a condition of interest at wave 1 were excluded in the analyses of onset for wave 2. Respiratory health was assessed at both baseline and follow-up, but the scope of respiratory health data collected and the mode of data collection changed for some factors, which limited the ability to assess change over time for some of the outcomes. The wave 2 component of the study collected information on respiratory symptoms and medical conditions, including sleep apnea and asthma, assessed via self-report questionnaire. Logistic, nominal, and ordinal regressions were used for between-group comparisons. Regression models were adjusted for age group, service branch, and rank estimated as of August 1990, and smoking status, alcohol use, BMI, and highest educational level attained at wave 1. New onset of sleep apnea was increased in high versus low symptom reporters (OR = 9.40, 95%CI 3.47–25.46) and also in moderate versus low symptom reporters (OR = 2.63, 95%CI 1.17–5.88). The authors found that the odds of obesity and alcohol use increased over time and that smoking halved; these findings in risk factors were similar across symptom groups. The findings from the Australian Gulf War Veterans' Health Study likely lack generalizability to studies of respiratory disorders in U.S. Gulf War veterans, primarily because 85% of the Australian Gulf war veterans were Navy personnel, who likely did not have the same exposures—even when off ship—as U.S. ground forces. Furthermore, no analyses were presented to compare differences in those who participated in wave 2 with those who did not, which was half the cohort, and therefore confounding by indication cannot be ruled out for wave 2 responders.

Synthesis

The committee identified and reviewed six studies that examined sleep apnea, three among post-9/11 service members and veterans and three among 1990–1991 Gulf War veterans. Prevalence of sleep apnea among post-9/11 veterans was relatively low and, for two of the studies, based on ICD codes in medical records. The prevalence of sleep apnea was higher among 1990–1991 Gulf War veterans and was based on self-report in the reviewed studies. Few of the studies reported effect estimates from comparisons of sleep apnea between deployed and non-deployed service members or veterans, and those that did, did not adjust for potential confounders, such as use of concurrent medications or conditions that may affect sleep. Therefore, as a whole, the available evidence on sleep apnea and associations with deployment are limited. A 2020 VA Office of Inspector General report indicates that sleep apnea has been the most prevalent service-connected disability of all the respiratory disabilities for which veterans received benefits since fiscal year 2013, which suggests that more attention to the issue would be appropriate (VA, 2020).

Conclusions

Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and the subsequent development of sleep apnea.

PULMONARY FUNCTION TESTING

Pulmonary function tests (PFTs) can be considered objective measures of how well the respiratory system is working. In epidemiologic studies, they may produce less outcome misclassification than self-reported measures and, potentially, less bias to the null. However, some common measurements—the forced vital capacity (FVC, the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible), the forced expiratory volume in 1 second (FEV_1, the amount of air that can be forcibly exhaled in 1 second after taking in the deepest breath possible), the ratio of FEV_1 over FVC (FEV_1/FVC), and some less common measurements, such as total lung capacity (TLC)—rely on the participant's cooperation. Pulmonary function tests can be grouped into three sets of measures that use different equipment and procedures: spirometry, which includes FEV_1, FVC, FEV_1/FVC, and forced expiratory flow between 25% and 75% of expired volume ($FEF_{25–75\%}$), sometimes performed before and after the administration of a bronchodilator; lung volumes, which include TLC, functional residual capacity (FRC), residual volume (RV), and airways resistance (R_{aw}); and diffusing capacity, which includes diffusing capacity of the lung to carbon monoxide (DLCO) and the ratio of DLCO to alveolar volume (DL/VA). In many studies, airflow obstruction is defined as a situation involving FEV_1/FVC <0.70 or less than the lower limit of normal based on reference equations from a normal population. There are also some more specialized and often less standardized test measures and methods, such as bronchoprovocation testing (e.g., methacholine challenge or bronchoprovocation); cardiopulmonary exercise testing; and air oscillation methods, such as the forced oscillation technique (FOT) and impulse oscillometry (IOS), which measures respiratory mechanics during normal breathing, distinguishing between small airway and large airway obstruction. Also included are exhaled gas analysis methods, such as exhaled nitric oxide, and multiple breath inert gas washout, which quantifies ventilation heterogeneity and uneven distribution of ventilation, of which the lung clearance index (LCI)[6] is the most commonly reported parameter.

Findings from spirometry are the most commonly reported. Spirometry is nearly universally performed when lung function is measured because it is well standardized, relatively easy to perform, and remains the gold standard test for assessing the presence of common airways disorders, even though it may not adequately reflect the hyperinflation of the thorax largely responsible for the symptom of dyspnea that often accompanies airways disorders (O'Donnell et al., 2001). Spirometry also has important clinical relevance as loss of spirometric volumes and/or flow rates are often predictive of respiratory dysfunction.

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports

Volumes 4 and 8 of the *Gulf War and Health* series of reports were consistent in concluding that "there appears to be no increase in respiratory disease among Gulf War veterans when examined with objective measures of disease. Pulmonary function studies have shown no significant excess of lung function abnormalities among Gulf War veterans" (IOM, 2006, p. 151, reproduced in IOM, 2010). The evidence was therefore classified as "limited/suggestive evidence of no association between deployment to the Gulf War and decreased lung function in the first 10 years after the war." In the absence of any new studies on objective measures of lung function, the Volume 10 report (NASEM, 2016), like the Volume 8 report, also concluded "that there is limited/suggestive evidence of no association between deployment to the Gulf War and decreased lung function." The 2011 IOM report *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan* used literature in surrogate populations (firefighters, municipal incinerator workers, and residents who lived near municipal incinerators) to evaluate the potential for effects of exposure to burn pits, because very little research had been done in theater veterans. That committee found limited or suggestive evidence of an association only for decreased pulmonary function in firefighters.

The Gulf War and Health conclusions were based primarily on four epidemiologic studies (Gray et al., 1999; Ishoy et al., 1999; Karlinsky et al., 2004; Kelsall et al., 2004). The first was an early cross-sectional survey, conducted in 1994, of 527 active-duty veteran Gulf War Navy mobile construction battalion personnel

[6] LCI is the cumulative expired volume at the point where end-tidal inert gas concentration falls below one-fortieth of the original concentration, divided by the FRC.

(Seabees) and an internal control group of 970 veteran Seabees from 14 commands who were not deployed to the Gulf War (Gray et al., 1999). Despite the fact that the Gulf War–deployed Seabees had a higher prevalence of respiratory symptoms than the nondeployed Seabees, cigarette smoking–adjusted mean spirometric measures of lung function were no different between the two groups. Ishoy et al. (1999) described a cross-sectional survey of 686 Danish Gulf War veterans (84% participation) deployed to the Persian Gulf during the period 1990–1997, mostly in peacekeeping roles, and 231 randomly selected nondeployed armed forces controls (58% participation) matched on age and sex. Again, in spite of those veterans who had been deployed in the Gulf War having a higher prevalence of respiratory symptoms than those who were not, mean spirometric measures of lung function were no different between the two groups. Although data on cigarette smoking were available, they were not used to adjust the lung function findings. Karlinsky et al. (2004) conducted a cross-sectional survey of a subset of participants selected from the 21,000 veterans who participated in the NHS and who lived close to a study examination center. Pulmonary function and self-reported respiratory symptoms were examined in 1,036 deployed and 1,103 nondeployed veterans who completed the clinical examination component of the third phase of the NHS. Spirometric measures were used to categorize study participants into the following five groups: normal, non-reversible airways obstruction, reversible airway obstruction, restrictive lung physiology, and small airway obstruction. Gulf War–deployed veterans and non–Gulf War–deployed veterans were similarly distributed across the five lung function categories. The distribution among lung function categories for those with exposure to the emissions from the 1991 destruction of a nerve agent storage complex at Khamisiyah, Iraq, did not differ from that of either other Gulf War–deployed or the nondeployed veterans. Although data on cigarette smoking were available and a history of tobacco smoking was more common in deployed than in nondeployed (51.1% vs 44.4%; $p = 0.03$), the analyses were not controlled for cigarette smoking.

Using results from the Australian Gulf War Veterans' Health Study, in a cross-sectional study that included spirometric testing of Australian military personnel (Kelsall et al., 2004), with spirometric test results available for 1,341 deployed veterans and 1,340 nondeployed comparison group subjects, mean FEV_1, FVC, peak expiratory flow rate, and $FEF_{25–75\%}$ lung function levels in Australian Gulf War veterans were largely no different from those of military personnel who were not deployed to the Gulf. There were small, statistically significant increases in those deployed in mean FEV_1/FVC (0.7%; 95%CI 0.2–1.1) and $FEF_{75\%}$ levels (0.05; 95%CI 0.01–0.10) relative to those not deployed. The adjusted differences between means were calculated using robust linear regression, adjusting for age, height, smoking, weight, atopy, rank, service, education, and marital status.

Another study considered in the Volume 4 report was a prospective cohort study of 125 British bomb disposal engineers deployed to Kuwait for 5 months, in which spirometry was performed before deployment and throughout deployment, together with monitoring of PM_{10} (PM less than 10 microns in diameter) and gaseous pollutants (Coombe and Drysdale, 1993). Monitored mean PM_{10} concentrations were exceedingly high (~400 $\mu g/m^3$), but gaseous pollutant concentrations were not. Although this was a relatively small study, it was unique given that spirometry was measured both before deployment to Kuwait and throughout the deployment. Of the possible spirometric measures available, the authors elected to report findings only on $FEF_{25–75\%}$. In the 100 participants who had both sets of spirometry, there was no average within-individual difference in the level of $FEF_{25–75\%}$ obtained pre-deployment and the level measured shortly before the end of deployment, stratified either by cigarette smoking status or by self-reported smoke exposure.

Update of the Scientific Literature on Lung Function

There were several studies identified that analyzed lung function in post-9/11 veterans (Butzko et al., 2019; Davy et al., 2012; Falvo et al., 2016a,b; Holley et al., 2016; Krefft et al., 2017, 2020; Madar et al., 2017; Matthews et al., 2014; Morris et al., 2014, 2019; Szema et al., 2011; Weinstein et al., 2016). In addition, two studies were identified that evaluated the impact of service in the 1990–1991 Gulf War on pulmonary function (Hines et al., 2013; Lindheimer et al., 2019).

Post-9/11 Veterans

Morris et al. (2014) conducted a study (STAMPEDE I) of 50 active-duty U.S. military personnel recruited within 6 months after they had returned from deployment to Iraq or Afghanistan, all of whom reported new-onset pulmonary symptoms. Part of the physical examinations included measures of changes in pulmonary function using spirometry and oscillatory resistance measures. No adjustments for confounders were made. Investigators found baseline obstruction to be present in eight (16%) patients; two of whom had moderate obstruction (FEV_1 <70% predicted), and six patients with mild obstruction (FEV_1 >70% predicted). In three patients, the FEV_1 was greater than 90% predicted. Seven of 44 (16%) had a positive methacholine bronchoprovocation test (defined as a 20% decrease in FEV_1 at or below 4 mg/mL of methacholine) and another five (11%) had "borderline" hyper-responsiveness with a 20% decrease above the 4 mg/mL concentration cut-point up to 16 mg/mL. Results were used to provide a preliminary diagnosis for the entire patient cohort, although a full diagnosis could not be made in 14 patients. The study had the advantage of using objective outcome measures, but it was mostly descriptive in nature. Conclusions that can be drawn from this study are limited by the small number of cases examined at one medical center, the likelihood of referral bias, and the study design that lacked a comparison group, so measures of association could not be estimated.

Weinstein et al. (2016) evaluated exertional dyspnea among post-9/11 deployed military personnel using the same population as Morris et al. (2014), but at the time of this study the total population had increased from 50 to 240 service members. The physical exams included the same pulmonary function tests as described for Morris et al. (2014). Evaluations included full pulmonary function testing, impulse oscillometry, exhaled nitric oxide measurement, methacholine challenge testing, exercise laryngoscopy, cardiopulmonary exercise testing, and direct visualization of the central airways via fiberoptic bronchoscopy. The article then focuses on the results of five men and one woman who had no underlying lung disease and were identified as having symptomatic excessive dynamic airway collapse only during high levels of exertion. No comparisons with other participants or with specific deployment factors were made. Therefore, while this finding may be interesting, it is quite limited and difficult to attribute dynamic collapse of the central airways to inhalational exposures in Southwest Asia.

Using data collected as part of STAMPEDE II, Morris et al. (2019) reported on respiratory health outcomes and changes in the lung function of Army soldiers recruited from Fort Hood, Texas, between 2011 and 2014 before (n = 1,693) and after (n = 843) deployment to Southwest Asia. Participants completed a baseline questionnaire on their respiratory health and underwent examinations that included chest radiography, spirometry, and impulse oscillometry; the questionnaire with additional questions on exposures was administered post-deployment, and each of the lung function tests was also repeated post-deployment. Obstruction on spirometry was defined as FEV_1/FVC below the lower limit of normal as defined by the National Health and Nutrition Examination Survey (NHANES) III reference values. Mean levels of percent predicted lung function (FEV_1, FVC, FEV_1/FVC) obtained using spirometry following deployment were slightly larger than those obtained before deployment, but this difference was not statistically significant. Results from the impulse oscillometry showed statistically significant improvement, with a reduction in resistance (at 5 Hz and 20 Hz) and reactance (at 5 Hz). A total of 116 (19%) individuals in the post-deployment cohort were found to have obstruction; 87 had obstruction before deployment, among 54 the obstruction persisted on post-deployment spirometry and in 33 the obstruction was no longer present on post-deployment testing. An additional 29 individuals had normal pre-deployment spirometry and developed obstruction after deployment. Using all post-deployment participants, no statistically significant change in spirometry values for those identified with obstruction were found. In individuals with pre- and post-deployment obstruction, there was a small improvement in FEV_1, FVC, and FEV_1/FVC. Of the 29 subjects who developed obstructive indices, 13 had an FEV_1 of >90% predicted. Nearly one-third of the pre-deployment obstructed and pre- and post-deployment obstructed groups also had FEV_1 of >90% predicted. Because certain factors may impact spirometry, subgroup analyses by cigarette smoking, self-reported asthma, and increased BMI were performed, and all three groups demonstrated slight improvement in post-deployment spirometry compared with pre-deployment values, but with only differences in FEV_1 % predicted ($p = 0.02$) and FVC % predicted ($p = 0.03$) in the high BMI stratum being statistically significant. Logistic regression models were used to predict obstruction after deployment, and only age ($p = 0.02$) and self-reported asthma ($p = 0.045$) were found to be significantly predictive (not obesity, smoking status, or sex). In soldiers with abnormal spirometry pre-deployment or history of asthma, no indication of worsening lung function was found post-deployment. This was a strong study in that it was large and collected measurements of lung function both before and after deployment, which allowed for a more direct assessment of deployment effects than is possible from cross-sectional studies of associations with exposure. However, the study would have been strengthened by including an analysis of mean within-subject change in lung function rather than a comparison of overall means pre- and post-deployment.

Morris et al. (2020) reported on the results of STAMPEDE III, an investigation of clinical lung diseases in 380 military personnel who had deployed to Southwest Asia and reported having chronic respiratory symptoms temporally related to deployment. Participants completed a deployment questionnaire (deployment history, airborne exposures, smoking status, and pulmonary symptoms before, during, and after deployment), answered questions from the VA Airborne Hazards and Open Burn Pit Registry, and underwent a history and physical examination. Pulmonary function testing consisted of spirometry, lung volume, diffusing capacity, impulse oscillometry, and bronchodilator testing. Other tests included methacholine challenge, exercise laryngoscopy, high-resolution CT scan, electrocardiogram, and transthoracic echocardiography. Asthma was the most common diagnosis (n = 87, 22.9%), based on obstructive spirometry/impulse oscillometry and evidence of airway hyperreactivity, and 57 patients (15.0%) had reactivity with normal spirometry. Airway disorders were diagnosed for 25 individuals with laryngeal disorders and 16 individuals with excessive dynamic airway collapse. Interstitial lung disease was identified in 6 individuals, and 11 individuals had fixed obstructive lung disorders (this latter category included four cases of COPD and two cases of emphysema). Isolated pulmonary function abnormalities were identified in 40 individuals, and 16 individuals had miscellaneous disorders. Nearly one-third of the study population (n = 122) had normal results and were classified as undiagnosed exertional dyspnea. The authors made many comparisons between different diagnostic categories for demographics, PFT, IOS, and underlying comorbidities, but no comparisons were made to differentiate among length or location of deployment or number of deployments and effects on lung function. This study provides an important description of pulmonary function among a group of military personal with chronic respiratory symptoms who were previously deployed to Southwest Asia, but because there is not a comparison group it is unclear whether service in Southwest Asia is associated with changes in lung function. While data were available, no adjustment or stratification was made for smoking status or specific reported exposures and results of PFTs.

In one of the few studies attempting to examine potential long-term effects of post-9/11 deployment, Falvo et al. (2016a) conducted a cross-sectional assessment of 124 post-9/11 veterans who had been referred to VA's WRIISC specialty clinic as part of a multiday clinical evaluation between May 2012 and February 2015. Standardized self-administered questionnaires were used to gather data on demographics, deployment length in Iraq or Afghanistan, frequency of deployment periods, smoking histories, and symptom histories. The total months in a deployment area of concern were used as a surrogate of exposure. Standard spirometry pre- and post-bronchodilator data were collected and related to the number of months deployed. The study was conducted on average 6.9 years after deployment when the average age of these veterans was 38 years. After adjustment for smoking, there was a statistically significant association between months deployed and increased percentage of bronchodilator change in FEV_1 ($p = 0.003$). Although almost all of the lung function test results were in the normal range, 26% of study participants had a positive response to a bronchodilator of at least a 12% and 200 mL improvement in FEV_1. This study has several limitations. The study sample is a highly selected group of veterans referred to a tertiary clinic, and information on deployment was self-reported. Furthermore, in the description of the statistical analysis, the equation for calculating percent FEV_1 response to bronchodilator was the following: ([pre-bronchodilator FEV_1 – post-bronchodilator FEV_1] / pre-bronchodilator FEV_1) × 100, which would be a negative value if there were a post-bronchodilator improvement, an improvement observed in the large majority of the participants. Presumably, this equation was an error in that the numerator should have the pre-bronchodilator value subtracted from the post-bronchodilator value, rather than the other way around. While no firm conclusions can be drawn from this study because of these limitations, it nevertheless points to the need for studies including longer follow-up time periods, rather than immediate post-deployment assessments.

Falvo et al. (2016b) conducted a retrospective review of pulmonary function testing, including DLCO, in 143 veterans referred to VA's WRIISC specialty clinic. The results of lung function tests were categorized into normal, restrictive, and obstructive. More than 75% of the sample had normal lung volumes and spirometry; however, an isolated reduction in DLCO was observed in 30% of the sample of post-9/11 veterans. The observation of an isolated reduction in DLCO is reported to be unusual in primary-care-seeking dyspneic patients (<1%), so this finding provides some evidence that deployment may be related to a reduction in lung function. The deployment length was similar between those with normal (12.9 months ± 8.7) and reduced (10.3 months ± 7.4) DLCO. This study suffers from many flaws, including having a small sample size and making no adjustment for confounders.

Butzko et al. (2019) tested the utility of the forced oscillation technique on 178 OEF/OIF veterans referred to WRIISC who had normal spirometry and chronic unexplained respiratory symptoms. In this sample of veterans, spirometry was normal in 71.3%, of whom 124 had acceptable forced oscillation technique data; 75% of the 124 who had normal spirometric measures had one or more abnormal measures on forced oscillation, which the investigators suggested indicated distal airways obstruction. However, no comparison group was available, which makes it difficult to draw any conclusions as to whether this finding is unusual or is one that would be expected in a comparable group of veterans not deployed to Iraq or Afghanistan. The clinical significance of these findings is therefore undetermined.

Szema et al. (2011) conducted a retrospective study using data collected by the Northport, New York, VA Medical Center Research and Development Committee. To examine if the deployed were more likely to have asthma or respiratory symptoms requiring the use of spirometry than nondeployed service members, they included U.S. military service members who were deployed to OEF/OIF (n = 1,816, 25%) or elsewhere (n = 5,335, 75%) (matched on age and gender) who were discharged from active duty and who were examined between March 1, 2004, and December 1, 2010. This study is a follow-on to Szema et al. (2010), which focused on asthma diagnosis. To be eligible for spirometry, patients must have had symptoms and a diagnosis in their medical record and be referred by a physician. For veterans who had spirometry, comparisons were made by deployment location. Of those who had spirometry, 34.9% were smokers compared with 5.1% of those who did not have spirometry. Also, 72% of those who had spirometry (and clinical symptoms warranting a diagnosis) were deployed to Iraq or Afghanistan. Service members who underwent spirometry were stratified by deployment location and then matched for age, height, and weight. FEV_1 and FVC were statistically significantly lower for those deployed in Iraq or Afghanistan than for those deployed elsewhere, but no difference was observed for FEV_1/FVC ($p = 0.63$). An important limitation of this study is that raw FEV_1 and FVC are largely meaningless unless adjusted for age, height, and sex. This is typically accomplished by using reference equations that incorporate age and height for men and women separately and reporting the percent of predicted values, which was not done. Those veterans deployed in Iraq or Afghanistan were shorter and older than those deployed stateside. Because both increased age in adults and shorter stature result in lower levels of lung function, the findings on FEV_1 and FVC reported in this study are uninterpretable. The study is also limited by a lack of adjustment of confounders.

Matthews et al. (2014) conducted a retrospective review of DoD electronic medical records to identify trends in the frequency and severity of COPD based on pulmonary function tests in service members relative to their deployment history. Inpatient and outpatient records were queried to identify active-duty personnel from all service branches with the ICD-9 code for either "emphysema" (492.8) or "chronic airway obstruction, not elsewhere classified" (496) for 5 consecutive years from 2005 to 2009. Individuals with diagnosis of asthma (493) or chronic bronchitis (490) were excluded. Medical records review was limited to those individuals with a minimum of three outpatient encounters with the listed diagnosis of COPD/emphysema during the study period. Deployment information was obtained from the AFHSC, and individuals were classified into deployers and nondeployers based on whether they had deployed to Southwest Asia during or since 2003. Clinical symptoms, smoking history, pulmonary function testing, and radiographs obtained during the diagnostic workup were reviewed. A total of 371 patients with diagnosed COPD or emphysema were identified; 194 (52.3%) had deployed and 177 (47.7%) did not deploy to Southwest Asia since 2003. Of those deployed, 68% had a documented history of smoking compared with 62% of those nondeployed. Specific comparisons were made for age, FEV_1 (% predicted), FEV_1 post-bronchodilator (% predicted) and percent change, FVC (% predicted), FEV_1/FVC, TLC, RV, and DLCO. Spirometry was documented in a total of 270 (73%) individuals, including both in the deployed (n = 155) and the nondeployed (n = 115) groups. According to t-tests, decreases in lung function were not statistically significantly different between the deployed and nondeployed individuals for all measures except TLC (% predicted) ($p = 0.03$). There was an overall reduction in the % predicted FEV_1 (75.5 ± 17.1%) compared with normal reference values and a corresponding decrease in the FEV_1/FVC (67.9 ± 10.4) consistent with airway obstruction. Mean % predicted TLC was 100.8 (± 15.2%), the % predicted RV was 116.7 (± 43.7%), and the % predicted DLCO was 83.4 (± 21.8), all of which were within normal predicted values. Airway obstruction was identified by spirometry in only 67% of the individuals diagnosed with COPD. Among individuals with a documented smoking history and spirometry data, 65% of those deployed and 46% of those nondeployed met established diagnostic criteria for COPD. Disease severity as measured by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, was similar for deployed and nondeployed subjects: 30% versus 33% for those with mild disease, 57% versus 60% for those with moderate disease, and 14% versus 7% for those diagnosed with severe disease. Although the investigators concluded that despite evidence of increased respiratory symptoms in deployed military personnel, the impact of deployment on increased diagnosis of COPD or severity of disease appears minimal, this study lacked a prospective design and adequate adjustment for confounders of the relationship between deployment and pulmonary function. It is clear from the analyses conducted that—in this relatively young population (average age 40)—only about half had an adequate workup to assess the diagnosis of COPD. For example, smoking history was missing in about 35% of cases, pulmonary function testing was recorded in only about 55% of cases, and among these only about 25% had documented obstruction and only about 25% had assessments for alpha-1 antitrypsin deficiency despite their relatively young ages.[7] The authors were aware of these limitations, which they speculate may be related to the nature of the retrospective databases, and they suggest that longer and more complete follow-up is necessary. Unfortunately, given the nature of the database being assessed, it is unlikely that further follow-up alone will be adequate. An alternative study design with prospective assessment would be needed because it is unlikely that the retrospective review of existing records will substantially improve.

Holley et al. (2016) conducted a retrospective review of 267 patients referred to the pulmonary clinics at Walter Reed National Military Medical Center and Fort Belvoir Community Hospital from February 2012 through May 2013 for unexplained respiratory complaints. All had at least one spirometry test performed following deployment in support of OEF/OIF, and the purpose of the study was to analyze associations between lung function and demographic and deployment characteristics. Spirometry was performed pre- and post-bronchodilator administration, and DLCO tests were performed in subsets of the veterans. Prevalence of abnormal spirometry was categorized as follows: 17% obstructed, 11% "restricted," and 3% mixed obstructed and restricted. Mean DLCO was 95% of predicted, and 10% were below the lower 5th percentile cutoff point. Only 6% responded to bronchodilator administration. Lung function measures (mean % predicted values for FEV_1, FVC, FEV_1/FVC, FEV_3/FVC, DLCO, and the carbon monoxide transfer coefficient) were not related to total number of deployments, deployment to Afghanistan versus other countries, deployment to Iraq versus other countries, total days deployed, months since the most recent deployment, reserve versus active duty, or land- versus sea-based deployments. Current or prior tobacco use was not associated with statistically significantly lower mean values for FEV_1, FVC, or FEV_1/FVC % predicted. However, because of the small sample size, this study had a limited ability to detect differences related to deployment.

Krefft et al. (2017) conducted a small pilot study to examine the role of lung clearance index as an early marker of lung injury in a sample of 24 healthy volunteers and 28 symptomatic veterans who had deployed to Southwest Asia in support of post-9/11 operations. The symptomatic deployers had cough, chest tightness, wheezing, shortness of breath, or decreased exercise tolerance during or following deployment. Individuals who were found to have other explanations for their respiratory symptoms were excluded. The healthy controls were at least 18 years of age, had no history of pre-existing lung disease, and reported no respiratory illness in the 4 weeks preceding enrollment and testing. Both groups underwent lung clearance index testing to identify whether abnormalities were present in the peripheral airways of the lung. As part of their clinical evaluation, the veteran group completed tests of pre- and post-bronchodilator spirometry, lung volumes, and DLCO in accordance with American Thoracic Society (ATS) standards. Abnormal spirometry was defined as an FVC percent predicted below the lower limit of normal (LLN), an FEV_1 percent predicted below the LLN, or an FEV_1/FVC ratio below the LLN. Spirometry reference values were obtained from NHANES III. Lung volume reference values were based on the 1995 ATS/European Respiratory Society (ERS) workshop, and reference values for DLCO were obtained from the Crapo prediction set. An abnormal

[7] Alpha-1 antitrypsin deficiency is a risk factor for COPD (NHLBI, 2020a).

cardiopulmonary exercise tolerance (volume of oxygen [VO_2] max <85% predicted) was observed in 52% of symptomatic deployers, abnormally elevated residual volume >120% was observed in 25% of symptomatic deployers, DLCO <80% predicted was observed in 21% of symptomatic deployers, abnormal spirometry was observed in 18% of symptomatic deployers, and $FEF_{25–75\%}$ <LLN was observed in 18% of symptomatic deployers. Of the 28 veterans with respiratory symptoms, 17 were found to have definite and 11 were found to have probable deployment-related lung disease. Lung clearance indexing tests were abnormal in 82% of the symptomatic veterans, but also in 54% of the healthy controls, and they were more often abnormal in symptomatic veterans than were other detailed tests. Using t-tests adjusted for age, smoking status, and BMI, mean lung clearance index scores were compared between the veteran and the control group; mean lung clearance index scores were not statistically significantly different in the veterans (7.42, 95%CI 7.13–7.71) than in the controls (7.06, 95%CI 6.74–7.39, p = 0.10). Given that there was no comparison group in this study for the PFT, this study provides limited evidence of the impact of deployment to the Southwest Asia theater on pulmonary function. The small sample of veterans was highly selective as they were all symptomatic and were seen at an occupational lung disease clinic.

Krefft et al. (2020) aimed to describe deployment-related respiratory disease and the diagnostic utility of resting and exercise PFT with a retrospective study of 127 military personnel, veterans, and civilian contractors who supported military operations in Southwest Asia with new-onset respiratory symptoms presenting between 2009 and 2017 and referred to a single occupational lung disease clinic. Detailed medical, occupational, and smoking histories were collected. Of the 127 patients, 113 underwent PFT including pre- and post-bronchodilator spirometry, lung volumes determined by plethysmography, and DLCO measurement. The authors used logistic regression to determine whether abnormal physiologic findings were predictive of those with deployment-related distal lung disease. The researchers observed decreased DLCO to be significantly associated with a deployment-related distal lung disease, defined based on histopathology. Low DLCO was found in those with both deployment-related distal lung disease and deployment-related asthma (OR = 7.9, 95%CI 1.01–62.6, p = 0.05), and in those with deployment-related distal lung disease without asthma (OR = 4.6, 95%CI 1.4–15.1, p = 0.01). No other abnormal physiologic findings were individually associated with deployment-related distal lung disease diagnosis. The researchers concluded that obtaining baseline spirometry in defense force personnel before deployment may be useful in identifying changes linked to deployment exposures. The study is limited for the committee's purposes because it includes only cases and does not including a control group.

Madar et al. (2017) retrospectively reviewed a series of biopsies of non-neoplastic lung disease that were evaluated at the Armed Forces Institute of Pathology or Joint Pathology Center from January 2005 through December 2012 in 391 service members (137 had deployed to Southwest Asia prior to biopsy [deployed] and 254 had not deployed before the biopsy [nondeployed]). According to electronic medical records, 41% of the deployed and 56% of the nondeployed personnel were prior smokers; whether changes in smoking habits occurred during deployment or at the time of biopsy is not documented. Spirometric measures were extracted from the medical records, and comparisons were made based on Southwest Asia deployment status using independent means t-tests. The nondeployed group had slightly lower FVC (77.1% vs 83.2%; p = 0.03) but no difference based on TLC (79.9% vs 81.8%, p = 0.66). DLCO was lower in the nondeployed group (58.4% vs 72.0%; p <0.05). In addition to the limitations of this study noted in Chapter 3, the results were applicable only to those with respiratory disease that required biopsy.

Other Coalition Forces Veterans Davy et al. (2012) performed a review of the respiratory health of Australian Defence Force personnel deployed to the Southwest Asia theater as part of the Middle East Area of Operations Prospective Health Study. The study population was defined as Australian Defence Force personnel who deployed after June 2010 and returned from that deployment by June 2012. Of the total eligible population of 3,074, a group of 156 completed pre- and post-deployment questionnaires, a physical examination, and spirometry test results that were usable for research purposes. FEV_1 and % predicted FEV_1 values from pre-deployment to post-deployment were found to be statistically significantly larger for those who deployed for 9–12 months (change in % predicted = 3.9, 95%CI 1.26–6.55) and lower for those who deployed for 6–7 months (change in % predicted = –2.80, 95%CI –4.42– –1.17) or 8 months (change in % predicted = –3.42, 95%CI –5.18– –1.67). These results suggest improved lung function following deployment in those deployed for a longer duration.

This finding may be a result of selection bias as those deployed for a longer duration may have been healthier than those deployed for shorter periods.

1990–1991 Gulf War Veterans

Hines et al. (2013) examined 37 1990–1991 Gulf War veterans who were enrolled in the VA Depleted Uranium Surveillance Program and had attended a biennial follow-up in 2011 to compare the likelihood of pulmonary health abnormalities in those with high body burdens of uranium (n = 12; >0.1 µg/g creatinine) versus those with low body burdens of uranium (n = 25; ≤0.1 µg/g creatinine). Participants attended a 3-day, inpatient clinical assessment that included a detailed medical and exposure history, physical examination, laboratory studies, and a comprehensive assessment of pulmonary health and function that included pulmonary function tests, CT chest-imaging studies, and IOS. Overall, pulmonary function tests were normal, and veterans with high urinary uranium content did not have statistically significantly different PFT values compared with those with low urinary uranium. No statistically significant differences in the prevalence of chest CT abnormalities or IOS between high and low urinary uranium groups were found. While the findings from this study made use of a rigorous exposure assessment through analysis of uranium in urinary samples, the findings are not particularly pertinent to this assessment, given that exposure to depleted uranium was uncommon.

Cardiopulmonary exercise testing was performed in a small number of lifelong nonsmoking veterans who were referred to VA's WRIISC specialty clinic (Lindheimer et al., 2019). Twenty veterans described as having Gulf War illness were compared with 14 unmatched controls (consisting of both veterans and civilians). Spirometry was performed in accordance with standard guidelines using commercially available equipment that was calibrated prior to each participant. Spirometric indices of FVC, FEV_1, and FEV_1/FVC were obtained and expressed as a percent of predicted. The researchers found that both the Gulf War illness and the control groups had a similar minute ventilation at maximal exercise, but those with Gulf War illness on average had a ventilatory pattern characterized by larger tidal volume (breath volume) and lower respiratory rate (breathing rate) compared with the controls in achieving the same minute ventilation (total volume of air expired each minute). These findings suggest that deployed veterans with Gulf War illness might have a different ventilatory pattern during exercise, but no information was provided about Gulf War veterans without Gulf War illness.

Synthesis

Volumes 4, 8, and 10 of the *Gulf War and Health* series concluded "that there was limited/suggestive evidence of no association between deployment to the Gulf War and decreased lung function in the first 10 years after the war." The new studies in 1990–1991 Gulf War veterans did not introduce evidence to support a revised conclusion. As described in Chapter 3, the grade of evidence, "Limited/Suggestive Evidence of No Association," is assigned when

> there are several adequate studies, covering the full range of levels of exposure that humans are known to encounter, that are consistent in not showing an association between an in-theater exposure and a respiratory health outcome in humans. In other cases, there is evidence from human or animal studies, but the heterogeneity of exposures, outcomes, and methods leads to inconsistent findings that preclude the committee from identifying an association between exposure and effect.

The studies included in this report differ from the findings of the previous *Gulf War and Health* reports in that they also include those who served in post-9/11 conflicts. The question to address now is whether the grade of evidence should remain the same based on studies of post-9/11 Gulf War exposures as the ones that were determined based on regarding exposures in the 1990–1991 Gulf War.

The most significant of the more recent studies is the relatively large STAMPEDE II study of those deployed to post-9/11 conflicts (Morris et al., 2019) in which measurements of lung function were performed both before and after deployment, allowing for a more direct assessment of deployment effects than is possible from cross-sectional studies of associations with exposure. The mean levels of percent predicted lung function obtained following deployment were slightly larger than those obtained before deployment. A limitation of this study is that the investigators missed an opportunity to carry out a more appropriate analysis of mean within-subject change in lung function rather than a comparison of overall means pre- and post-deployment, which assumes that the two measures are independent—which they are not given that the two measures were obtained from the same individuals. The most likely impact of carrying out the proper analysis would typically be to reduce the variance in the effect measures and the degrees of freedom of the statistical test used to test for differences; that is, the variance of the lung function studies done either before or after deployment would be greater than the variance of the individual differences in level of lung function, which would have resulted in greater power to detect a difference between the pre- and post-level of lung function. The difference in means of the pre- and post-deployment lung function (as was done), however, should theoretically be the same as the mean of the within-individual differences. This difference was still detected in the published analysis in spite of the poorer power. An additional advantage of carrying out a paired within-individual analysis is the ability to evaluate subgroups of individuals with different patterns of lung function change, allowing for more focused analyses or clinical follow-up.

Other recent studies summarized earlier that assessed effects of deployment were plagued by an absence of comparison groups (Butzko et al., 2019), were analyzed in such a way as to be hard to interpret (Falvo et al., 2016a; Szema et al., 2011), or were based on a population that may not represent all theater veterans (Madar et al., 2017). These studies do not add to or detract from the evidence of no association with level of lung function.

Associations with exposure were not observed among studies that used IOS (or FOT), cardiopulmonary exercise testing, bronchial responsiveness, or LCI, while demonstrating the promise of these tests in assessing abnormalities of lung function in Southwest Asia, to date, in the absence of appropriate comparison groups, they have been of little value in assessing the role of Southwest Asia exposures. Falvo et al. (2016a) studied the response to a bronchodilator in relation to self-reported duration of deployment, but the study was limited by the use of a highly selected sample and self-reported information on deployment. The one study in which IOS was done both pre- and post-deployment found slight improvement in the oscillometric measures after deployment (Morris et al., 2019); however, the authors did not use an analysis that accounted for the paired nature of the data for this analysis either.

Deterioration of lung function is most likely to be observed with longitudinal studies that include pre- and post-deployment measures of lung function. The findings of Morris et al. (2019) and others have been used to argue that there is no role for surveillance spirometry in those being deployed to or returning from deployment in the theater who are asymptomatic. The arguments are based on concerns about cost and measurement reliability and about the very low frequency of detecting abnormalities in those individuals without symptoms or pre-existing respiratory conditions. While these points are valid, there remain at least two important questions that could be addressed with surveillance spirometry: (1) Would pre-deployment spirometry be useful in detecting those at risk of deployment-related respiratory problems? and (2) Would pre-deployment spirometry be useful in the assessment of post-deployment respiratory problems? The latter question is based on an understanding that baseline measurements of lung function allow for an assessment of change in function, whereas post-deployment measurements alone do not. For example, someone may have had a relatively high level of lung function prior to deployment and experienced a marked fall in lung function related to deployment but still have a post-deployment level within the normal range. Conversely, someone may have had a relatively low level of lung function at baseline with little or no change in lung function following deployment. With only a post-deployment measurement, both may have had a similar level of lung function measured post-deployment, but the first experienced a concerning deployment-related decline in lung function while the second did not. A post-deployment spirometry alone could not distinguish the two, whereas pre- and post-deployment spirometry could. Furthermore, because of the great concern about Gulf War exposures triggering irritant-induced asthma, surveillance spirometry before deployment performed before and after inhalation of a bronchodilator would be even more useful in assessing post-deployment respiratory problems.

An additional issue that has not been addressed by studies of in-theater exposures and lung function to date is that of the long-term or chronic impacts of exposures on lung function. Studies to address that question would require some form of surveillance lung function measurements. Improved exposure measurement could improve confidence in the evidence of theater exposure on health effects. In light of all of the above, the question as to the value of surveillance spirometry should therefore remain open.

Conclusions

The current committee concurs with previous committees and concludes that there is limited or suggestive evidence of no association between deployment to the 1990–1991 Gulf War and changes in lung function. Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and subsequent deterioration of lung function in post-9/11 veterans. Chapter 5 includes observations and recommendations for future research that may provide greater insight on this issue.

LOWER AIRWAY DISORDERS

The lower airways, where gas conduction occurs, consist of the trachea, bronchi, and bronchioles. The trachea divides into the bronchi and the bronchioles through an extensive branching network ending with the terminal bronchioles. The airways then lead to the respiratory bronchioles, alveolar ducts, and alveolar sacs (alveoli), where gas exchange occurs, allowing oxygen molecules to cross from the alveoli to the capillaries (Tortora and Dickerson, 2018).

Diseases of the lower airway occur from many different physiological processes and include asthma, COPD (including emphysema and chronic bronchitis), bronchiolitis, interstitial lung diseases (including hypersensitivity pneumonitis, sarcoidosis, acute eosinophilic pneumonia, pulmonary alveolar proteinosis, and idiopathic interstitial pneumonias), and infectious diseases that impact the lower airway (including acute bronchitis, pneumonia, and tuberculosis). Diseases of pulmonary vascular circulation, such as pulmonary embolism, were not considered. Lower respiratory diseases that have been studied in theater veterans are summarized below. Each section begins with a description of the condition, its known causes and frequency of occurrence, and any common challenges in interpreting findings of the studies of it before presenting summaries of the identified epidemiologic studies in veterans. As for the Upper Airway Disorders section, each condition section ends with a synthesis followed by a conclusion on the strength of association between deployment to Southwest Asia and the respiratory condition of interest.

Asthma

Asthma is a chronic inflammatory disease of the airways that causes symptoms of coughing, wheezing, shortness of breath, and chest tightness that are accompanied by a narrowing of the airways causing airflow obstruction (GINA, 2019). The symptoms and severity of airflow obstruction vary over time, and “asthma attacks” are often triggered by environmental and occupational exposures (Mayo Clinic, 2018a). Environmental triggers include indoor and outdoor allergens and airborne pollutants, such as biologic allergens (dust mites, cockroaches, animal dander, and mold), environmental tobacco smoke, irritant chemicals, traffic pollution, ground-level ozone, and combustion byproducts (Chabra and Gupta, 2019). Occupational exposures can either cause asthma (“occupational asthma”) or exacerbate existing asthma (“work-exacerbated asthma”). In some cases, occupational exposures can both cause asthma and perpetuate ongoing symptoms. Work-exacerbated asthma can be assessed by documenting the relationship between the timing of symptoms with workplace activity or exposures as well as by documenting changes in lung function (Hennenberger et al., 2011; Redlich et al., 2014).

Asthma is a common disease in the United States and affects 7.7% of adults over 18 years of age.[8] The annual incidence of occupational asthma ranges from 12 to 170 cases per million people working. The prevalence of adult asthma that is occupational is estimated to be 5% to 15% across many different industries (Chabra and Gupta,

[8] See https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_A-2.pdf (accessed August 19, 2019).

2019). Reportedly, asthma is associated with service in the Southwest Asia theater. A few retrospective studies have observed a higher prevalence of new-onset asthma among Southwest Asia veterans than among those not deployed (Rivera et al., 2018), and since 2003 the prevalence of asthma has been increasing among those receiving VA care (Pugh et al., 2016).

In order to study asthma it is necessary to have a standard case definition. Asthma is defined, according to international guidelines, as "a heterogeneous disease usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation" (GINA, 2019). The gold standard in research is often a physician diagnosis of asthma or evidence of bronchial hyperresponsiveness demonstrated through physiologic PFT, such as methacholine challenge tests (Coates et al., 2017) or pre- and post-bronchodilator spirometry (Graham et al., 2019; Sá-Sousa et al., 2014).

Outcome measures in asthma research include the assessment of asthma control based on standard questionnaires, spirometry, asthma exacerbations, and health-related quality of life. Asthma control is defined by the presence of daytime and nighttime asthma symptoms and the risk of future exacerbations. Spirometry is another outcome that is a crucial component in assessing asthma. The variables of interest include FEV_1, FVC and FEV_1/FVC ratio, and bronchodilator responsiveness (change in FEV_1 or FVC after bronchodilator administration according to standard protocols) (Graham et al., 2019). These are typically assessed over time, which allows for the evaluation of within-person changes. Asthma exacerbations should be assessed using a standard approach, such as that put forward in the ATS/ERS consensus statement in standardizing endpoints for asthma clinical trials (Reddel et al., 2009).

Asthma exacerbations should be assessed within a standard approach (Reddel et al., 2009), which may include severe, moderate, and mild exacerbations. Frequently, severe exacerbations include the need for systemic corticosteroids or acute care use, such as an unscheduled doctor visit, emergency department visit, or hospitalization. Moderate exacerbations include the need for additional asthma controller medications. Mild exacerbations are more challenging to assess and are likely reflected in standard measures of asthma control (loss of control on asthma questionnaires is equivalent to a mild exacerbation).

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports

As noted in previous reports that focused on veterans deployed to the Southwest Asia theater (IOM, 2006, 2010; NASEM, 2016, 2017), asthma and related symptoms, such as wheezing and shortness of breath, have consistently been a concern among veterans after deployment. Nonetheless, the Volume 10 committee concluded that there was insufficient or inadequate evidence to determine whether an association exists between deployment to the Gulf War and respiratory disease, based on cohort studies of 1990–1991 Gulf War–deployed and nondeployed service members from four countries (Australia, Denmark, United Kingdom, and United States). Committees for Volumes 4, 8, and 10 did not make separate conclusions for asthma. The committees for Volumes 6 and 8 concluded that there was inadequate or insufficient evidence to determine whether an association exists between deployment to the Gulf War and respiratory disease. This conclusion was a change from Volume 4, in which that committee concluded that respiratory symptoms were strongly associated with Gulf War deployment when using comparison groups of nondeployed veterans. The Volume 10 committee concurred with the Volume 8 committee. It concluded that based on the literature reviewed in previous volumes and the few new studies, there was insufficient or inadequate evidence to determine whether an association exists between deployment to the 1990–1991 Gulf War and respiratory disease.

The next part of this section summarizes the results of asthma outcomes that were reported in the 19 studies of service members of veterans that examined diagnoses or self-reported asthma included in prior *Gulf War and Health* reports (Cowan et al., 2002; Dursa et al., 2016b; Eisen et al., 2005; Goss Gilroy Inc., 1998; Gray et al., 2002; Iowa Persian Gulf Study Group, 1997; Kang et al., 2000, 2009; Karlinsky et al., 2004; Kelsall et al., 2004; Lange et al., 2002; Li et al., 2011; Sim et al., 2015; Simmons et al., 2004; Smith et al., 2006; Steele, 2000; Unwin, 1999; VA, 2014a,b). The studies of 1990–1991 Gulf War veterans showed mixed results. Several of these studies examined multiple respiratory outcomes, grouped symptoms and conditions, relied on self-reports of respiratory diagnoses and symptoms, and did not adjust for known confounders, such as obesity. The studies are summarized below, beginning with studies of U.S. veterans, followed by UK, Canadian, and Australian veterans. Background information on large studies is provided for context.

1990–1991 U.S. Gulf War Veterans Large cohort studies of 1990–1991 Gulf War veterans include VA's NHS and several that focused on state-specific cohorts or cohorts with particular military jobs. Several cohorts of foreign military forces have also been assembled and followed, and these studies are described after the studies of U.S. veterans.

National Health Survey of Gulf War Era Veterans and Their Families As described in Chapter 3, VA conducted a population-based study consisting of three waves to examine the prevalence of health outcomes and symptoms in deployed Gulf War veterans and Gulf War–era veterans, known as the NHS. Three studies analyzed and reported on asthma collected from wave 1 (Eisen et al., 2005; Kang et al., 2000; Karlinsky et al., 2004), two publications reported on asthma collected from wave 2 (Kang et al., 2009; Li et al., 2011), and one publication examined outcomes of asthma using data collected from wave 3 (Dursa et al., 2016b). The design and details of the NHS are described in Chapter 3.

Kang et al. (2000) used information collected as part of the NHS to estimate the prevalence of symptoms and other health outcomes in Gulf War veterans (n = 15,000) compared with era veterans (n = 15,000). Population prevalence rates were calculated using statistical analysis techniques to account for the stratified random sampling of unequal probabilities of selecting various strata. The estimated population prevalence of asthma during the 12 months prior to the survey was 4.7% for the deployed and 3.7% for the nondeployed (RD = 0.97, 95%CI 0.91–1.03), a statistically significant difference; however, estimates were not adjusted for smoking or other factors.

Karlinsky et al. (2004) examined pulmonary function and self-reported pulmonary histories (including self-reported respiratory symptoms, physician visits and hospitalizations, and outcomes of asthma, bronchitis, and emphysema) in 1,036 deployed and 1,103 nondeployed veterans who completed the clinical examination component of the third phase of the NHS. Deployed veterans were statistically significantly more likely than nondeployed veterans to self-report a history of smoking (OR = 1.31, 95%CI 1.03–1.67), but there was no difference for self-reported asthma (OR = 0.90, 95%CI 0.50–1.62), self-reported physician visits for pulmonary complaints (which included asthma) (OR = 1.07, 95%CI 0.51–2.24), or self-reported pulmonary hospitalizations (which again included asthma) (OR = 0.91, 95%CI 0.13–6.51). Estimates were not adjusted for demographic factors or smoking status.

Eisen et al. (2005) performed a cross-sectional analysis on health outcomes collected in a subset of 1,061 deployed and 1,128 nondeployed Gulf War veterans (the same population used by Karlinsky et al., 2004) who completed the clinical examination component of the third phase of the NHS. The investigators examined several outcomes, including "obstructive lung disease," which was defined as

> a history of lung disease (asthma, bronchitis, or emphysema) or pulmonary symptoms (wheezing, dyspnea on exertion, or persistent coughing with phlegm) and either the use of bronchodilators or at least 15% improvement in FEV_1 after a short-acting bronchodilator. (Eisen et al., 2005, p. 884)

No difference in these outcomes was found between deployed and nondeployed veterans (OR = 0.91, 95%CI 0.52–1.59) in analyses that were adjusted for age, sex, race, years of education, cigarette smoking, component (active versus reserves or National Guard), service branch, and rank. Similarly, no difference for the grouped outcome of "asthma, bronchitis, or emphysema" (OR = 1.07, 95%CI 0.65–1.77), adjusted using the same factors as above, was found for deployed versus nondeployed participants.

Kang et al. (2009) assessed changes in the health status of 1990–1991 Gulf War–deployed and era veterans using data collected as part of the follow-up survey conducted 10 years after the 1995 baseline survey of the NHS. Participants were from the same population used in the baseline survey. A total of 6,111 deployed veterans and 3,859 nondeployed era veterans participated in the follow-up survey. The prevalence of self-reported doctor-diagnosed asthma was 16.0% among the deployed and 12.7% among the nondeployed. The risk of asthma was statistically significantly higher for deployed veterans than for era veterans after adjusting for age, gender, race, BMI, current cigarette smoking, rank, service branch, and unit component (active versus National Guard or reserve) (RR = 1.24, 95%CI 1.12–1.38). The study was limited by a low response rate and lacked a mechanism for verification of self-reports.

Using data collected as part of the same follow-up survey as Kang et al. (2009), Li et al. (2011) also assessed changes in the health status of Gulf War–deployed and era veterans using data from the 1995 baseline survey compared with data collected on the same group of participants in a 2005 follow-up survey. Repeated measurement data were used from 5,469 deployed Gulf War veterans and 3,353 nondeployed era veterans who participated in both surveys. The prevalence of self-reported doctor-diagnosed asthma among the deployed decreased from 5.2% in 1995 to 4.9% in 2005, but the difference did not show a true decrease because the timeframe queried about the doctor's diagnosis was different between the surveys (12 months for 1995 versus 4 weeks for 2005). Among the era veterans, the prevalence of self-reported doctor-diagnosed asthma increased from 3.5% in 1995 to 4.0% in 2005. Neither change was found to be statistically significant. Persistence risk ratios and incidence risk ratios were calculated after adjustment for demographic and military service characteristics (age <46 years or ≥46 years in 2005, gender, race, rank, service branch, service component, BMI, and current cigarette smoking) through Mantel-Haenszel stratified analysis. Deployed veterans were statistically significantly less likely to report persistent asthma than era veterans (RR = 0.76, 95%CI 0.59–0.97), although the deployed had a nonstatistically significant increased risk of new-onset asthma (RR = 1.26, 95%CI 0.94–1.68).

Dursa et al. (2016b) conducted a 2012–2013 follow-up survey that collected data from 8,104 deployed and 6,148 era veterans who had participated in the (1993–1995) NHS reported by Kang et al. (2000). An increased risk of self-reported asthma was observed in Gulf War–deployed veterans when compared with the nondeployed veterans (10.2% vs 9.0%; OR = 1.22, 95%CI 1.04–1.44), after adjustment for age, race, sex, BMI, smoking status, service branch, and unit component.

Other Studies of U.S. 1990–1991 Gulf War Veterans As first described in the Respiratory Symptoms section, Gray et al. (2002) re-examined the question of symptoms and exposures among deployed and nondeployed Seabees by expanding the deployed and nondeployed cohorts that were first reported in Gray et al. (1999) to include all Seabees who had been on active duty during the time of the Gulf War regardless of whether they remained on active duty, were in the reserve, or had separated from service (n = 11,868 participants, participation rate = 67.4%). Participants were divided into three exposure groups: 3,831 who had been deployed to the Gulf War, 4,933 who had been deployed elsewhere, and 3,104 who had not been deployed. Those who had been deployed to the Gulf theater had statistically significantly higher odds of ever smoking than the nondeployed Seabees (OR = 3.09, 95%CI 2.79–3.42) and higher odds of current smoking than both Seabees deployed elsewhere (OR = 1.20, 95%CI 1.09–1.31) and nondeployed Seabees (OR = 2.68, 95%CI 2.37–3.04). Gulf theater–deployed Seabees also reported a greater frequency of lung diseases (not defined in the paper) than those Seabees who were deployed elsewhere (OR = 1.43, 95%CI 0.86–2.39) and nondeployed Seabees (OR = 1.68, 95%CI 0.91–3.12), but neither estimate was statistically significant. When asked about asthma and several other medical problems experienced in the past 12 months, Gulf theater–deployed Seabees reported higher frequencies of all 33 outcomes. Following adjustment for age, gender, active-duty versus reserve status, race/ethnicity, current smoking, and current alcohol drinking, ORs for asthma were increased but did not reach statistical significance for Gulf theater–deployed Seabees compared with Seabees deployed elsewhere (OR = 1.36, 95%CI 0.99–1.87), but the odds of asthma were statistically significantly increased for Gulf theater–deployed Seabees relative to nondeployed Seabees (OR = 1.82, 95%CI 1.23–2.69).

As described in Respiratory Symptoms, the "Iowa study" was a cross-sectional survey of a representative sample of 4,886 military personnel from all service branches who were randomly selected from those who had listed Iowa as their home of record at the time of enlistment (Iowa Persian Gulf Study Group, 1997). Trained examiners used standardized questions, instruments, and scales to interview the participants. This work led to future research on what would become known as Gulf War illness. As part of this work, the prevalence of self-reported symptoms and illnesses among deployed Gulf War personnel versus nondeployed personnel included asthma. Both deployed and nondeployed groups were stratified by regular military versus National Guard/reserve. The estimated prevalence of asthma was 6.7% of deployed regular military personnel, 9.4% of deployed National Guard/reserves, 3.8% of nondeployed regular military personnel, and 6.1% of nondeployed National Guard/

reserves. Differences in the prevalence rates of asthma were calculated and adjusted for age, sex, race, service branch, and rank. There was a statistically significant increase in asthma for all deployed versus nondeployed personnel (prevalence difference = 2.3, 95%CI 0.7–3.9) and deployed versus nondeployed National Guard/reserve personnel (prevalence difference = 2.9, 95%CI 0.5–5.2). No statistically significant difference in asthma prevalence was found for deployed versus nondeployed regular personnel (prevalence difference = 1.8, 95%CI –0.3–3.8).

As also first described in Respiratory Symptoms, Steele (2000) conducted a population-based survey of veterans who listed Kansas as their home state of record (1,548 deployed and 482 nondeployed); the primary intention was to examine factors that might have been related to Gulf War illness. The survey asked about 16 specific medical or psychiatric conditions, 37 symptoms, locations during the Gulf War (including whether the veterans were notified about the Khamisiyah demolitions), and vaccinations. Physician-diagnosed or physician-treated asthma that was reported to have occurred post-1990 was much greater for deployed Gulf War veterans (n = 63) than for the nondeployed veterans (n = 9), and the odds of having asthma were statistically significantly increased after adjustment for sex, age, income, and education level, but not smoking status (OR = 2.08, 95%CI 1.02–4.26).

Smith et al. (2006) conducted a large study that examined DoD administrative data of post-deployment hospitalization events at DoD facilities among active-duty service members with one deployment in order to compare the experience of Gulf War veterans (August 1, 1990–July 31, 1991) with that of personnel deployed to Southwest Asia after the war for peacekeeping missions or to Bosnia (1995–1998). Complete deployment and demographic data were available for 455,465 Gulf War veterans, for 249,047 post-war Southwest Asia–deployed personnel, and for 44,341 Bosnia-deployed personnel. Data were collected from these groups on hospitalization encounters for any cause and for 14 broad ICD-9-CM diagnostic categories (including respiratory system) as well as for specific diagnoses, including asthma. No statistically significant differences in asthma hospitalization were found between Gulf War–deployed service members and the Southwest Asia peacekeeping service members (HR = 1.22, 95%CI 0.96–1.56) or the Bosnia-deployed service members (HR = 0.86, 95%CI 0.56–1.31). Analyses were adjusted for demographic factors (gender, age, marital status, race/ethnicity) and military characteristics (pay grade, service branch, occupation, pre-deployment hospitalization), but not for smoking status.

VA provided the *Gulf War and Health* Volume 10 committee with a health care use report for Gulf War–deployed and Gulf War–era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories. For each category of disease, the 10 most frequent diagnoses for deployed and nondeployed Gulf War veterans who sought health care in VA between 2002 and 2013 were presented. A veteran can have multiple diagnoses with each health care encounter and therefore may be counted in multiple categories, but the person is counted only once in any single diagnostic category. A total of 286,995 Gulf War–deployed and 296,635 era veterans received care at VA over the approximately 11-year period (VA, 2014a,b). These VA health care users represent 46% of all deployed Gulf War veterans and 36% of all nondeployed era veterans. Concerning the diseases of the respiratory system (ICD-9 categories 460–519), asthma was diagnosed in 16.7% of 105,481 deployed Gulf War veterans and in 16.5% of 97,539 nondeployed veterans. No effect estimates were calculated.

Studies with Modeled Exposure to Oil-Well Fire Smoke Three studies of U.S. service members or veterans (Cowan et al., 2002; Lange et al., 2002; Smith et al., 2002) specifically examined asthma diagnoses or symptoms associated with modeled exposure to oil-well fires. Cowan et al. (2002) conducted a case–control study of 873 Gulf War veterans with a diagnosis of asthma in the medical record versus 2,464 controls without asthma or other respiratory system diagnoses who were participants in the DoD Comprehensive Clinical Evaluation Program. Demographic information was obtained from the DoD Gulf War Registry, and oil-well fire smoke exposure was based on the National Oceanic and Atmospheric Administration atmospheric advection and diffusion model. For those with self-reported exposure, the odds of asthma were statistically significantly increased (OR = 1.56, 95%CI 1.23–1.97); this increase remained with cumulatively modeled intermediate and high exposure and when the data were adjusted for sex, age, race, military rank, and smoking history. The effect was seen in former smokers and never smokers, but not current smokers.

Lange et al. (2002) used a cross-sectional study design to examine exposure to smoke from oil-well fires (self-reported and modeled) and self-reported asthma symptoms assessed via structured interviews conducted 5 years after the 1990–1991 Gulf War for a subset of 1,560 Iowa veterans. Modeled exposures were developed using a geographic information system to integrate spatial and temporal records of smoke concentrations with troop movements ascertained from Global Positioning Systems records during the period of oil-well fires (February–October 1991). Exposure was presented by quartiles. The overall prevalence of asthma symptoms was 8.3% for the study population; current smokers had more than twice the prevalence of symptoms of asthma than never smokers (13.3% vs 4.9%, respectively). ORs (adjusted for sex, age, race, military rank, smoking history, military service, and level of preparedness for war [based on the responses to six questions]) showed asthma increased with increasing self-reported exposure, but not when exposure to smoke from oil-well fires was modeled, limiting the support for an increased risk of asthma symptoms among these Gulf War veterans. The use of population-based sampling improved the generalizability of the results.

Smith et al. (2002) used DoD hospitalization data (ICD-9-CM codes) from August 1991 through July 1999 and exposure models to examine associations between respiratory diseases, including asthma, among 405,142 active-duty service members who served in the 1990–1991 Gulf War at the time of the oil-well fires. Service members were categorized as exposed (n = 337,077) and nonexposed (n = 68,065) to oil-well fires and no statistically significant difference was found for hospitalizations due to asthma between exposed (n = 745) and nonexposed (n = 135) veterans (RR = 0.90, 95%CI 0.74–1.10) after adjustment for demographic and military characteristics (not specified). However, asthma is not typically a condition that requires hospitalization.

Other Coalition Forces Veterans Using results from 1,424 deployed veterans and 1,548 nondeployed comparison veterans who participated in the Australian Gulf War Veterans' Health Study conducted in 2000–2002, Kelsall et al. (2004) reported no difference in self-reported asthma or doctor-diagnosed asthma overall (OR = 1.2, 95%CI 0.9–1.5; effect estimates were the same for both self-report and doctor-diagnosed), adjusted for age, height, smoking, weight, atopy, rank, service, education, and marital status. The current use of an asthma medication was not different between deployed and comparison veterans (OR = 1.4, 95%CI 0.9–2.2), adjusted for the same factors. Kelsall et al. (2004) then used a more specific definition of asthma, including an attack of asthma or being woken by an attack of shortness of breath at any time in the previous 12 months or current use of asthma medication, and applied the same model adjustments. The odds of suggestive asthma were statistically significantly increased for deployed veterans compared with the nondeployed veterans (OR = 1.4, 95%CI 1.1–1.9). A fourth category of asthma—doctor-diagnosed in 1991 or later and rated as a possible or probable diagnosis—was no different between deployed and nondeployed veterans (OR = 1.2, 95%CI 0.8–1.8), adjusted for service type, rank, age, education, and marital status only. A subgroup analysis was conducted that examined exposure to smoke from oil-well fires (no exposure compared with any, low, or high) among the deployed veterans, using only the more specific definition of asthma. No difference in asthma was found for any, low, or high exposure, or for exposure to dust storms, or for deployments that were completed before versus after the air war.

Using data collected from the Australian Gulf War Veterans' Follow Up Health Study conducted in 2011–2013 (described in detail in Chapter 3, and for other results cited throughout this chapter), Sim et al. (2015) found that self-reported asthma was not statistically significantly different for Gulf War veterans (14.4%) than for the comparison group (12.2%) (RR = 1.13, 95%CI 0.86–1.50). Estimates were adjusted for age group, service branch, and rank estimated as of August 1990, for any atopy at baseline, and for current smoking status (never, former, current smoker). Self-reported, doctor-confirmed asthma was reported by 12.6% of Gulf War and 11.2% of comparison veterans, frequencies that were similarly not statistically significantly different when adjusted for the same demographic, lifestyle, and military factors (RR = 1.09, 95%CI 0.81–1.47). Subcategories of asthma attack in the last 12 months (RR = 1.56, 95%CI 0.89–3.74) and currently taking asthma medication (RR = 1.42, 95%CI 0.91–2.21) were also not statistically significantly different for Gulf War and era veterans.

Two studies assessed asthma in UK Gulf War veterans. Simmons et al. (2004) used data collected as part of a large mail survey on British Gulf War veterans. The exposed cohort consisted of all UK Gulf War veterans, and the unexposed cohort consisted of a random sample of nondeployed UK military personnel from the same period. The survey was designed largely to assess reproductive outcomes among Gulf War veterans. However, it contained open-ended questions about their current health and changes in their health since 1990 that were then categorized into outcomes, including asthma and respiratory problems not otherwise specified. Although the numbers of surveys returned in the study were large (25,084 by Gulf War veterans and 19,003 by era veterans), the participation rates were low (47.3% and 37.5% of male and female Gulf War veterans, respectively, and 57.3% and 45.6% of male and female nondeployed veterans, respectively). Approximately 61% of Gulf War veterans reported at least one new medical symptom or disease since 1990, compared with 37% of nondeployed veterans. Asthma was reported by 2.6% of Gulf War respondents and 2.1% of era veterans. After adjusting for age at survey, service, and rank at time of Gulf War, serving status at the time of the survey, alcohol consumption, and smoking, the odds of reporting asthma were significantly increased among Gulf War respondents compared with era veterans (OR = 1.2, 95%CI 1.1–1.4).

Unwin et al. (1999) conducted a cross-sectional postal survey from 1997 to 1998 to compare the health profiles of veterans and military service members from the United Kingdom (n = 8,195; overall response rate 65.1%). The study population was randomly selected, and the sample was stratified into three cohorts: deployed Gulf War veterans and military service personnel (n = 2,961) who served in the Gulf region between September 1, 1990, and June 30, 1991 (response rate = 70.4%); deployed military personnel who had served in Bosnia (n = 2,620) between April 1992 and February 1997 (response rate = 61.9%); and veterans and military personnel who were in the armed forces on January 1, 1991 (n = 2,614) but were not deployed to the Gulf War (era cohort) (response rate = 62.9%). Women were oversampled, but the data analysis was restricted to men only because the roles and background health complaints of females were different from those reported by males. ORs were calculated, and the proportions of symptoms, disorders, and exposures were compared between the Gulf cohort and the two comparison cohorts. Study investigators controlled for potential confounders, including sociodemographic (age, marital status, education, employment), military (rank, still serving or discharged), and lifestyle (smoking, alcohol consumption) factors. Asthma was reported by 6.5% of respondents in the Gulf War cohort, 4.5% of the Bosnia cohort, and 3.7% of the era cohort. Gulf War cohort participants had higher odds of asthma than Bosnia cohort participants both in the logistic regression model that controlled for sociodemographic and lifestyle variables (OR = 1.2, 95%CI 0.9–1.6) and in the logistic regression model that controlled for sociodemographic variables plus the general health questionnaire (OR = 1.2, 95%CI 0.8–1.6); however, neither of these results was statistically significant. Compared with era veterans, Gulf War participants reported statistically significantly increased odds of asthma both in the logistic regression model that controlled for sociodemographic and lifestyle variables (OR = 1.8, 95%CI 1.4–2.4) and in the logistic regression model that controlled for sociodemographic variables plus general health questions (OR = 1.6, 95%CI 1.2–2.1). The strengths of this study included the use of two different military control groups that came from a large, randomly selected, population-based study population and the fact that it accounted for pre-existing health status and cigarette smoking. One of its limitations was its reliance on unverified self-reported medical symptoms and conditions; however, the committee believed, based on the results of the analyses presented, that differential non-response and recall bias were both unlikely.

Using the results of a survey mailed to the entire cohort of Canadian Gulf War veterans who had been deployed to the Gulf War and a comparison group of personnel who had deployed elsewhere during the same period (overall response rate was 64.5%), Canadian Gulf War veterans were found to have statistically significantly higher odds of reported asthma (OR = 2.64, 95%CI 1.97–3.55) than elsewhere-deployed veterans when adjusted for tobacco smoking, income, and rank (Goss Gilroy Inc., 1998).

Post-9/11 Veterans The AFHSC (2010) examined medical encounters of U.S. Army and Air Force personnel 36 months after deployment between 2005 and 2007 to Joint Base Balad, Contingency Operating Base Speicher, or Camp Taji in Iraq (all three of which used burn pits for waste management); to Camp Beuhring or Camp Arifjan in Kuwait (which did not use burn pits); or to installations in the Republic of Korea. Service members who were never deployed and stationed only in the continental United States in the same period were used as the comparison population. Asthma was examined using Poisson models that were adjusted for sex, birth year, marital status, race/ethnicity, education, smoking status, physical activity, service branch, military rank, pay grade, and occupation. IRRs for asthma were statistically significantly lower for troops deployed to Joint Base Balad (IRR = 0.81, 95%CI 0.73–0.91) and Korea (IRR = 0.91, 95%CI 0.86–0.96) compared with the nondeployed U.S. cohort. No differences in asthma were found for those deployed to Camps Arifjan, Buehring, or Taji compared with the nondeployed U.S. cohort. The investigators also conducted additional analyses using data from the baseline and first follow-up cycles of the Millennium Cohort Study. Multivariable logistic regression adjusted for the same factors as used in the Poisson models was used to compare the adjusted odds of asthma associated with three metrics of exposure within a 5-mile radius of the documented burn pits: dichotomous deployment near the documented burn pits, cumulative days exposed to the burn pits (presented by quartiles), and exposure to the burn pits at three different campsites (Balad, Taji, or Speicher). The incidence of new-onset asthma was 1.62% for participants with putative exposure to burn pits and 1.63% for the nonexposed. For new-onset asthma, there was no statistically significant difference between service members deployed outside of a 5-mile radius of a burn pit location and those deployed within that radius (OR = 0.89, 95%CI 0.66–1.19). Deployment of cumulative days exposed within 5 miles of the documented burn pits was not associated with increased risk for new-onset asthma for any of the quartiles of exposure compared with the nonexposed group. Furthermore, the odds of new-onset asthma associated with exposure at specific campsites were not increased compared with those deployed outside of the 5-mile radius (p = 0.59).

The committee responsible for the 2017 National Academies report *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry* carried out an analysis of the initial months of data gathered from respondents to the registry's questionnaire (NASEM, 2017). The data were derived from the first 13 months of completed questionnaires (n = 46,404), representing approximately 1.0% of the 1990–1991 Gulf War veterans and 1.7% of post-9/11 veterans who met the registry's eligibility criteria. Outcomes of asthma were characterized by self-reports of health care provider diagnoses, while exposures to burn pits and other airborne hazards were determined by self-report and by DoD data on the number and location of deployments; 13.0% of respondents self-reported asthma during or after deployment. The committee also synthesized exposure metrics by combining the responses to questions regarding specific exposures. Analyses—which controlled for sex, age, education level, BMI, smoking status, unit component, rank, service branch, and occupation—indicated that the airborne exposure measures had strong and consistent associations with a self-report of asthma. These associations were observed for several indicators of burn pit exposure as well as for a range of other deployment exposures, such as exposures to diesel/exhaust/fuel, construction, dust, and combat. However, the report detailed a number of issues with the quality and limitations of the registry's information, which led the committee to conclude that the results of the analyses could not be taken at face value and that the identified associations might be an artifact of the population's selection and the limitations of the self-reported exposure and disease data.

Update of the Scientific Literature on Asthma

This section presents studies of service members and veterans who served in the post-9/11 conflicts followed by studies of veterans who served in the 1990–1991 Gulf War. Within each population, studies that analyzed data from the same cohort are presented together.

Studies that merely described asthma among theater veterans were excluded from consideration. Dursa et al. (2016a) and Cypel et al. (2016) aimed to evaluate asthma diagnoses among Southwest Asia veterans, but neither study evaluated the impact of deployment on asthma diagnosis, and therefore neither study is summarized. Dursa et al. (2016a) evaluated differences in asthma among VA health care users and nonusers. Cypel et al. (2016) examined the sociodemographic, military, and health characteristics of current cigarette smokers, former smokers, and nonsmokers among OEF/OIF veterans and estimated the smoking prevalence to better understand cigarette use in this population. Similarly, Dursa et al. (2019) examined differences in asthma and COPD (among other health outcomes) between females and males who were deployed and nondeployed to the 1990–1991 Gulf War, but differences in asthma prevalence between deployed and nondeployed veterans were not reported, limiting the usefulness of this analysis in informing associations between deployment to Southwest Asia and respiratory outcomes. STAMPEDE I, II, and III, which are all detailed in the PFT section, also presented the prevalences of asthma in their study populations (Morris et al., 2014, 2019, 2020). In STAMPEDE I, asthma was diagnosed in eight participants (16.0%) (Morris et al., 2014). In STAMPEDE II soldiers with abnormal spirometry pre-deployment or asthma history (n = 39) had no indication of worsening lung function post-deployment. Logistic regression models were used to predict obstruction after deployment, and self-reported asthma (p = 0.045) was found to be significantly predictive. In STAMPEDE III, asthma was diagnosed in 87 patients (22.9%) based on obstructive spirometry/impulse oscillometry and evidence of airway hyperreactivity (Morris et al., 2020). Other studies were identified that reported the total number of individuals with asthma but did not conduct comparisons of this information (Butzko et al., 2019; Morris et al., 2013; Sanders et al., 2005) and therefore are not summarized.

Post-9/11 Veterans This section includes several studies from the large cohorts that the committee was asked to pay particular attention to as well as smaller studies that used a population from a particular region or care center.

Smith et al. (2008) used self-reported clinician-diagnosed health data from regular, active-duty participants from the first panel (2001–2003) of the Millennium Cohort Study (n = 37,798) to compare the agreement of 38 medical conditions, which included asthma, with that obtained from electronic medical records based on ICD-9-CM codes. Any diagnostic code for these 38 conditions in any portion of the medical record indicated agreement with a self-reported medical condition of interest. Both positive and negative agreement were used to compare self-reported data with those from electronic medical records. Prevalence was 5.8% (95%CI 5.6–6.0) for self-reported asthma and 3.9% (95%CI 3.7–4.1) for electronic medical record–documented asthma; 1.9% was exclusively recorded in the electronic medical records. The positive agreement between self-report and electronic medical records for asthma was 42.0%, and negative agreement (the condition was not reported either by self-report or found in the medical record) was 97.1%. When reports of asthma were examined by length of service (0–5, 6–10, 11–15, and ≥16 years), the self-reported prevalence of asthma was higher than what was recorded in the electronic medical records.

Smith et al. (2009) examined newly reported asthma and other respiratory conditions among 46,077 Millennium Cohort Study participants who completed baseline (2001–2003) and follow-up (2004–2006) questionnaires. Multivariable logistic regression was used to compare the adjusted odds of new asthma relative to deployment status (deployed versus nondeployed) stratified by service branch and adjusted for sex, birth year, marital status, race/ethnicity, education, smoking status, service component, military pay grade, and occupational code. Because personnel in different service branches are likely to experience different deployment-related exposures, analyses were stratified by service branch. The adjusted OR for newly reported asthma in deployed versus nondeployed personnel varied, though not statistically significantly for any of the branches, with the highest observed in Army personnel (OR = 1.06, 95%CI 0.77–1.44) and the lowest in Marine Corps personnel (OR = 0.56, 95%CI 0.15–1.98). When the analysis was restricted to deployed cohort members with self-reported information on deployment location (n = 9,861), the investigators stated that the odds of asthma were not statistically different in any of the deployment locations examined, but estimates were not provided.

Smith et al. (2012) investigated the effects of exposure to documented open-air burn pits within 2, 3, or 5 miles on asthma and other respiratory outcomes among Millennium Cohort Study Army and Air Force participants who were deployed to Iraq or Afghanistan after January 1, 2003, and who completed the baseline questionnaire and one of the follow-up assessment cycles through 2008. After excluding individuals with missing data, 20,077 participants who had deployed were included in the analyses of new-onset asthma. Similar proportions of newly reported asthma in 2007 were found for those exposed and nonexposed within 3 miles of a burn pit (1.7% vs 1.6%, respectively). At the end of follow-up, after adjusting for demographic, behavioral, and military characteristics, the odds of newly reported asthma were statistically significantly increased for women (OR = 1.78, 95%CI 1.38–2.32) and Army personnel (OR = 2.27, 95%CI 1.70–3.03), whereas both those who did and did not meet standards for aerobic activity were at reduced risk for asthma compared with those who could not perform aerobic activity. Three proxy exposure metrics were modeled, and analyses were adjusted for demographic and military characteristics, smoking status, and physical activity. Newly reported asthma was not statistically significantly associated with deployment within 3 miles of burn pits (OR = 0.94, 95%CI 0.70–1.27) when compared with deployments to other regions of Iraq or Afghanistan with no documented burn pit exposure. Similarly, deployments within 3 miles of each of the three burn pit sites compared with deployments outside this radius were not associated with increased odds of new-onset asthma: Joint Base Balad (OR = 0.84, 95%CI 0.56–1.25), Camp Taji (OR = 1.53, 95%CI 0.91–2.58), or Camp Speicher (OR = 0.76, 95%CI 0.42–1.38). Similarly, increasing number of cumulative days of exposure within a 3-mile radius of the burn pits was not associated with new-onset asthma compared with cohort members with no burn pit exposure (p = 0.63). The findings of no association with new-onset asthma for deployment status, cumulative deployment length, and camp location were consistent when examining the risk within 5 miles of the burn pits.

Rivera et al. (2018) examined the risk factors for new-onset asthma among eligible Millennium Cohort Study participants (n = 75,770) deployed to Iraq, Afghanistan, noncombat zones, or sea locations during OIF or OEF. The exposure of interest was combat deployment in support of OEF/OIF during the entire follow-up period (October 2000–October 2006), and participants were categorized as nondeployed, deployed without combat, and deployed with combat. The Contingency Tracking System database at the Defense Manpower Data Center (DMDC) was used to extract deployment information. Within the study population, 1,055 (4.6%) of women and 1,452 (2.7%) of men developed asthma during the follow-up time period. Women and men who were not deployed had the highest rates of new-onset asthma (5.0% and 3.1%, respectively), followed by individuals with combat experience (4.4% and 2.7%, respectively). Women reported higher rates of new-onset asthma than men for all strata: exposure of interest, demographic factors, birth year, marital status, education, BMI, military service, service component, occupation, pay grade, smoking status, environmental exposures, stressors, and posttraumatic stress disorder. Among those who deployed and had combat experience, both men and women had a statistically significantly increased risk for new-onset asthma (RR_{men} = 1.30, 95%CI 1.14–1.47; RR_{women} = 1.25, 95%CI 1.05–1.46) compared with men and women who did not deploy, after adjusting for all covariates. No statistically significant differences were found for the association between new-onset asthma and multiple deployments. There was a statistically significant association between a deployment duration of 401–600 days and new-onset asthma in men (RR = 1.35, 95%CI 1.02–1.78), after adjustment for demographic and military factors, including prior deployment to Bosnia, Kosovo, or Southwest Asia between January 1, 1998, and September 1, 2001. The three other deployment lengths that were evaluated (1–200 days, 201–400 days, and >600 days) were not associated with increased asthma. The limitations of this study include the potential for recall or reporting bias, that there was no validation of self-reported new-onset asthma diagnosis with medical charts, the fact that the exact timing of asthma onset could not be ascertained as the questionnaire assessed onset of asthma over the past 3 years, and that questions regarding combat exposure were not specific to a particular deployment.

Using data collected as part of the NewGen Study, Barth et al. (2014) examined the association between deployment to Southwest Asia and self-reported doctor-diagnosed asthma among 13,162 deployed and 7,401 nondeployed veterans. The unweighted and weighted prevalence of asthma was calculated and stratified by diagnosis before or after 2001, and logistic regression was used to calculate adjusted ORs for deployment status and asthma. The models were adjusted for birth year, sex, service branch, unit component, race/ethnicity, education, and smoking status. Separate models were constructed for diagnosis before 2001 and during or after 2001. For those diagnosed before 2001, the weighted prevalence for asthma was higher in the deployed than in the nondeployed (3.7% vs 2.0%). Among those with respiratory disease diagnosed in 2001 or later, the weighted prevalence of asthma was again higher in the deployed than in the nondeployed veterans (3.4% vs 3.3%). Among those diagnosed during or after 2001, the deployed group had odds of asthma that were similar to those of the nondeployed veterans (OR = 1.08, 95%CI 0.89–1.30), but for those diagnosed prior to 2001 the odds of asthma were statistically significantly lower among deployed versus nondeployed veterans (OR = 0.57, 95%CI 0.47–0.70).

Barth et al. (2016a) again used data from the NewGen study to expand on the analysis by Barth et al. (2014) to examine the prevalence of self-reported doctor-diagnosed respiratory diseases and their association with self-reported respiratory exposures during military service for OEF/OIF deployed and nondeployed veterans. Logistic regression analyses were used to calculate weighted, adjusted odds of asthma stratified by deployment status and controlled for sex, birth year, race/ethnicity, education, smoking status, unit component, and service branch, and number of OEF/OIF deployments. A total of 1,366 veterans self-reported asthma (802 deployed and 559 nondeployed). Among the deployed veterans, statistically significant increased odds of asthma were observed for all specific exposures and for both the high-exposure and low-exposure categories; the highest odds for asthma were for those categorized as high exposure (OR = 1.49, 95%CI 1.01–2.20) and with dust and sand as a specific exposure (OR = 1.46, 95%CI 1.06–2.00). For nondeployed veterans, statistically significant increased odds of asthma were also observed for all specific exposures and for both the high-exposure and low-exposure categories; the highest odds for asthma were again for those with categorized as high exposure (OR = 1.92, 95%CI 1.40–2.62) but highest for burning trash or feces as a specific exposure (OR = 1.64, 95%CI 1.29–2.08). These results show that exposures were associated with the development of asthma in both deployed and nondeployed groups, but the confidence intervals for the adjusted ORs all overlap between the deployed and nondeployed groups.

Abraham et al. (2014) built on the AFHSC (2010) analysis by adding an additional 12 months of follow-up (for a total of 48 months) of personnel deployed to four Southwest Asia theater sites with and without burn pits, along with those deployed to Korea and a comparison population of service members who stayed in the United States. Compared with the rate for nondeployed personnel, the rate of medical encounters for new-onset asthma (defined as one hospitalization or at least two outpatient encounters with ICD-9 code 493) among personnel deployed to the four in-theater sites was elevated (IRR = 1.54, 95%CI 1.33–1.78), adjusted for age, gender, race, and military rank. Information on smoking was not factored into the analyses. Compared with the nondeployed U.S. group, rates for bases with burn pits (IRR = 1.59, 95%CI 1.35–1.87) and without burn pits (IRR = 1.39, 95%CI 1.07–1.79) were also statistically significantly elevated for new-onset asthma (as well as for Joint Base Balad and Camp Arifjan, individually). Compared with the rate for personnel stationed in Korea, the rates of medical encounters for asthma were no different between personnel stationed in sites with and without exposure to burn pits. As compared with military personnel deployed at bases without burn pits (Arifjan and Buehring), there was no difference in rates of asthma among those deployed in areas with burn pits (Balad and Taji) (IRR = 0.93, 95%CI 0.69–1.25). These findings indicate that the risk of new-onset asthma is elevated but that the risk is not associated with burn pits specifically.

The analyses by Sharkey et al. (2015) also used the same deployed and nondeployed populations as the AFHSC (2010) analysis but used a larger U.S.-based reference population and included an additional 12 months of data. Their methods also differed from those of Abraham et al. (2014); all three studies are discussed in greater detail in Chapter 3. This retrospective cohort study used Poisson models that were adjusted for age, pay grade, sex, race, and service branch. As was found in the AFHSC (2010) analysis, the risks of respiratory illnesses for personnel deployed to four Southwest Asia bases and Korea were all similar to, or statistically significantly lower than, the risks for personnel who remained in the United States. IRRs were reported for each base location, but no comparisons between bases with and without burn pits were made. IRRs for new-onset asthma (ICD-9-CM: 493) were statistically significantly lower for personnel deployed to Joint Base Balad, Iraq—which had a burn pit—at both the 36-month follow-up (IRR = 0.81, 95%CI 0.73–0.91) and the 48-month follow-up (IRR = 0.82, 95%CI 0.74–0.91) compared with the nondeployed U.S. cohort. The same statistically significantly lower risk was observed for troops deployed to Korea compared with the nondeployed U.S. group at 36 months (IRR = 0.91, 95%CI 0.86–0.96) and 48 months (IRR = 0.91, 95%CI 0.86–0.97). There were no statistically significant differences in new-onset asthma for the other deployed locations compared with the nondeployed cohort. Information on smoking was only available for Air Force personnel, and the authors report that no significant difference in risk for any of the health outcomes of interest was found after adjusting for smoking status.

Baird et al. (2012) examined the post-deployment respiratory health status of U.S. Army personnel potentially exposed to emissions from the fire at the Al-Mishraq sulfur plant near Mosul, Iraq, in 2003. Two were groups potentially exposed to the sulfur fire smoke plume—personnel involved in fighting the fire (n = 191) and personnel presumably downwind during the time of the fire (n = 6,341). These were compared with two unexposed groups: those who deployed to the area after the fire was extinguished (n = 2,284) and those deployed to other Southwest Asia locations contemporaneously with the time of the fire (n = 1,869). Asthma encounters (ICD-9-CM 493) were statistically significantly less likely for the potentially exposed personnel downwind of the fire than for the group deployed to the area after the fire was extinguished (standardized mortality ratio [SMR] = 0.62, 95%CI 0.53–0.71), but there was no difference between the downwind personnel and the contemporaneously deployed group. Firefighters were less likely to have post-deployment medical encounters for asthma than the contemporaneously deployed group (SMR = 0.91, 95%CI 0.29–1.87) and the group deployed to the area after the fire (SMR = 0.62, 95%CI 0.20–1.27), although neither difference was statistically significant. The inverse association for observed asthma may reflect the short follow-up time and the young age of the population being studied as well as the lack of adjustment for other potentially important confounders, including smoking and other environmental or occupational exposures, between the sulfur-fire exposed and unexposed groups.

Abraham and Baird (2012) conducted a case-crossover study of short-term (i.e., 0- and 1-day lagged) exposures to ambient PM less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$) and less than 10 microns in diameter (PM_{10}) and cardiovascular and respiratory medical encounters (ICD-9 460–519) among 2,838 U.S. military personnel deployed to Southwest Asia. PM exposure was assessed using data collected over a period of approximately 1 year at 15 military bases, including 6 sites in Iraq, 4 in Kuwait, 2 in Afghanistan, 1 in Qatar, and 1 in the United Arab Emirates. Site-specific estimates were first obtained and then pooled using meta-analytic techniques to generate OR for a 10-µg/m^3 increase in $PM_{2.5}$ or PM_{10}. Ambient levels were routinely high at the bases assessed, but no statistically significant associations between PM and respiratory outcomes were observed in the young, relatively healthy, deployed military population. Of the 343 encounters for COPD and allied conditions (ICD-9 490–496), though, 327 (95%) were reported to be for asthma (ICD-9 493). Following adjustment for temperature, barometric pressure, and relative humidity, all pooled effect estimates at lag 0 and lag 1 were close to 1.0, and none achieved statistical significance. Similar results were obtained in sensitivity analyses in models that evaluated 2-day lagged exposures as well as PM estimates using imputed data for missing values. No consistent pattern was found for associations between PM and asthma or any other condition (specific effect estimates not presented). The adjusted ORs for a 10-µg/m^3 increase in ambient $PM_{2.5}$ and a qualifying medical encounter were not statistically significant for the current (lag_0) day (OR = 0.92, 95%CI 0.77–1.11) and previous (lag_1) day (OR = 1.01, 95%CI 0.95–1.07). The estimates for a 10-µg/m^3 increase in PM_{10} were again not statistically significant at lag_0 (OR = 0.99, 95%CI 0.97–1.03) and lag_1 (OR = 1.00, 95%CI 0.97–1.02). Overall, increases in ambient PM were not found to increase asthma incidence. This study is one of the few studies with objectively measured exposure, the strengths and limitations of which are summarized in Chapter 3.

Sharkey et al. (2016) extended the analysis of the AFHSC (2010) report by adding additional Army or Air Force personnel who were deployed to Kabul (n = 5,670) and Bagram (n = 34,239) Air Force Bases in Afghanistan—sites with similar, poor air quality—and Manas Air Force Base in Kyrgyzstan (n = 15,851), a site with relatively better air quality, and extended the follow-up period of active-duty personnel to 12 years. Asthma cases were defined as a study participant having either one inpatient or at least two outpatient health care encounters labeled with ICD-9-CM-coded asthma-related visits. Deployment-location-specific IRRs for asthma were calculated after excluding any study participants with a history of diagnosis of asthma, and the models were adjusted for age, rank (defined at the start of follow-up), sex, and race. Information on smoking was available only for Air Force personnel, and the authors report no evidence of confounding as RRs were similar with and without adjustment for smoking status. IRRs were highest for active-duty service members deployed to Kabul compared with the U.S. reference group (IRR = 1.61, 95%CI 1.22–2.12), but there were no differences when compared with the Korea (IRR = 1.01, 95%CI 0.69–1.49), Manas (IRR = 1.03, 95%CI 0.72–1.49), or Bagram (IRR = 1.01, 95%CI 0.75–1.35) reference groups, after adjusting for age, sex, and military rank.

Liu et al. (2016) examined the associations between assumed geographic and self-reported burn pit emissions exposure and respiratory and cardiovascular outcomes in participants of VA's Airborne Hazards and Open Burn Pit Registry. The study included 4,343 participants who completed the registry questionnaire by April 30, 2015, and, of these, 2,663 participants deployed for at least 30 days from January 1, 2003, to June 30, 2007, within 2 miles of burn pits in Joint Base Balad or Camp Taji in Iraq, and 1,680 participants were deployed for at least 30 days to Kuwait (but not to Joint Base Balad or Camp Taji) during that timeframe. There were no documented burn pits at Kuwait bases. Two surrogate measurements of burn pit emissions exposure were used in the analysis: days of deployment near burn pits and self-reported total hours of burn pit smoke exposure. Associations were presented by quartiles of burn pit exposure. Self-reported diagnoses were compared with VA medical record information for 2,857 respondents who used VA health care at least once between January 2007 and November 2015. Participants who reported having been diagnosed with a condition before deployment were excluded from both the analyses of self-report and the comparisons with VA medical records for that condition. All demographic characteristics (except marital status), military characteristics, and other factors, such as in-person clinical examination request and smoking status, were found to be statistically significantly associated with deployment days within 2 miles of the burn pit sites. Associations between demographic, lifestyle (with exception of smoking), and military service variables and self-reported burn pit smoke exposure amount were all found to be statistically significantly associated with self-reported burn pit smoke exposure. Models were adjusted for demographic, lifestyle (including smoking status), and military service characteristics. No statistically significant associations were found for any of the quartiles of deployment time within 2 miles of the burn pit locations and asthma, either from self-report or as identified in VA medical records, after adjusting for demographic, lifestyle, and military service variables. Likewise, no statistically significant associations were found for any of the quartiles of total hours of burn pit smoke exposure and asthma, either from self-report or as identified in VA medical records, after adjusting for demographic, lifestyle, and military service variables. This study is most limited by the use of self-reported exposures and by the fact that the study population consists of a self-selected group of individuals.

Pugh et al. (2016) conducted a retrospective cohort study to examine the prevalence of chronic lung diseases, including asthma, based on ICD-9-CM codes and military deployment using VA health care data from 760,621 U.S. veterans deployed to combat operations in Iraq or Afghanistan who received care from VA between October 1, 2002, and September 30, 2011. The prevalence of asthma was calculated for each year between 2003 and 2011 using the number of unique OEF/OIF veterans who received care from VA during the year as the denominator for that year, and the data were examined for any changes in prevalence during that time. Generalized estimating equations analysis was used to determine if the log-odds of having a diagnosis of asthma increased from 2003 to 2011; estimates were adjusted for demographic characteristics, multiple deployments, tobacco use, and traumatic brain injury (TBI). Over the study period, 25,592 (3.4%) individuals had a diagnosis of asthma; they were more likely to be male, white, and to have served in the Army; 26.5% were classified as tobacco users, and 14.6% had a TBI diagnosis. Based on the generalized estimating equations analysis and controlling for demographic and clinical characteristics, the odds of diagnosis of asthma were statistically significantly higher in 2011 than in other earlier years of the study. Moreover, the odds of asthma were statistically significantly increased for the 31–40 years and 41–50 years age groups (but not ≥51 years) compared with the ≤30 years age group, as well as for those with a TBI diagnosis (OR = 1.47, 95%CI 1.42–1.53) and tobacco users (OR = 1.17, 95%CI 1.14–1.21). Individuals who had multiple deployments were statistically significantly less likely to have a recorded asthma diagnosis (OR = 0.93, 95%CI 0.91–0.96) than individuals with only one deployment. Although the study population was large and included a more objective measure of asthma using ICD-9-CM codes, the temporal sequence between deployment and the onset of asthma is unknown, and the population was limited to those who received care within the VA health system. Because the veterans studied may have been too young for many to have developed symptoms of chronic pulmonary diseases, these results may be subject to both selection and ascertainment biases. Although it appears that what was reported as change in prevalence by year is really incidence of new diagnoses; however, new cases may be a mixture of incident and prevalent cases, with some patients coming to VA to receive care when disease becomes severe enough to need treatment, and therefore these are prevalent cases that are considered incident in that they were not previously counted.

Szema et al. (2010) conducted a retrospective cohort study—described previously in the pulmonary function section—in U.S. military service members who were deployed to OEF/OIF or elsewhere (matched on age and gender) using data collected by the Northport, New York, VA Medical Center Research and Development Committee to examine if the deployed were more likely to have asthma or respiratory symptoms requiring the use of spirometry than were nondeployed service members. The clinical guidelines for a diagnosis of asthma at Veterans Affairs Medical Centers include

> recurrent episodes of respiratory symptoms (cough, wheeze, dyspnea, and exercise-induced shortness-of-breath) with spirometric evidence of airway obstruction based on the forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) or forced expiratory flow at 25–75% at rest, with improvement of symptoms after bronchodilators. (Szema et al., 2010, p. e68)

Spirometry was obtained, when available, from patient medical records. Asthma diagnoses for military personnel aged 18–45 years were examined among patients who were residents of Long Island, and who were discharged from active duty and were examined between March 1, 2004, and May 1, 2007. Service members were grouped by deployment location (Iraq/Afghanistan for a 1-year tour of duty versus United States) and by ICD-coded diagnosis of asthma in VA records. Crude ORs stratified by gender and age group were calculated for associations between deployment and asthma. Of the 6,233 patients in the study sample, 290 had asthma—61 (6.6%) of deployed and 229 (4.3%) of nondeployed—and the odds of asthma were increased for deployed service members compared with nondeployed service members (OR = 1.58, 95%CI 1.18–2.11). This study is most limited by the selection bias resulting from using a study population based on one VA clinic, which may have a different distribution of risks for asthma than the rest of the post-9/11 population. Furthermore, study investigators used deployment during

2003–2007 as a crude measure of exposure, making it likely that misclassification of exposure occurred. Although ICD-coded asthma diagnoses were used, it was not clear if people with pre-existing asthma were removed from the population. Spirometry was performed on only a subset of asthmatics, and no pre-spirometry measures were available for comparison. Finally, only crude ORs were presented, and no adjustment for several potential confounders was included.

Abraham et al. (2012) conducted a cohort and nested case–control study to evaluate the relationship between deployment and respiratory system diseases (ICD-9 460–519) in U.S. military personnel. Cases (n = 532) of post-deployment diagnosis of obstructive pulmonary disease, defined as ICD-9-CM codes 490–496, and controls (n = 2,128) were selected from those who were free of respiratory diagnoses within 6 months before their deployment. Controls were matched on the year of case definition and the year of the last encounter during the study period for controls as well as the total number of post-deployment medical encounters. Conditional logistic regression analyses were used to examine the independent effects of the number of deployments at diagnosis and of the cumulative time in theater up to diagnosis on post-deployment obstructive pulmonary disease encounter, controlling for potential confounders (gender, age, grade, occupation, time in theater, number of deployments, service branch, and tobacco-related diagnoses). The vast majority of obstructive pulmonary disease encounters were for either asthma (46%) or bronchitis (50%). Adjusted odds of having an obstructive pulmonary disease encounter were not different for multiple deployers compared with single deployers (OR = 1.08, 95%CI 0.82–1.42). This study had several limitations, such as a lack of measurement of smoking and a lack of specific deployment-related exposure assessments. Additionally, given that asthma and other obstructive lung diseases were all considered together, the study findings do not provide specific information on the impact of service in Southwest Asia and asthma.

1990–1991 Gulf War Veterans Four studies of 1990–1991 Gulf War veterans and outcomes of asthma were identified since the publication of the *Gulf War and Health: Volume 10* report; three studies examined U.S. Gulf War veterans. Three of those are cohort studies, and the fourth is a meta-analysis of studies that compared Gulf War–deployed and Gulf War–era–nondeployed veterans. These are presented before the study of new-onset asthma in Australian Gulf War veterans.

Hines et al. (2013) conducted a small study using 24-hour creatinine-corrected urinary uranium as a validated marker of exposure in 1990–1991 Gulf War veterans who were enrolled in the VA Depleted Uranium Surveillance Program and had attended a biennial follow-up in 2011 (n = 37) to compare the likelihood of pulmonary health abnormalities in those with high body burdens of uranium (n = 12; >0.1 μg/g creatinine) versus those with low body burdens of uranium (n = 25; ≤0.1 μg/g creatinine). Two participants self-reported asthma, and both had low urinary uranium, providing some evidence that depleted uranium may have limited impact on asthma. Of these two veterans with self-reported asthma, one was a never smoker and one was an ever smoker, which did not result in any statistically significant differences of asthma by smoking status.

Zundel et al. (2019) compared survey results from a follow-up survey of a cohort of 1990–1991 Gulf War veterans (401 males and 47 females) who returned from deployment in 1991 through Fort Devens, Massachusetts, with data from the 2013–2014 NHANES (n = 2,949). The veterans were asked to report if a doctor had ever diagnosed them with any of nine chronic medical conditions, including asthma. The analyses were restricted to veterans of white race with at least a high school education, and they were stratified by sex. The analyses were also weighted to account for demographic differences between cohorts. The prevalence of asthma was higher among the Fort Devens cohort than reported by NHANES for men (13.6% vs 10.9%, respectively), but the difference was not statistically significant (OR = 1.29, 95%CI 0.75–2.23). For women, the prevalence of asthma was lower among the Fort Devens cohort than among the NHANES cohort (10.3% vs 18.6%, respectively), but the difference was not statistically significant (OR = 0.50, 95%CI 0.22–1.17). When the prevalence of asthma was compared for men stratified by age group (40s, 50s, and 60s), no difference between Fort Devens and NHANES was found for any of the age groups. For the Ft. Devens exposure analyses, there were no differences on any of the demographic variables between veterans who were exposed and those who were unexposed to chemical or biologic warfare or pyridostigmine bromide pills, but analyses for exposure were adjusted for gender and current smoking status. For those exposed to chemical or biologic warfare, the prevalence of asthma was higher than among the unexposed (18.5% vs 10.3%, respectively), but this difference was not statistically significant (OR = 1.94, 95%CI 0.90–4.20).

Similarly, the prevalence of asthma was slightly higher for those exposed to pyridostigmine bromide pills than for the unexposed (12.5% vs 11.5%, respectively), but this difference was not statistically significant (OR = 1.13, 95%CI 0.51–2.51). Finally, asthma prevalence was compared between men and women of the Fort Devens cohort; no difference in prevalence was found after adjustment for age, race, education, and current smoking (OR = 1.57, 95%CI 0.53–4.68). This study has several limitations, including its generalizability, its use of self-reported conditions, and its low response rate.

In a meta-analysis of 21 studies published through 2017 on prevalence of health symptoms, including asthma, representing more than 129,000 1990–1991 Gulf War–deployed and nondeployed era veterans, Maule et al. (2018) found that in pooled analyses a higher combined prevalence of asthma was found for deployed than for era veterans (4.8% vs 3.4%, respectively). ORs were reported for each outcome along with I^2 statistics (a measure of the heterogeneity, or the percentage of variation across studies that is due to heterogeneity rather than chance). The odds of asthma were statistically significantly increased for Gulf War veterans compared with era veterans (OR = 1.38, 95%CI 1.20–1.58; seven studies), and the heterogeneity was substantial ($I^2 = 0.47$). The meta-analytic approach could not address concerns about either selection biases or information biases (due to self-reports of symptoms), concerns that were common in all of the included studies. Moreover, the committee also notes that some other important deficiencies in the published studies, such as individual design and population selection, and their impacts on the findings were not addressed.

Other 1990–1991 Gulf War Coalition Forces Veterans As first described in the section on Sleep Apnea, Gwini et al. (2016) examined new onset of self-reported conditions in deployed Australian Gulf War veterans using data collected from wave 1 (conducted 10 years after the Gulf War) and wave 2 (conducted about 10 years after wave 1 and 20 years after the Gulf War) of the Australian Gulf War Veterans' Health Study. Both wave 1 and wave 2 used a questionnaire to collect information on general health, physical and psychological health, military service history, and exposures during deployment, and they also included a comprehensive health assessment, a full physical examination, blood work, and fitness tests for each individual. For this analysis, Gulf War veterans were grouped into low (n = 272), moderate (n = 328), and high (n = 80) symptom reporting groups at wave 1 and assessed at wave 2 for selected symptoms and disease diagnosis to determine new onset or the incidence of particular conditions, one of which was asthma. Those who reported the prevalence of a condition of interest at wave 1 were excluded in the analyses of onset for wave 2. Logistic, nominal, and ordinal regressions were used for between-group comparisons. Regression models were adjusted for age group, service branch, and rank estimated as of August 1990, smoking status, alcohol use, BMI, and highest educational level attained at wave 1. New-onset asthma was no different between the high- and the low-symptom reporters (OR = 2.12, 95%CI 0.44–10.22) or between the moderate- and the low-symptom reporters (OR = 0.51, 95%CI 0.12–2.10). The authors found that the odds of obesity and alcohol use increased over time, and the odds of smoking halved; these findings were similar across symptom groups. The findings from the Australian Gulf War Veterans' Health Study likely lack generalizability to studies of respiratory disorders in U.S. Gulf War veterans, primarily because 85% of the Australian Gulf war veterans were Navy personnel, who likely did not have the same exposures—even when off ship—as U.S. ground forces. Furthermore, no analyses were presented to compare differences in those who participated in wave 2 with those who did not, which was half the cohort, and therefore confounding by indication cannot be ruled out for wave 2 respondents.

Lung Function and Asthma Severity

Some recent studies have used tests of lung function to assess whether Gulf War exposures affect asthma severity.

DelVecchio et al. (2015) reviewed DoD medical records from the Medical Evaluation Board to identify 400 consecutive active-duty Army personnel from 2005 to 2009 with an ICD-9 code for asthma who underwent fitness-for-duty evaluations for asthma. Of these 400, spirometry was performed on 355, of whom 227 were also assessed for bronchodilator response, and another subset had a methacholine challenge study. Deployment information was obtained from the AFHSC. Spirometry was compared between those deployed (defined as having been deployed to Southwest Asia at least once for at least 60 days) and those not deployed. Among the deployed, comparisons were also made between those diagnosed with asthma pre-deployment and those diagnosed post-deployment.

FEV_1 (% predicted), either pre- or post-bronchodilator, and FEV_1/FVC were not significantly different in those deployed compared with those not deployed. Among those deployed there were no differences in those diagnosed with asthma pre-deployment versus those diagnosed post-deployment. The rationale for making these comparisons is not clear. It is not obvious what is learned by comparing the level of lung function in those deployed who had a diagnosis of asthma before deployment and those who had a diagnosis only after deployment. What is of interest here is whether asthma severity, as reflected by measures of lung function or bronchial responsiveness, is worsened with deployment-related Gulf War exposures. This study provides no information that bears on that question.

Although not published at the time of writing, the committee reviewed a submitted paper, Woods et al. (2018),[9] which updated the DelVecchio et al. (2015) study to include information on 642 active-duty Army personnel with a diagnosis of asthma. The record review was expanded to include those deployed to Southwest Asia between 2003 and 2015. Only 71 individuals had both pre- and post-deployment spirometry. The use of inhaled corticosteroids or long-acting beta agonists, medications commonly used to manage all but very mild or intermittent chronic asthma, was very infrequent (6.6% and 5.3%, respectively), indicating that these individuals for the most part had very mild asthma (Michael J. Morris, Pulmonary Disease Service, Brooke Army Medical Center, personal communication, October 4, 2019). Mean pre- and post-deployment FEV_1 was 86% of predicted and 87% of predicted, respectively, and not statistically significant ($p = 0.56$). FVC was 94% of predicted and 95% of predicted, respectively, and again not statistically significant ($p = 0.46$). In the subgroup of individuals with bronchodilator testing who had worse baseline control of asthma, pre- and post-deployment FEV_1 was 80% and 84% of predicted ($p = 0.16$) and FVC was 92% and 97% of predicted ($p = 0.04$), respectively. No statistically significant change in pre- and post-deployment inhaled corticosteroid and long-acting beta agonist use was reported. The authors reported a trend for increased FEV_1 and increased FVC after deployment in the group that had bronchodilator testing as well as for those who had worse baseline control of asthma prior to deployment. The comparison of lung function measures both pre- and post-deployment in those with asthma in this study, which is the only study in which this was done, more directly addresses the question of asthma severity and Southwest Asia exposures than DelVecchio et al. (2015). Although the statistical power of this study to detect adverse effects of deployment is limited, the findings provide evidence that deployment was not associated with worsening of asthma in those with very mild or intermittent asthma, at least as measured by spirometry and response to bronchodilator. Whether asthma control was worse during deployment was not addressed.

In a retrospective observational cohort study of 1,193 active-duty soldiers and contractors returning from OEF or OIF deployment through a single processing center, Roop et al. (2007) used a questionnaire to compare the prevalence, severity, and impact of respiratory symptoms occurring in asthmatics and nonasthmatics. The questionnaire collected information on demographics; smoking history, including changes to patterns during deployment; and the respiratory outcomes of shortness of breath, cough, wheezing, sputum production, chest pain/tightness, and allergy symptoms (sneezing, rhinorrhea, or eye irritation). Respondents were asked about the timing of these outcomes (before or during deployment) and to rank the frequency of respiratory symptoms. They were also asked whether respiratory symptoms impeded job activities and whether they sought medical attention for breathing problems during deployment. Those who reported a previous diagnosis of asthma were asked about the diagnosis method and the frequency of day/night asthma symptoms (e.g., shortness of breath, wheezing, cough). For a subgroup analysis, well-controlled asthmatics were identified as those reporting daytime asthma symptoms "never" or "less than two times per week" and nocturnal symptoms "never" or "less than once per month," based on established guidelines. Asthmatic respondents were asked about medication use (e.g., daily to control their asthma or as needed) and to name the medications. Comparisons were made between nonasthmatics and asthmatics, between well-controlled and uncontrolled asthmatics, and between smokers and nonsmokers. McNemar's test was used to compare changes in the variable distribution during deployment versus before deployment. The mean age of participants was 38 ± 11 years, 83% ($n = 977$) were male, and 31% ($n = 375$) were past or present smokers. A previous asthma diagnosis was reported by 61 individuals (5%). New or increased symptoms of shortness of breath during deployment (mean change in Borg dyspnea score, 2.4 ± 2.0) were reported by 155 (13%). During deployment, the respiratory symptoms reported to have increased most were cough (37%) and allergic rhinitis symptoms (38%). During deployment respiratory symptoms affected job performance in 153 participants (13%). A total of 186 participants (16%) sought

[9] Woods et al. (2018) is available from the National Academies' public access file.

medical attention for respiratory complaints; of these, 52 received a temporary duty limitation. Of those seeking medical attention, 19 were hospitalized, of whom 6 required evacuation from the area and 6 required evacuation from the theater of operations. Before deployment, subjects with a history of asthma noted a higher prevalence of all respiratory symptoms and reported more trouble performing their military duties. During deployment, these individuals continued to report more chest wheezing ($p < 0.001$) and sputum production ($p < 0.05$) than nonasthmatics, but statistically significant differences between those with and without asthma were not observed for cough, chest tightness, or allergic symptoms. During deployment, asthmatic personnel continued to have more respiratory symptoms while performing military duties and sought medical attention more frequently than nonasthmatic personnel (44% vs 14%; $p < 0.001$). The increased percentage of persons reporting respiratory symptoms and functional limitations during deployment was similar in those with and without asthma. Among those who were asymptomatic before deployment, there was no statistically significant difference in the proportion of asthmatics and nonasthmatics who developed new symptoms during deployment. Of those who had reported being asthmatic before deployment, 55 (90%) reported taking medications only as needed. Sixteen (26%) asthmatic individuals were considered poorly controlled, and they reported statistically significantly more wheezing, cough, sputum production, and chest pain/tightness than those in the well-controlled group, both before and during deployment ($p < 0.05$ for all symptoms). The poorly controlled group also reported more difficulty with physical training than the well-controlled group ($p < 0.05$). Poorly controlled asthmatics sought medical attention for respiratory symptoms more often than well-controlled asthmatics (n = 11, 69% vs n = 14, 35%; $p < 0.05$). About 11% of respondents were past smokers, and 20% (n = 234) were active smokers at the time of the survey. During deployment, 59% of the active smokers reported smoking more heavily, and 12% reported smoking less. Both before and during deployment those with a history of smoking reported a higher prevalence of all respiratory symptoms except allergies. There was no significant difference in the performance of field duties between smokers and nonsmokers. Smoking rates were similar among asthmatics (n = 21, 34%) and nonasthmatics (n = 350, 31%), but it was more common in the poorly controlled asthmatics group than in the well-controlled group (n = 10, 63% vs n = 8, 20%; $p < 0.01$). During deployment, after controlling for smoking, compared with well-controlled asthmatics the poorly controlled asthmatics had significantly more wheezing, cough, sputum production ($p < 0.01$ for all), and chest pain/tightness ($p < 0.05$) as well as greater difficulty passing the physical fitness test, running in formation, and wearing the chemical protective mask ($p < 0.05$ for all). Although there was a 95% response rate to the questionnaire and the study sample size was relatively large, there were several limitations to this study. All information was based on self-report, with no medical record or other objective test validation. The authors noted the possibility of underreporting by those fearing curtailment to professional opportunities and overreporting by those seeking disability or benefits. The number of self-reported asthmatics was relatively small, and the study sample was derived from soldiers redeployed through one processing center. The authors also noted that few of the respondents were in traditional combat specialties (infantry, armor, field artillery) but also said that many deployed to Southwest Asia undergo activities and exposures that are similar to those of traditional combat soldiers. Those who were evacuated from theater with severe respiratory problems may not have been redeployed and thus would have been excluded from the sample.

Synthesis

Based on the asthma studies of 1990–1991 Gulf War veterans summarized previously in *Gulf War and Health* Volumes 4, 8, and 10 and new studies reviewed in that population in this report, the committee found no evidence of a difference in asthma diagnoses among studies of Gulf War veterans.

Studies of asthma among post-9/11 veterans were mixed in terms of observing a relationship between asthma diagnosis and deployment to Southwest Asia. Among the Millennium Cohort studies there were mixed results, but each analyzed slightly different research questions. Smith et al. (2009) was a null study and observed that deployers had similar proportions reporting asthma. Smith et al. (2012) observed that women and army personnel had increased odds of an asthma diagnosis but did not observe an association with deployments to regions with burn pits compared with other regions of Iraq and Afghanistan. Rivera et al. (2018) observed that women and men who had combat experience had an increased risk of a new asthma diagnosis. NewGen studies also showed varying relationships between deployment to Southwest Asia and asthma. Barth et al. (2014) found no difference between asthma diagnosis after 2001 comparing deployed with nondeployed veterans. Barth et al. (2016a) found associations between some exposures and asthma, but the risks of those exposures were similar between the deployed and nondeployed groups.

Other studies that examined the impact of specific exposures on asthma did not observe a positive association. Baird et al. (2012), who evaluated the influence of exposure to the Al Mishraq sulfur mine fire on asthma, observed that asthma encounters were less likely for firefighters and other highly exposed groups. Abraham et al. (2012) observed that increases in ambient PM did not increase asthma incidence. Using data from the burn pits registry, Liu et al. (2016) observed no association between burn pit exposure and asthma.

Studies not mentioned in the Statement of Task also had mixed results. The studies of the AFHSC and similar studies that used DoD medical records data had findings that differed slightly due to differences in reference groups or exposure estimates. Abraham et al. (2014) observed that the rates of medical encounters for asthma were higher among those deployed to Southwest Asia than among the nondeployed and that rates of medical encounters for asthma were similar between those deployed to Southwest Asia and those deployed to Korea. On the other hand, Sharkey et al. (2015) observed largely null associations with deployment and asthma development and had a larger comparison group than Abraham et al. (2014). Sharkey et al. (2016) observed an increased incidence of asthma among those deployed to Kabul compared with the U.S. reference group, but not compared with the other control locations. Pugh et al. (2016) examined the impact of multiple deployments to theater and found no association between multiple deployments and asthma incidence. Szema et al. (2010) found associations between deployment to theater and asthma incidence compared with those in a U.S.-based comparison group.

One of the reasons for the observation of these mixed findings is that the military has been allowing more active-duty service members with asthma. Specifically, during the times of these study periods there were changes in the ability to obtain a medical waiver for asthma and in the policy of including asthma as a diagnosis that medically disqualified individuals from enlistment. These changes resulted in an increasing prevalence of asthma as a chronic lung disease, and such temporal changes may have influenced study findings (Garshick, 2019). Another limitation is that all of the studies relied on either participant self-report of asthma, which may lead to an over-reporting of outcomes (Smith et al., 2008), or apply administrative data, which may under-report cases by excluding encounters outside of a specific medical system (such as VA or DoD health systems) and may only identify the most severe encounters. Epidemiologic studies that use standardized measures of evaluating asthma, such as those recommended in the ATS/ERS consensus statement in standardizing endpoints for asthma clinical trials (Reddel et al., 2009), may be more likely to find an association if there is one.

The question of deployment-related worsening of asthma as determined by spirometric measures was addressed essentially by only one study that was submitted but not yet published. That study (Woods et al., 2018), as did the Morris et al. (2019) study, described in detail in the PFT section, used both pre- and post-deployment spirometry, but in contrast to the Morris et al. (2019) study, Woods et al. (2018) used paired analyses where appropriate. The study provided evidence that deployment was not associated with a persistent worsening of asthma in those with very mild or intermittent asthma, at least when asthma severity was assessed by spirometry and response to bronchodilator. Whether asthma control was worse during deployment was not addressed. Roop et al. (2007) used standard questionnaires to compare the prevalence, severity, and impact of respiratory symptoms occurring in asthmatics and nonasthmatics. They found that during deployment, asthmatic personnel had more respiratory symptoms while performing military duties and sought medical attention more frequently than nonasthmatic personnel, but the results may suffer from recall bias due to the retrospective nature of the design. Studies evaluating the impact of deployment on asthma control and risk of exacerbations should be considered, especially given that the prevalence of asthma has been increasing among those receiving VA care since 2003 (Pugh et al., 2016) and that there are likely more people with asthma in the military due to the changes in the policies for receiving medical waivers.

Conclusions

Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and the subsequent development of asthma.

Chronic Obstructive Pulmonary Disease, Emphysema, and Chronic Bronchitis

COPD is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and by airflow obstruction that is due to airway or alveolar abnormalities. The most common cause of COPD is cigarette smoking (NHLBI, 2020b), but it can also be the result of exposure to noxious particles or gases. The term "COPD" is applied to a family of obstructive pulmonary diseases that primarily includes chronic bronchitis and emphysema.

Chronic bronchitis is an inflammation of the lining of the bronchial tubes that is manifested by mucous hypersecretion and defined as a cough and or phlegm production four to six times per day, 4 or more days per week for more than 3 months of the year. The symptoms can include cough, mucous production, wheezing, and difficulty breathing. The most common cause of chronic bronchitis is cigarette smoking. Outdoor air pollution and vapors, dusts, gases, and fumes in the indoor environment or workplace can also contribute to the condition. Chronic bronchitis is a relatively common illness in the United States, with an estimated prevalence of 3.4% in adults over 18 years of age in 2018 (CDC, 2018).

Emphysema is another phenotype of COPD that is characterized by the destruction of the elastic fibers of the alveolar walls resulting in the collapse of small airways, air trapping, and impaired expiratory airflow. As is true for chronic bronchitis, smoking is the most common cause of emphysema, but workplace exposure to some vapors, dusts, gases, and fumes as well as to indoor biomass smoke and other pollutants has also been linked to the disease. Emphysema had an estimated prevalence of 1.3% in adults over 18 years of age in the United States in 2018 (CDC, 2018).

Over the past several years, there has been a concerted effort to establish standardized clinical assessment criteria for the diagnosis of chronic bronchitis and emphysema. Standardized questions about the symptoms of cough, sputum production, wheeze, and dyspnea have been used for over 40 years to define chronic bronchitis (Ferris, 1978). For COPD and emphysema, spirometric testing has been used to establish the diagnosis and to assess the severity of disease. The standard clinical measurement is the ratio of a person's FEV_1, to his/her FVC. While a post-bronchodilator fixed FEV_1/FVC ratio of less than 0.7 is generally considered a spirometric criterion for airflow limitation (GOLD, 2018), age-adjusted FEV_1/FVC at the lower limit of normal (from large-scale representative general populations) has been offered as an alternative (Shirtcliffe et al., 2007). The two methods produce minor differences in scoring in that GOLD yields a slightly higher estimate of false-negative diagnoses in younger subjects (less than age 40) and a slightly greater number of false-positives in older populations (over age 50) (Culver, 2006). Because most studies to date have been done in relatively young populations, the impact of using these different criteria would be greater. This concern does not influence the committee's conclusion because the incidence of COPD was consistently observed to be relatively low across studies. There have also been efforts to advance other diagnostic tools, such as CT scans, to confirm the anatomical lesions associated with suspected airways obstruction.

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports

Studies of COPD, chronic bronchitis, and emphysema in active-duty personnel and veterans who have served in the Southwest Asia theater have been reviewed in multiple previous volumes of the National Academies *Gulf War and Health* series (IOM, 2005, 2006, 2010; NASEM, 2016) and related reports (IOM, 2011; NASEM, 2017). The only time when conclusions regarding these outcomes were specifically offered in these earlier reports was in Volume 3 (IOM, 2005), which addressed health effects related to exposure to fuels, combustion products, and propellants. The committee responsible for that report—which relied on literature published through early 2004 and which considered studies of occupationally exposed populations in addition to military personnel and veterans—came to the following determinations from its assessment of the epidemiologic evidence:

- There is inadequate/insufficient evidence of an association between exposure to combustion products and the development of COPD as defined by irreversible airflow obstruction.
- There is inadequate/insufficient evidence of an association between short-term exposure (less than 1 year) to combustion products and chronic bronchitis.

- There is inadequate/insufficient evidence of an association between exposure to combustion products and the development of emphysema.
- There is inadequate/insufficient evidence to determine whether an association exists between exposure to fuels and any specific, nonmalignant respiratory outcomes, including bronchitis and emphysema.

Later literature reviews presented in Volumes 4, 8, and 10 (IOM, 2006, 2010; NASEM, 2016) addressed non-cancerous respiratory disease in general. As noted elsewhere in this chapter, the committees responsible for those reports concluded that the then-available literature constituted insufficient or inadequate evidence to determine whether an association existed between deployment to the theater and respiratory disease, including COPD, chronic bronchitis, and emphysema. Neither *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan* (IOM, 2011) nor *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry* (NASEM, 2017) drew conclusions about specific respiratory health outcomes.

The committee responsible for the 2017 National Academies report *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry* carried out an analysis of the initial months of data gathered from respondents to the registry's questionnaire (NASEM, 2017). The data were derived from the first 13 months of completed questionnaires (n = 46,404), representing approximately 1.0% of the 1990–1991 Gulf War veterans and 1.7% of post-9/11 veterans who met the registry's eligibility criteria. Health outcomes were characterized by self-reports of health care provider–diagnosed conditions; exposures to burn pits and other airborne hazards were based on self-report and on DoD data on the numbers and locations of deployments. A total of 14.3% of respondents self-reported emphysema, chronic bronchitis, or COPD during or after deployment. The committee synthesized exposure metrics by combining the responses to questions regarding specific exposures. A number of analyses were conducted using these measures, controlling for age, sex, smoking history, and BMI. In summary, these indicated that the airborne exposure measures had strong and consistent associations with a self-report of diagnosed emphysema, chronic bronchitis, or COPD. The associations were observed for several indicators of burn pit exposure as well as for a range of other deployment exposures, such as exposures to diesel/exhaust/fuel, construction, dust, and combat. However, the report detailed a number of issues with the quality and limitations of the registry's information, which led the committee to conclude that the results of the analyses could not be taken at face value and that the identified associations might be an artifact of the population's selection and the limitations of the self-reported exposure and disease data.

The sections below summarize salient results from epidemiologic studies that address COPD, chronic bronchitis, emphysema, and other allied conditions in military and veteran populations who served in the Southwest Asia theater and Afghanistan. Summaries of some of those studies that are recapped elsewhere in the chapter or in previous reports are more abbreviated. In the course of their work, the committee identified relevant studies dating from before the publication of Volume 10 that had not been previously addressed in National Academies reports. These are placed in the Update of the Scientific Literature section, even though they are from earlier times. Studies are categorized by country, beginning with those addressing U.S. veterans; those resulting from the same research initiative are grouped together.

1990–1991 Gulf War Veterans The 1995 NHS, a population-based study of U.S. Gulf War veterans, yielded information used by multiple investigators to examine chronic obstructive lung disease in military personnel deployed to the theater compared with nondeployed era veterans. The population prevalence rates were calculated using statistical analysis techniques to account for a stratified random sampling of unequal probabilities of selecting various strata. Regarding bronchitis specifically, Kang et al. (2000) found that compared with nondeployed era veterans, Gulf War–deployed veterans had a statistically significantly higher self-reported prevalence of bronchitis (not differentiated between acute or chronic) experienced in the 12 months before the survey: 11.2% for deployed versus 7.7% for the nondeployed (RD = 3.57, 95%CI 3.48–3.66); however, estimates were not adjusted for smoking or other factors.

Eisen et al. (2005) performed a cross-sectional study on health outcomes collected from a subset of 1,061 deployed and 1,128 nondeployed Gulf War veterans who responded to the NHS and who completed the clinical examination component of the third phase of the NHS. No increase in the prevalence of self-reported asthma, bronchitis, or emphysema (presented as a group) was observed among the deployed veterans compared with nondeployed veterans in models that adjusted for age, sex, race, years of education, cigarette smoking, component (active versus reserves or National Guard), service branch, and rank (OR = 1.07, 95%CI 0.65–1.77). Obstructive lung disease was defined by the investigators as "a history of lung disease (asthma, bronchitis, or emphysema) or pulmonary symptoms (wheezing, dyspnea on exertion, or persistent coughing with phlegm) and either the use of bronchodilators or at least 15% improvement in FEV_1 after a short-acting bronchodilator" (Eisen et al., 2005, p. 884). Given this definition, no increase in obstructive lung disease was observed among deployed personnel (OR = 0.91, 95%CI 0.52–1.59) adjusted as above. However, information presented in a companion paper by Karlinsky et al. (2004)—summarized next—indicates that "bronchitis" was not differentiated as acute or chronic during data collection, weakening the relevance of the paper to an evaluation of COPD.

Karlinsky et al. (2004) examined data on the same deployed 1990–1991 Gulf War veterans and nondeployed Gulf War–era veterans population as Eisen et al. (2005). A total of 1,036 deployed and 1,103 nondeployed veterans met their selection criteria. In this analysis, the odds for current prevalence of self-reported bronchitis (not specified as acute or chronic) (OR = 1.08, 95%CI 0.50–2.34) and emphysema (OR = 4.45, 95%CI 0.74–26.68) were not different between the cohorts. Estimates were not adjusted (including for smoking history, although smoking data were collected). Demographic variables were similar in the deployed and nondeployed groups, and a history of tobacco smoking was more common in deployed veterans than in nondeployed veterans (51% vs 44%). Other limitations of the study include inadequacies in the description of the sampling strategy used and offering no explanation of how the groups were matched for analysis purposes.

Kang et al. (2009) used data from the 10-year follow-up of the NHS baseline survey to obtain self-reports of physician-diagnosed chronic medical conditions in the same population. A statistically significant excess of self-reported, physician-diagnosed chronic bronchitis or emphysema was found among 6,111 deployed Gulf War veterans compared with 3,859 nondeployed era veterans (RR = 1.47, 95%CI 1.30–1.65), adjusted for age, gender, race, rank, service branch, unit component, BMI, and current cigarette smoking.

Dursa et al. (2016b) conducted a 2012–2013 cross-sectional follow-up survey that collected data from 8,104 deployed and 6,148 era veterans who had participated in the 1993–1995 NHS (Kang et al., 2000). Both the NHS and follow-up assessments of it are described in greater detail in Chapter 3. A statistically significant difference between the deployed and nondeployed veterans in self-reports of physician-diagnosed COPD was found (8.4% vs 6.3%; OR = 1.48, 95%CI 1.23–1.78). The OR was adjusted for age, race, sex, BMI, smoking status, service branch, and unit component. The Volume 10 (NASEM, 2016) committee that previously reviewed this paper noted that this result must be viewed with caution because the diagnosis of COPD was taken from a retrospective assessment of VA records in which the proportion attributed to "bronchitis, not otherwise specified" (ICD-9 490) was included as part of those counted as having new-onset COPD.

Two additional relevant studies of veterans of Southwest Asia theater conflicts were previously addressed in earlier National Academies *Gulf War and Health* reports.

Lange et al. (2002) used a cross-sectional study design to examine exposure to smoke from oil-well fires (self-reported and modeled) and self-reported bronchitis symptoms assessed via structured interviews conducted 5 years after the 1990–1991 Gulf War for a population-based sample of 1,560 Iowa veterans. Modeled exposures were developed using a geographic information system to integrate spatial and temporal records of smoke concentrations, with troop movements ascertained from Global Positioning Systems records during the period of oil-well fires (February–October 1991). Exposure was presented by quartiles. Cases of bronchitis were assessed on the basis of self-reported cough and phlegm production, but these questions pertained to symptoms in the preceding month only; the overall prevalence of bronchitis symptoms was 4.7% for the study population. Current smokers had more than twice the prevalence of bronchitis symptoms as never smokers (6.3% vs 3.0%, respectively). There was no association between the modeled measure of exposure to oil-fire smoke and symptoms of bronchitis for any of the quartiles or with increasing magnitude of exposure. In contrast to the modeled exposures, there was a statistically significant association observed between the self-reported measure of exposure to oil-fire smoke and symptoms of bronchitis, whereby the risk of bronchitis increased with increasing magnitude of exposure, and the relationship for most quartiles was statistically significant. All effect models were adjusted for sex, age, race, military rank, smoking history, military service, and level of preparedness for war (based on the responses to six questions). The use of population-based sampling improves the generalizability of the results. Its major weakness was the failure to use a standard epidemiologic definition of bronchitis, making it impossible to distinguish between acute and chronic symptoms.

Smith et al. (2002) used DoD hospitalization data (ICD-9-CM codes) from August 1991 through July 1999 and exposure models to retrospectively examine associations between respiratory diseases, including chronic bronchitis and emphysema, among 405,142 active-duty service members who served in the 1990–1991 Gulf War at the time of the oil-well fires. Service members were categorized as exposed (n = 337,077) and nonexposed (n = 68,065) to oil-well fires. There was no difference in modeled exposure to oil-well fires and the risk of hospitalization for chronic bronchitis adjusted for age, length of service, salary and pay grade, oil-well smoke exposure status, and number of days in the Gulf theater between exposed (n = 45) and nonexposed (n = 11) veterans (RR = 0.78, 95%CI 0.38–1.57). Similarly, there was no statistically significant difference between exposed (n = 48) and nonexposed (n = 8) veterans for emphysema (RR = 1.36, 95%CI 0.62–2.98), adjusted for unspecified demographic and military characteristics. Because most adults who have chronic bronchitis are never hospitalized for the condition, this analysis would not be expected to have captured most cases, only those that are most severe, which is evident from the relatively small number of cases identified over the 8-year period. No information was available on cigarette smoking or other exposures that may be related these outcomes.

Other 1990–1991 Gulf War Coalition Forces Veterans Two studies of cohorts of veterans of the Australian Defence Force include information on COPD and related diseases.

Using data collected from 1,424 deployed veterans and 1,548 nondeployed comparison veterans who participated in the 2000–2002 Australian Gulf War Veterans' Health Study, Kelsall et al. (2004) conducted an analysis of respiratory health outcomes, including chronic bronchitis. The results of other respiratory outcomes have been reported in the applicable outcomes sections of this chapter. As part of the medical assessment and physical examination, spirometric tests were performed, and a respiratory questionnaire was administered. Three definitions were applied for chronic bronchitis, and modeled effect estimates controlled for age, height, weight, smoking, atopy, rank, service, education, and marital status. Self-reported, doctor-diagnosed chronic bronchitis prevalence was not different between deployed and comparison veterans (OR = 1.1, 95%CI 0.9–1.5). The second definition for chronic obstructive bronchitis—"cough for as long as 3 months in each of the past 2 years and FEV_1/FVC <70%" (Kelsall et al., 2004, p. 898)—again found no difference between deployed and comparison veterans (OR = 1.0, 95%CI 0.4–2.3). For the third definition used—"doctor-diagnosed bronchitis first diagnosed in 1991 or later and rated as a possible or probable diagnosis" (Kelsall et al., 2004, p. 899)—deployed veterans were found to have higher adjusted OR (OR = 1.9, 95%CI 1.2–3.1). A so-called working definition of emphysema was used that yielded no difference between deployed and comparison veterans (OR = 1.0, 95%CI 0.8–1.4). The authors identified the strengths of their study as including its objective measures of health and the use of a randomly sampled military comparison group, and its potential weaknesses as including recall bias and unidentified confounding factors, such as work exposures.

Using data collected from the Australian Gulf War Veterans' Follow Up Health Study conducted in 2011–2013, which was collected 10 years after the 2000–2002 baseline investigation and 20 years after the 1990–1991 Gulf War, Sim et al. (2015) examined data on 697 deployed veterans and 659 nondeployed veterans. Deployed veterans were no more likely to report a doctor-confirmed diagnosis of chronic bronchitis (RR = 1.03, 95%CI 0.74–1.43) but more likely to report emphysema or COPD (RR = 2.14, 95%CI 0.60–7.66), although neither result was statistically significant. Estimates were adjusted for age group, service branch, and rank estimated as of August 1990 as well as for any atopy at baseline and current smoking status (never, former, current smoker). When a standardized symptom-based definition of chronic bronchitis was applied, a statistically significant difference was observed (RR = 1.51, 95%CI 1.17–1.96), adjusted for the same demographic, military, and lifestyle characteristics. The researchers note that the number of self-reported, doctor-confirmed chronic bronchitis cases was significantly elevated at baseline (number not reported), which affected their calculation at follow-up, as did the small number of cases of emphysema or COPD (eight in deployed personnel; four in the comparison group).

Post-9/11 Veterans The AFHSC (2010) examined medical encounters of U.S. Army and Air Force personnel 36 months after deployment to Joint Base Balad, Contingency Operating Base Speicher, or Camp Taji in Iraq (all three of which used burn pits for waste management); Camp Buehring or Camp Arifjan in Kuwait (which did not use burn pits); or to installations in the Republic of Korea, from 2005 to 2007. Service members who were never deployed and stationed only in the continental United States in the same period were used as a comparison population. IRRs of COPD were calculated using Poisson models that were adjusted for sex, birth year, marital status, race/ethnicity, education, smoking status, physical activity, service branch, military rank, pay grade, and occupation. COPD was statistically significantly lower for troops deployed to Joint Base Balad (IRR = 0.91, 95%CI 0.84–0.99), Camp Buehring (IRR = 0.62, 95%CI 0.44–0.88), and Korea (IRR = 0.83, 95%CI 0.78–0.88) than for the nondeployed U.S. cohort. No differences in COPD incidence were found for those deployed to Camps Arifjan or Taji compared with the nondeployed U.S. cohort. The investigators also conducted additional analyses using data from the baseline and first follow-up cycles of the Millennium Cohort Study. Multivariable logistic regression was used to compare the adjusted odds—using the same factors as used in the Poisson models, including smoking and physical activity—of COPD associated with three metrics of exposure within a 5-mile radius of the documented burn pits: dichotomous deployment near the documented burn pits, cumulative days exposed to the burn pits (presented by quartiles), and exposure to the burn pits at three different campsites (Balad, Taji, or Speicher). The incidence of newly reported chronic bronchitis or emphysema was 1.54% for participants with putative exposure to burn pits and 1.46% for the nonexposed group. Deployment within 5 miles of a documented burn pit was not associated with increased odds for newly reported chronic bronchitis or emphysema (OR = 0.87, 95%CI 0.64–1.18; p = 0.36). In addition, no association of chronic bronchitis or emphysema was found for cumulative days in proximity to a burn pit for any of the quartiles of exposure compared with the nonexposed group. An analysis that examined the outcomes at Joint Base Balad, Contingency Operating Base Speicher, and Camp Taji separately found that the odds of chronic bronchitis or emphysema were not increased in association with deployment within 5 miles of the sites compared with those deployed outside of the 5-mile radius (p = 0.33).

Update of the Scientific Literature on COPD, Emphysema, and Chronic Bronchitis

Epidemiologic studies of COPD, chronic bronchitis, or emphysema in Southwest Asia theater veterans that have not previously been addressed in National Academies reports are summarized below, grouped by the source of the data and addressed in order of their publication. Studies of post-9/11 U.S. veterans are presented first, followed by studies of post-9/11 coalition forces, and the sections end with summaries of U.S. 1990–1991 Gulf War veterans. Some additional studies that were identified were not included in this section because they were descriptive studies, did not include a comparison group, or grouped COPD, emphysema, and chronic bronchitis with several other outcomes that made these outcomes indistinguishable. Such studies included publications from the STAMPEDE initiative (Morris et al., 2014, 2020) and one in veterans who had been referred to VA's WRIISC specialty clinic (Butzko et al., 2019).

Post-9/11 Veterans The Millennium Cohort Study—an ongoing prospective epidemiologic research effort intended to evaluate the impact of military exposures, including deployment, on long-term health outcomes—has published three papers to date (early 2020) that address the respiratory health outcomes addressed in this section.

Smith et al. (2008) used self-reported, clinician-diagnosed health data from regular, active-duty participants from the first panel (2001–2003) of the Millennium Cohort Study (n = 37,798) to compare the agreement of 38 medical conditions, which included chronic bronchitis and emphysema, with that obtained from electronic medical records based on ICD-9-CM codes. Any diagnostic code for these 38 conditions in any portion of the medical record indicated agreement with a self-reported medical condition of interest. Both positive and negative agreement were used to compare self-reported data with those from electronic medical records. The prevalence of chronic bronchitis was 3.3% (95%CI 3.1–3.4) for self-reported and 4.0% (95%CI 3.8–4.2) for electronic medical record–documented cases; 3.5% were exclusively recorded in the electronic medical records. The positive agreement between self-report and electronic medical records for chronic bronchitis was 12.9%, and negative agreement was 96.7%. The prevalence of emphysema was 0.6% (95%CI 0.5–0.7) for self-reported and 0.2% (95%CI 0.1–0.2) for electronic medical record–documented cases; 0.2% were exclusively recorded in the electronic medical record. The positive agreement between self-report and electronic medical records for emphysema was 2.7% and negative agreement (the condition was not reported either by self-report or found in the medical record) was 99.6%. When reports of chronic bronchitis were examined by length of service (0–5, 6–10, 11–15, and ≥16 years), for all periods the self-reported prevalence of chronic bronchitis was lower than what was recorded in the electronic medical records.

Smith et al. (2009) examined newly reported chronic bronchitis and emphysema and other respiratory conditions among 46,077 Millennium Cohort Study participants who completed baseline (2001–2003) and follow-up (2004–2006) questionnaires. Logistic regression was used to compare the adjusted odds of new chronic bronchitis or emphysema (grouped) in relation to deployment status (deployed versus nondeployed) stratified by service branch and adjusted for sex, birth year, marital status, race/ethnicity, education, smoking status, service component, military pay grade, and occupational code. The adjusted OR for newly reported chronic bronchitis or emphysema in deployed versus nondeployed personnel varied according to service branch, though it was not statistically significant for any of the branches, with the highest OR observed in Army personnel (OR = 1.25, 95%CI 0.94–1.67) and the lowest in Navy and Coast Guard personnel (OR = 0.79, 95%CI 0.42–1.46). When the analysis was restricted to deployed cohort members with self-reported information on deployment location (n = 9,861), the investigators stated that the odds of chronic bronchitis or emphysema were not statistically different in any of the deployment locations examined, although estimates were not provided.

Smith et al. (2012) investigated the effects of exposure to documented open-air burn pits within 2, 3, or 5 miles on chronic bronchitis or emphysema and other respiratory outcomes among Millennium Cohort Study Army and Air Force participants who were deployed to Iraq or Afghanistan after January 1, 2003, and who completed the baseline questionnaire and one of the follow-up assessment cycles through 2008. After excluding individuals with missing data, 3,585 individuals who deployed within 3 miles of a burn pit were compared with 18,712 individuals who deployed to Iraq or Afghanistan but outside that zone for the analyses of new-onset chronic bronchitis or emphysema. Similar proportions of newly reported chronic bronchitis or emphysema in 2007 were found for those exposed within 3 miles of a burn pit and those nonexposed (1.5% vs 1.6%, respectively). At the end of follow-up, and after adjusting for demographic, behavioral, and military characteristics, the odds of newly reported chronic bronchitis or emphysema were statistically significantly increased for women (OR = 1.77, 95%CI 1.36–2.30), consistent smokers (OR = 1.61, 95%CI 1.24–2.10), and Army personnel (OR = 1.82, 95%CI 1.38–2.41), whereas younger individuals and those who did and did not meet the standards for aerobic activity were at reduced risk for chronic bronchitis or emphysema compared with those who could not perform aerobic activity. Three proxy exposure metrics were modeled, and the analyses were adjusted for demographic and military characteristics, smoking status, and physical activity. Neither newly reported chronic bronchitis nor emphysema was statistically significantly associated with deployment within 3 miles of burn pits (OR = 0.91, 95%CI 0.67–1.24) when compared with deployments to areas with no documented burn pit exposure and adjusted for demographic, behavioral, and military covariates. Similarly, no statistically significant associations for new-onset chronic bronchitis or emphysema were found when those deployed at each of the three sites with documented burn pits (Joint Base Balad, Camp Taji, or Camp Speicher) were compared with those deployed outside of the 3-mile radius exposure window. An increasing number of cumulative days of exposure within a 3-mile radius of the burn pits was not associated with the adjusted odds of new-onset chronic bronchitis or emphysema compared with cohort members with no burn pit exposure ($p = 0.76$). Findings of no association with new-onset chronic bronchitis or emphysema for deployment status, cumulative deployment length, and camp location were consistent when examining the risk within 5 miles of the burn pits.

Using data collected as part of the NewGen Study, Barth et al. (2014) examined the association between deployment to Southwest Asia and self-reported doctor-diagnosed bronchitis (did not distinguish between acute and chronic) among 13,162 deployed and 7,401 nondeployed veterans. Unweighted and weighted prevalence of bronchitis were calculated and stratified by diagnosis before or after 2001, and logistic regression was used to calculate adjusted ORs for deployment status and bronchitis. The models were adjusted for birth year, sex, service branch, unit component, race/ethnicity, education, and smoking status. Separate models were constructed for diagnosis before 2001 and during or after 2001. For those diagnosed before 2001, the weighted prevalence for bronchitis was higher in the nondeployed than in the deployed (4.5% vs 6.6%), and deployment was associated with statistically significant decreased odds of bronchitis (OR = 0.73, 95%CI 0.63–0.84). Among those with respiratory disease diagnosed in 2001 or later, the weighted prevalence of bronchitis was slightly higher in the deployed than in the nondeployed veterans (5.9% vs 5.3%), and there was no difference in the odds of bronchitis between the deployed and nondeployed groups (OR = 1.12, 95%CI 0.96–1.30).

Barth et al. (2016a) again used data from the NewGen study to expand on the analysis by Barth et al. (2014) to examine the prevalence of self-reported doctor-diagnosed respiratory diseases and their association with self-reported respiratory exposures during military service for OEF/OIF deployed and nondeployed veterans. Logistic regression analyses were used to calculate weighted, adjusted odds of bronchitis (not specified as chronic or acute) stratified by deployment status and controlled for sex, birth year, race/ethnicity, education, smoking status, unit component, service branch, and number of OEF/OIF deployments. A total of 2,588 veterans self-reported bronchitis (1,615 deployed and 970 nondeployed). Among deployed veterans, the highest odds for bronchitis were for those categorized as high exposure (OR = 2.49, 95%CI 1.70–3.63) and for diesel, kerosene, or other petrochemical fumes as a specific exposure (OR = 1.79, 95%CI 1.48–2.16). For nondeployed veterans, statistically significant increased odds of bronchitis were observed for all specific exposures and for both the high-exposure and low-exposure categories; the highest odds for bronchitis for specific exposures were for smoke for oil fires (OR = 1.67, 95%CI 1.33–2.09) and industrial pollution (OR = 1.67, 95%CI 1.38–2.03). These results show that exposures were associated with the development of bronchitis in both deployed and nondeployed groups, but the confidence intervals for the adjusted ORs all overlap between the deployed and nondeployed groups.

Abraham et al. (2014) built on the AFHSC (2010) analysis by adding an additional 12 months of follow-up (for a total of 48 months) of personnel deployed to four Southwest Asia theater sites with and without burn pits, along with those deployed to Korea and a comparison population of service members who stayed in the United States. The IRR of medical encounters for "COPD and allied conditions" was the same for those deployed to in-theater locations as for nondeployed personnel after adjustment for age, gender, race, and military rank (IRR = 1.12, 95%CI 0.96–1.31). Other models—which examined rates for personnel at in-theater bases with and without burn pits, and for personnel at the individual bases—all yielded no difference in adjusted IRRs compared with the U.S. group of service members. Information on smoking was not factored into the analyses. When service members deployed to in-theater locations were compared with those deployed to Korea, however, a statistically-significant increase for COPD and allied conditions was observed (IRR = 1.24; 95%CI 1.03–1.48). Additional analyses that adjusted for the same demographic and military factors found that the difference was statistically significant for personnel at the two bases without burn pits (IRR = 1.37; 95%CI 1.04–1.82) but not for personnel at the two with burn pits (IRR = 1.16; 95%CI 0.95–1.43). While the study found that deployment to the Southwest Asia theater, but not necessarily potential exposure to burn pits, was associated with an elevated post-deployment rate of COPD and allied conditions, smoking was not factored into these analyses, and that smoking behavior during deployment is a likely plausible causal intermediate between deployment and the incidence of respiratory conditions needs to be considered.

The analyses by Sharkey et al. (2015) also used the same deployed and nondeployed populations as the AFHSC (2010) analysis but used a larger U.S.-based reference population and included an additional 12 months of data. Its methods also differ from Abraham et al. (2014); all three studies are discussed in greater detail in Chapter 3. This retrospective cohort study used Poisson models that were adjusted for age, pay grade, sex, race, and service branch to calculate IRRs for COPD (ICD-9-CM 490–492, 494–496) at two time periods: up to 36 months after the baseline data were gathered and up to 48 months afterwards. Outcome ascertainment was limited to encounters that occurred at a military hospital or care center. At 36 months of follow-up, the risks of COPD at the four Southwest Asia bases and Korea sites examined were all similar to, or statistically significantly lower than (Balad, Buehring, and Korea), the risks for personnel who remained in the United States. Similar results were found at the 48-month follow-up, with Balad, Buehring, and Korea again showing statistically significantly lower adjusted incidence rates of COPD compared with the U.S. cohort. No observed association between COPD and serving at locations with burn pits was found.

Sharkey et al. (2016) extended the analysis of the AFHSC (2010) report by adding additional populations of Army or Air Force personnel who were deployed to Kabul (n = 5,670) and Bagram (n = 34,239) Air Force Bases in Afghanistan—sites with similar, poor air quality—and Manas Air Force Base in Kyrgyzstan (n = 15,851)—a site with relatively better air quality—and extended the follow-up period of active-duty personnel to 12 years. COPD cases were identified when an individual had either an inpatient or at least two outpatient health care encounters labeled with ICD-9-CM 490–492 or 494–496 in any diagnosis coding position. IRRs were calculated and adjusted for age, sex, race, and military rank. No statistically significant differences for COPD were found between the Kabul cohort and the other location cohorts.

Liu et al. (2016) examined the associations between assumed geographic and self-reported burn pit emissions exposure and respiratory and cardiovascular outcomes in participants in VA's Airborne Hazards and Open Burn Pit Registry (first described in the Asthma section). The study included 4,343 participants who completed the registry questionnaire by April 30, 2015; of these, 2,663 participants deployed for at least 30 days from January 1, 2003, to June 30, 2007, within 2 miles of burn pits in Joint Base Balad or Camp Taji in Iraq, and 1,680 participants were deployed for at least 30 days to Kuwait (but not to Joint Base Balad or Camp Taji) during that timeframe. There were no documented burn pits at Kuwait bases. Two surrogate measurements of burn pit emissions exposure were used in the analysis: days of deployment near burn pits and self-reported total hours of burn pit smoke exposure. Associations were presented by quartiles of burn pit exposure. Self-reported diagnoses were compared with VA medical record information for 2,857 respondents who used VA health care at least once between January 2007 and November 2015. Participants who reported having been diagnosed with a condition before deployment were excluded from both the analyses of self-report and the comparisons with VA medical records for that condition. All demographic characteristics (except marital status), military characteristics, and other factors, such as in-person clinical examination request and smoking status, were found to be statistically significantly associated with deployment days within 2 miles of the burn pits sites. Associations between demographic, lifestyle (with exception of smoking), and military service variables and self-reported burn pit smoke exposure amount were found to be statistically significantly associated with self-reported burn pit smoke exposure. Models were adjusted for demographic, lifestyle (including smoking status), and military service characteristics. A strong exposure–response association was found between cumulative days deployed within a 2-mile radius of a burn pit and self-reported emphysema, chronic bronchitis, or COPD (p-trend = 0.01; n = 537). The same association was not observed, however, when VA medical record diagnoses (ICD-9 491, 492, and 493.2) were used in place of the self-report (p-trend = 0.88; n = 104). When the number of self-reported hours per day of burn pit smoke exposure was used as the measure in place of days deployed near a burn pit, the exposure–response association with self-reported emphysema, chronic bronchitis, or COPD was strongly statistically significant (p-trend = 0.0005; n = 527), but the association did not persist when VA medical records diagnoses were instead used to characterize the diseases (p-trend = 0.40; n = 100). The limited correlation between self-reported diagnoses and the diagnoses recorded in VA medical records may suggest a misidentification of self-reported health conditions, which in turn implies that analyses performed using self-reported diagnoses may likewise be affected. This study is most limited by the use of self-reported exposures and the fact that the study population consists of a self-selected group of individuals.

Abraham and Baird (2012) conducted a case-crossover study of short-term (i.e., 0- and 1-day lagged), exposures to ambient $PM_{2.5}$ and PM_{10} and cardiovascular and respiratory medical encounters (ICD-9 460–519) among 2,838 U.S. military personnel deployed to Southwest Asia. PM exposure was assessed using data collected over a period of approximately 1 year at 15 military bases. Site-specific estimates were first obtained and then pooled using meta-analytic techniques to generate OR for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ or PM_{10}. Ambient levels were routinely high at the bases assessed, but no statistically significant associations between PM and respiratory outcomes were observed in the young, relatively healthy deployed military population. Of the 343 encounters for COPD and allied conditions, though, 327 (95%) were reported to be for asthma (ICD-9 493), indicating that 16 could be attributed to all of the other ICD-9 codes, including COPD, emphysema, and chronic bronchitis. Specific estimates for the association of PM exposure and COPD and related conditions were not calculated.

Baird et al. (2012) examined the post-deployment respiratory health status of U.S. Army personnel potentially exposed to emissions from the fire at the Al-Mishraq sulfur plant near Mosul, Iraq, in 2003. Two were groups potentially exposed to the sulfur fire smoke plume—personnel involved in fighting the fire (n = 191) and personnel presumably downwind during the time of the fire (n = 6,341). These were compared with two unexposed groups: those who deployed to the area after the fire was extinguished (n = 2,284) and those deployed to other Southwest Asia locations contemporaneously with the time of the fire (n = 1,869). Age-adjusted standardized morbidity ratios, for COPD encounters (ICD-9-CM 490–496, inclusive) were statistically significantly lower for the potentially exposed personnel downwind of the fire compared with the group deployed to the area after the fire was extinguished (standardized morbidity ratio = 0.62, 95%CI 0.53–0.71). The age-adjusted standardized morbidity ratio for COPD and allied conditions was not statistically significantly different from 1.0 when firefighters were compared with the contemporaneously deployed group (morbidity ratio = 0.73, 95%CI 0.27–1.43), but it was statistically significantly decreased when firefighters were compared with the group deployed to the area before or after the fire (morbidity ratio = 0.41, 95%CI 0.15–0.79). The authors acknowledge that the inverse association for COPD that was observed may reflect the short follow-up time and the young age of the population being studied and note that significant confounders, including smoking and other environmental or occupational exposures were not controlled for in the analysis.

As previously described in the Pulmonary Function Testing section, Matthews et al. (2014) conducted a retrospective review of DoD electronic medical records to identify trends in the frequency and severity of COPD according to PFTs in service members based on their deployment history. Inpatient and outpatient records were queried to identify active-duty personnel from all service branches with the ICD-9 code for either "emphysema" (492.8) or "chronic airway obstruction, not elsewhere classified" (496) for 5 consecutive years from 2005 to 2009. Individuals with a diagnosis of asthma (493) or chronic bronchitis (490) were excluded. The medical records review was limited to those individuals with a minimum of three outpatient encounters with the listed diagnosis of COPD/emphysema during the study period. Deployment information was obtained from the AFHSC, and individuals were classified into deployers and nondeployers based on whether they had deployed to Southwest Asia during or since 2003. Clinical symptoms, smoking history, PFT, and radiographs obtained during the diagnostic workup were reviewed. A total of 371 patients with diagnosed COPD or emphysema were identified; 194 (52.3%) had deployed and 177 (47.7%) had not deployed to Southwest Asia since 2003. Of the deployed, 68% had a documented history of smoking, compared with 62% of the nondeployed. Specific comparisons were made for age, FEV_1 (% predicted), FEV_1 post-bronchodilator (% predicted) and percent change, FVC (% predicted), FEV_1/FVC, TLC, RV, and DLCO, and they are presented in the summary of this study in the Pulmonary Function Testing section. Among the individuals with a documented smoking history and spirometry data, 65% of those deployed and 46% of those nondeployed met established diagnostic criteria for COPD. The disease severity, as measured by the GOLD criteria, was similar for deployed and nondeployed individuals: 30% versus 33% for those with mild disease, 57% versus 60% for those with moderate disease, and 14% versus 7% for those diagnosed with severe disease. Although the investigators concluded that the impact of deployment on increased diagnosis of COPD or severity of disease appeared minimal, this study lacked a prospective design and adequate adjustment for confounders of the relationship between deployment and pulmonary function. In this relatively young population (average age 40), only about half had an adequate workup to assess the diagnosis of COPD.

Pugh et al. (2016) conducted a retrospective cohort study to examine the prevalence of chronic lung diseases, including COPD, based on ICD-9-CM codes and military deployment using VA health care data from 760,621 U.S. veterans deployed to combat operations in Iraq or Afghanistan who received care from VA between October 1, 2002, and September 30, 2011. The prevalence of COPD was calculated for each year between 2003 and 2011 using the number of unique OEF/OIF veterans who received care from VA during the year as the denominator for that year. and the data were examined for any changes in prevalence during that time. Generalized estimating equations analysis was used to determine if the log-odds of having a diagnosis of COPD increased from 2003 to 2011. Estimates were adjusted for demographic characteristics, multiple deployments, tobacco use, and TBI to determine if log-odds of diagnosis increased from 2003 to 2011. Over the study period, 5,998 (0.8%) individuals had a diagnosis of COPD.[10] They were more likely to be male, white, and have served in the Army; their average age was 42 years; 56.9% were classified as tobacco users; and 16.2% had a TBI diagnosis. In comparison, the average age of those without lung disease was 34 years, and 21% were tobacco users. A consistent and statistically significant pattern of increasing prevalence of COPD was found in the cohort, with an average increase in the log-odds per year of 0.06 (95%CI 0.05–0.08) after controlling for demographic, military, and personal characteristics, including smoking. Based on the generalized estimating equations analysis and controlling for demographic and clinical characteristics, the odds of diagnosis of COPD

[10] Defined as chronic bronchitis (ICD-9-CM 491), emphysema (492), bronchiectasis (494), and chronic airway obstruction, not elsewhere classified (496).

were statistically significantly higher in 2011 than in the other, earlier years of the study. Moreover, the odds of COPD were statistically significantly increased for all age groups over 30 years as well as for those with a TBI diagnosis (OR = 1.51, 95%CI 1.38–1.64) and tobacco users (OR = 4.45, 95%CI 4.18–4.73). Individuals who had multiple deployments were statistically significantly less likely to have a COPD diagnosis (OR = 0.92, 95%CI 0.86–0.98) than individuals with only one deployment. As would be expected from general population trends, the prevalence increased with age, and women were less likely than men to have a COPD diagnosis. The nature of exposures during deployment could not be assessed; however, reports of blast injury as reflected by TBI were also associated with increasing rates of COPD. Confirmation of the diagnosis of COPD with pulmonary function measurement was not available, and the authors pointed out that, because the use of VA resources is voluntary[11] and because the veterans studied may have been too young for many to have developed symptoms of chronic pulmonary diseases, these results may be subject to both selection and ascertainment biases. Although it appears that what was reported as change in prevalence by year is really incidence of new diagnoses; however, new cases may be a mixture of incident and prevalent cases, with some patients coming to VA to receive care when disease becomes severe enough to need treatment, and therefore these are prevalent cases that are considered incident in that they were not previously counted.

Krefft et al. (2017) conducted a small pilot study to examine the role of lung clearance index as an early marker of lung injury in a sample of 24 healthy volunteers and 28 symptomatic veterans who had deployed to Southwest Asia in support of post-9/11 operations. The 28 veterans had been referred to an occupational lung disease clinic for evaluation of unexplained respiratory symptoms (cough, chest tightness, wheezing, shortness of breath, or decreased exercise tolerance) with onset during or following deployment. The control group consisted of individuals who were at least 18 years of age, had no history of pre-existing lung disease, and reported no respiratory illness in the 4 weeks preceding enrollment and testing. Participants underwent lung clearance index testing to identify whether abnormalities were present in the peripheral airways of the lung. As part of their clinical evaluation, members of the deployed group completed tests of pre- and post-bronchodilator spirometry, lung volumes, and diffusing capacity and also had cardiopulmonary exercise tolerance testing and chest CT scans. Surgical lung biopsies were performed on 17 of the 28 deployers. Of the 28 with respiratory symptoms, 17 were found to have definite and 11 were found to have probable deployment-related lung disease, which was defined as the presence of one or more of these findings: emphysema/hyperinflation, bronchiolitis, and granulomatous pneumonitis in a deployer with respiratory symptoms. Given that the controls did not undergo PFT, that the small sample of veterans is highly selective as they were all symptomatic and were seen at an occupational lung disease clinic, and that specific diagnoses of the deployed were grouped as deployment-related lung disease, as well as the other limitations described in Chapter 3, this study has limited utility in examining the impact of deployment to the Southwest Asia theater on occurrence of respiratory disease.

Krefft et al. (2020) aimed to describe deployment-related respiratory disease and the diagnostic utility of resting and exercise PFT with a retrospective study of 127 military personnel, veterans, and civilian contractors who supported military operations in Southwest Asia, with new-onset respiratory symptoms presenting between 2009 and 2017 and referred to a single occupational lung disease clinic. Of the 127 patients, 113 underwent PFTs, the results of which are described in the summary of this study under the Pulmonary Function Testing section of this chapter. Lung biopsies were performed in 52 patients (51 video-assisted thoracoscopic surgeries, 1 transbronchial cryobiopsy) and reviewed for several diagnoses. The most common abnormality on the 52 lung biopsies was hyperinflation/emphysema, seen in 69% of the biopsies. All the biopsies had at least one of the three case definition findings of distal lung disease (hyperinflation/emphysema, bronchiolitis, and granulomatous pneumonitis). Deployment distal lung disease was diagnosed in 87 of the 127 patients. Comparisons were made between those with and without histologic findings of distal lung disease (controlling for age), however, these findings are not specific to COPD or emphysema. Thus, this study is limited for the committee's purposes because it includes only cases that are grouped as distal lung disease and does not include a nondeployed or elsewhere-deployed control group.

Abraham et al. (2012) conducted a cohort and nested case–control study to evaluate the relationship between deployment and respiratory system diseases (ICD-9 460–519) in U.S. military personnel. Cases (n = 532) of post-

[11] Veterans who use VA services are more likely to report that they have multiple medical conditions than those who do not (Meffert et al., 2019).

deployment diagnosis of obstructive pulmonary disease, defined as ICD-9-CM 490–496, and controls (n = 2,128) were selected from those who were free of respiratory diagnoses within 6 months before their deployment. Controls were matched on the year of case definition and the year of the last encounter during the study period as well as on the total number of post-deployment medical encounters. Conditional logistic regression analyses were used to examine the independent effects of the number of deployments at diagnosis and the cumulative time in theater up to diagnosis on post-deployment obstructive pulmonary disease encounter, controlling for potential confounders (gender, age, grade, occupation, time in theater, number of deployments, service branch, and tobacco-related diagnoses). The study does not provide any specific information on COPD, chronic bronchitis, or emphysema. The majority of obstructive pulmonary disease encounters were for either asthma (46%) or bronchitis (50%). No statistically significant difference in odds of an obstructive pulmonary disease encounter was found for multiple deployers relative to single deployers (OR = 1.08, 95%CI 0.82–1.42). This study had several limitations, such as a lack of measurement of smoking and a lack of specific deployment-related exposure assessments. Additionally, given that asthma and other obstructive lung diseases were all considered together, the findings do not provide specific information on the impact of service in Southwest Asia and COPD.

Other Coalition Force Veterans Davy et al. (2012) performed a review of the respiratory health of Australian Defence Force personnel deployed to the Southwest Asia theater as part of the Middle East Area of Operations Prospective Health Study. The study population was defined as Australian Defence Force personnel who deployed after June 2010 and returned from that deployment by June 2012. Information on smoking behavior, self-reported exposures, length of time in theater, and other potential influences were collected but were not presented. Of the total eligible population of 3,074, 156 completed pre- and post-deployment questionnaires and a physical examination that yielded spirometry test results of sufficient quality to be usable for research purposes. The investigators found that four participants met the GOLD criteria at pre-deployment only, five at post-deployment only, and four at both pre- and post-deployment. They commented that, aside from these findings, “the respiratory health of this sample was well within the normal range” (Davy et al., 2012, p. 247). Information on smoking behavior, self-reported exposures, length of time in theater, and other potential influences was collected but was not presented relative to the COPD observations. Furthermore, because of the small sampling fraction of the eligible population that was studied, the results are not generalizable.

Saers et al. (2017) examined the prevalence of self-reported chronic bronchitis in a random sample of 1,032 Swedish military personnel who were either currently or previously stationed in Kosovo (in the period 2005–2008) or Afghanistan (2008–2009) compared with that of a 1:1 matched Swedish general population sample that included matching on age, gender, smoking habits, BMI, and education level. Additional methodologic details of this study are provided in the summary of this study that appears in the Respiratory Symptoms section. Chronic bronchitis was identified by affirmative response to the question “Are you used to having a cough almost every day with sputum production that lasts for at least 3 months every year during the winter?” The prevalence of chronic bronchitis over the preceding 12 months was statistically significantly greater in the military personnel than in the matched population (12.3% vs 8.2%; p = 0.003). The prevalence was no different in the 682 service personnel stationed in Afghanistan from those stationed in Kosovo. In those stationed in Afghanistan, there was a significantly higher prevalence of chronic bronchitis in those exposed to sandstorms than in those not exposed to sandstorms (13.6% vs 7.3%; p = 0.04). Although the design of this study was limited and therefore the inferences that can be made based on its results are also limited, the finding of no difference in symptom prevalence between those stationed in Kosovo and those stationed in Afghanistan calls into question the role of Southwest Asia deployment as a cause of the differences in prevalence relative to the general population.

1990–1991 Gulf War Veterans Hines et al. (2013) conducted a small study using 24-hour creatinine-corrected urinary uranium as a validated marker of exposure in 1990–1991 Gulf War veterans who were enrolled in the VA Depleted Uranium Surveillance Program and had attended a biennial follow-up in 2011 to compare the likelihood of pulmonary health abnormalities in those with high body burdens of uranium (n = 12; >0.1 μg/g creatinine) versus those with low body burdens of uranium (n = 25; ≤0.1 μg/g creatinine). No statistically significant differences were observed for respiratory symptoms, abnormal pulmonary function values, or the prevalence of chest

CT abnormalities in those with high (n = 12) versus low (n = 12) urinary uranium. In the 22 participants in whom one or more parenchymal nodules were observed based on CT, 15 had emphysema (42%), but this was reported to be mild in 12 of them, and those with a history of smoking were significantly more likely to have emphysema (p = 0.001) than those with no history of smoking. While the findings from this study made use of a rigorous exposure assessment through analysis of uranium in urinary samples, the findings are not particularly pertinent to this assessment, given that exposure to depleted uranium was uncommon.

Khalil et al. (2018) described the study design for the Gulf War Era Cohort and Biorepository and provided preliminary results from the pilot phase of the effort, which had enrolled 1,275 veterans, 900 of whom had deployed to Southwest Asia. Self-reported health outcomes of symptoms (in the past year) and health care provider–diagnosed conditions were reported stratified by users (n = 584) and nonusers (n = 679) of VA health care in the past year. A supplemental table for the paper that was posted to the web reported that of the 1,275 subjects who responded to the survey question asking whether a doctor or other health care provider had told them that they had chronic lung disease (COPD, emphysema, or bronchitis), 82 (6.4%) answered yes (9.2% of VA users and 4.0% of nonusers). While the reported proportions of veterans with chronic lung disease seems higher than expected, there was no formal assessment of differences in the frequency of chronic lung disease between VA users and nonusers. Furthermore, there were no comparisons between deployed and nondeployed veterans and, therefore, these results do not inform questions about the role of Gulf War deployment on increased risk of chronic lung disease.

Zundel et al. (2019) compared survey results from a cohort of 1990–1991 Gulf War veterans (401 males and 47 females) who returned from deployment in 1991 through Fort Devens, Massachusetts, with data from the 2013–2014 NHANES (n = 2,949). The veterans were asked to self-report if a doctor had ever diagnosed them with any of nine chronic medical conditions, including chronic bronchitis. Analyses were restricted to veterans of white race with at least a high school education and stratified by sex. Analyses were weighted to account for demographic differences between cohorts. The prevalence of chronic bronchitis was higher among the Fort Devens cohort than NHANES for men (10.2% vs 2.59%, respectively), and the difference was statistically significant (OR = 4.50, 95%CI 2.02–10.03). Similarly, the prevalence of chronic bronchitis was higher among women of the Fort Devens cohort than NHANES (13.2% vs 10.6%, respectively), but in this case the difference was not statistically significant (OR = 1.28, 95%CI 0.43–3.82). When the prevalence of chronic bronchitis was compared for men stratified by age group (40s, 50s, and 60s), no difference between Fort Devens and NHANES was found for men in their 40s. However, chronic bronchitis was statistically significantly higher for Fort Devens men than for NHANES men in their 50s (OR = 3.94, 95%CI 1.24–12.51) and 60s (OR = 4.83, 95%CI 1.09–22.36), although the estimates were not precise. For the Fort Devens exposure analyses, veterans who were exposed and unexposed to chemical or biologic warfare or pyridostigmine bromide pills did not differ on any of the demographic variables. For those exposed to chemical or biologic warfare, the prevalence of chronic bronchitis was higher than for the unexposed (16.0% vs 5.7%, respectively), and the difference was statistically significant (OR = 4.00, 95%CI 1.43–11.20) adjusted for gender and current smoking status. Similarly, the prevalence of chronic bronchitis was higher for those exposed to pyridostigmine bromide pills than for the unexposed (13.1% vs 8.0%, respectively), but this difference was not statistically significant (OR = 1.66, 95%CI 0.68–4.09). Finally, prevalence of chronic bronchitis was compared between men and women of the Fort Devens cohort; no difference in prevalence was found after adjustment for age, race, education, and current smoking (OR = 0.46, 95%CI 0.18–1.18). This study has several limitations, including its generalizability, use of self-reported conditions, and low response rate.

Synthesis

Studies of COPD, chronic bronchitis, and emphysema in active-duty personnel and veterans who have served in the Southwest Asia theater have been reviewed in multiple previous volumes of the National Academies *Gulf War and Health* series (IOM, 2005, 2006, 2010; NASEM, 2016) and related reports (IOM, 2011; NASEM, 2017), but with one exception—Volume 3 (IOM, 2005)—non-cancerous respiratory diseases were grouped under a single conclusion of "insufficient or inadequate evidence to determine whether an association existed between deployment to the theater and respiratory disease." This conclusion was based in part on analyses of data from the population-based NHS, conducted in 1995, that found no difference in risks or odds of deployment to Southwest Asia in support of the 1990–1991 Gulf War and outcomes of COPD, chronic bronchitis, or emphysema when adjusted for smoking. However, follow-up surveys of veterans who participated in the NHS conducted 10 years later found increased risks of COPD, chronic bronchitis, or emphysema after adjustment for demographic and military factors as well as smoking behavior. Studies that categorized deployed service members by specific exposures encountered in theater, such as oil-well fires, that also accounted for length of deployment or levels of exposures (Lange et al., 2002; Smith et al., 2002) and also adjusted for demographic, military, and smoking found no association with chronic bronchitis or emphysema. Likewise, results from the population-based study of Australian Gulf War veterans, also adjusted for demographic and military characteristics and smoking, found no increased odds of emphysema or self-reported doctor-diagnosed chronic bronchitis compared with nondeployed veterans, except for bronchitis first diagnosed in 1991 or later. A follow-up study of the Australian veterans conducted 10 years after the baseline analysis again found that after adjustment for demographic and military factors and current smoking status, deployed veterans were not statistically significantly more likely to report a doctor-confirmed diagnosis of chronic bronchitis, emphysema, or COPD. When a standardized symptom-based definition of chronic bronchitis was applied, a statistically significant difference was observed adjusted for the same demographic, military, and lifestyle characteristics.

The committee identified and evaluated 21 studies that evaluated associations between deployment to Southwest Asia and COPD, chronic bronchitis, or emphysema; 18 among post-9/11 veterans and 3 studies among 1990–1991 Gulf War veterans. The studies differ in how exposure was evaluated (e.g., deployment versus specific in-theater exposures), and which outcomes were addressed (some studies grouped one or more of these outcomes, others presented estimates for each outcome separately, and some included only one of these outcomes). Findings from these more recent studies are largely in line with those reported previously in the *Gulf War and Health* series, with mostly null associations between deployment and COPD, chronic bronchitis, and emphysema.

Of the cohorts specified in the Statement of Task, three studies were identified and assessed that used data collected from the Millennium Cohort Study (Smith et al., 2008, 2009, 2012) and two studies used NewGen data (Barth et al., 2014, 2016a) to examine outcomes of chronic bronchitis and emphysema. The most informative of these studies was Smith et al. (2009), which examined newly reported chronic bronchitis and emphysema (grouped) among 46,077 Millennium Cohort Study participants, and found that newly reported chronic bronchitis or emphysema (adjusted for smoking and other factors) in deployed versus nondeployed personnel varied by service branch, but none was statistically significantly elevated. When the analysis was restricted to deployed cohort members with self-reported information on deployment location, the odds of chronic bronchitis or emphysema were not statistically different in any of the deployment locations examined. The results from Smith et al. (2012) are described below along with other studies that examined burn pit–specific exposures and associations with COPD, chronic bronchitis, or emphysema. The two studies that used data collected as part of the NewGen Study (Barth et al., 2014, 2016a) examined the association between deployment to Southwest Asia and self-reported, doctor-diagnosed bronchitis (they did not distinguish between acute and chronic). When year of diagnosis was stratified by before or after 2001, adjusted odds (which included smoking) of bronchitis differed. For those diagnosed before 2001, deployment was associated with statistically significant decreased odds of bronchitis, but among those with respiratory disease diagnosed in 2001 or later, there was no difference in the odds of bronchitis between the deployed and nondeployed groups (Barth et al., 2014). Barth et al. (2016a) then examined specific military exposures and found that the highest adjusted odds (which again included smoking) of bronchitis among deployed veterans were for those categorized as “high exposure” and who self-reported as exposed to diesel, kerosene, or other petrochemical fumes. Nondeployed veterans also had statistically significant increased odds of bronchitis for all specific exposures and for both the high-exposure and low-exposure categories. These results show that exposures were associated with development of bronchitis in both deployed and nondeployed groups, but the confidence intervals for the adjusted ORs all overlap between the deployed and nondeployed groups.

In contrast to use of deployment to the Southwest Asia Theater of Military Operations as a metric for exposure, some studies examined specific exposures (e.g., burn pits [Abraham et al., 2014; AFHSC, 2010; Liu et al., 2016; Sharkey et al., 2015; Smith et al., 2012], fires and fumes from oil wells or sulfur plants [Baird et al., 2012; Barth et al., 2016a], blast [Pugh et al., 2016], or depleted uranium [Hines et al., 2013]) upon which to draw an assessment. In a study of prevalence of self-reported chronic bronchitis in a random sample of Swedish military personnel who were either currently or previously stationed in Kosovo or Afghanistan compared with that of a matched Swedish general population sample, Saers et al. (2017) found that the prevalence of chronic bronchitis over the preceding 12 months was statistically significantly greater in the military personnel than in the matched population, but prevalence was no different in the service personnel stationed in Afghanistan than in those stationed in Kosovo. In those stationed in Afghanistan, there was a significantly higher prevalence of chronic bronchitis in those exposed to sandstorms than in those not exposed to sandstorms. Among the three studies that examined COPD, chronic bronchitis, or emphysema in U.S. 1990–1991 Gulf War veterans, few inferences can be made on the association of deployment and these outcomes because the sample sizes were small (Hines et al., 2013), did not make comparisons based on deployment to Southwest Asia (Khalil et al., 2018), or they used a highly selected sample and comparison that do not allow for generalizations (Zundel et al., 2019).

Several studies examined exposures of post-9/11 service members or veterans to burn pits, and the association with COPD, chronic bronchitis, or emphysema was mixed, with a majority finding no association. Three studies used overlapping data (although period of follow-up and size of the nondeployed population were different for each) of medical encounters several years after deployment to areas with or without burn pits or stationed in Korea compared with those who were never deployed and remained in the continental United States (Abraham et al., 2014; AFHSC, 2010; Sharkey et al., 2015). In general, risk of COPD was not increased for troops deployed to burn pit locations relative to the nondeployed U.S. service members in analyses that both did and did not adjust for smoking and other demographic and military factors. Deployment within 5 miles of a documented burn pit was not associated with increased odds for newly reported chronic bronchitis or emphysema compared with deployments outside of the 5-mile radius, and no association of chronic bronchitis or emphysema was found for cumulative days in proximity to a burn pit for any of level of exposure compared with the nonexposed group (AFHSC, 2010). Abraham et al. (2014), who did not adjust for smoking, found that COPD and allied conditions were statistically significantly increased for personnel at the two bases without burn pits but not for the two locations with burn pits relative to the nondeployed U.S. population. Sharkey et al. (2015) also found that the risks of COPD at the same bases as examined by the AFHSC (2010) and Abraham et al. (2014) were all similar to, or statistically significantly lower than, the risks for personnel who remained in the United States at 36 months and 48 months of follow-up. No observed association between COPD and locations with burn pits was found. Based on comparisons with the Korean-stationed group, these studies support that deployment to the Southwest Asia theater, but not necessarily potential exposure to burn pits, may be associated with an elevated post-deployment rate of COPD and allied conditions. Sharkey et al. (2016) extended their 2015 analysis by adding locations in Afghanistan, sites with poor air quality similar to those previously assessed, and a base in Kyrgyzstan, that had relatively better air quality, and they extended the follow-up period of active-duty personnel to 12 years. No statistically significant differences for COPD (identified by ICD-9-CM codes) were found between the Kabul cohort and the other location cohorts. In an analysis of Millennium Cohort Study data to examine the effects of exposure to documented open-air burn pits within 2, 3, or 5 miles on chronic bronchitis or emphysema, Smith et al. (2012) found that adjusted odds of newly reported chronic bronchitis or emphysema were statistically significantly increased for women, consistent smokers, and Army personnel. When three proxy measures of burn pit exposures were examined, no associations were found for deployment within 3 miles of burn pits and new-onset chronic bronchitis or emphysema when compared with deployments to areas with no documented burn pit exposure; for individual sites with documented burn pits compared with those deployed outside of the 3-mile radius exposure window; or for an increasing number of cumulative days of exposure within a 3-mile radius of the burn pits compared with cohort members with no burn pit exposure. Findings of no association with new-onset chronic bronchitis or emphysema for deployment status, cumulative deployment length, and camp location were consistent when examining the risk within 5 miles of the burn pits. Finally, Liu et al. (2016) examined the associations between assumed geographic and self-reported burn pit emissions exposure (within 2 miles) and self-reported emphysema, chronic bronchitis, or COPD in participants of VA's Airborne Hazards and Open Burn Pit Registry. Burn pit emissions exposure was determined by quartiles of days of deployment near burn pits and, separately, quartiles of self-reported total hours of burn pit smoke exposure. Self-reported diagnoses were compared with VA medical record information. Smoking was not found to be statistically significantly associated with self-reported burn pit smoke exposure. A strong exposure–response association was found between cumulative days deployed within a 2-mile radius of a burn pit and self-reported emphysema, chronic bronchitis, or COPD (adjusted for smoking), but the same association was not observed when VA medical record diagnoses (based on ICD-9 codes) were used in place of self-report. Likewise, when the number of self-reported hours per day of burn pit smoke exposure was used as the measure of exposure, the exposure–response association with self-reported emphysema, chronic bronchitis, or COPD was strongly statistically significant, but the association did not persist when VA medical records diagnoses were instead used to characterize the diseases.

Several studies used ICD-9 codes to examine associations with COPD, chronic bronchitis, or emphysema and deployment or specific deployment-related exposures. Baird et al. (2012) examined post-deployment respiratory health status of U.S. Army personnel potentially exposed to emissions from the fire at the Al-Mishraq sulfur plant in Iraq in 2003 and found inverse associations for COPD (statistically significantly lower morbidity ratios for fighters, and separately, the potentially exposed personnel downwind of the fire compared with the group deployed to the area after the fire was extinguished), which may reflect a relatively short follow-up time and lack of adjustment for significant confounders, including smoking and other environmental or occupational exposures. Pugh et al. (2016) conducted a retrospective cohort study to examine the prevalence of chronic lung diseases, including COPD, based on ICD-9-CM codes and military deployment, using VA health care data. Over the study period, 5,998 (0.8%) individuals had a diagnosis of COPD (ICD-9-CM 491, 492, 494, 496); 56.9% were classified as tobacco users compared with 21% who did not have lung disease. Odds of COPD were statistically significantly increased for all age groups over 30 years, for those with a TBI diagnosis, and tobacco users. Individuals who had multiple deployments were statistically significantly less likely to have a COPD diagnosis compared with individuals with only one deployment, adjusted for demographic characteristics, multiple deployments, tobacco use, and TBI. The nature of exposures during deployment could not be assessed; however, reports of blast injury as reflected by TBI were also associated with increasing rates of COPD.

A number of issues remain unresolved in the assessment of the relationship between airborne hazards exposure in the Southwest Asia theater and COPD. There is—as is the case in almost all airborne hazards research in military and veteran populations—a lack of specification in defining exposure. Most of the studies the committee reviewed use deployment status as an exposure proxy, and when specific deployment locations are taken into account, the details of duration or intensity are often missing. On the diagnostic side, either self-report or (more rarely) chart review is most often used to document the conditions. The committee was forced to rely on studies that used retrospective administrative databases rather than planned investigations, which greatly weakened their ability to draw informed conclusions.

In addition, there seems to be a lack of understanding, when these studies are reported of the need to account for the fact that few of the veterans examined have reached an age when one would expect to see increased risk of being diagnosed as having COPD—an expectation that derives from the well-established association between chronic cigarette smoking and the disease.[12] This is further confounded by the practice followed in multiple studies of treating bronchitis as a singular outcome, rather than differentiating between the acute and chronic forms of the disease.

Conclusions

Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and subsequent development of chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. It notes that one would expect chronic obstructive pulmonary disease to be detectable only after a longer period of follow-up than was available for most of these studies. Chapter 5 includes a description of epidemiologic study designs that might, if it were possible to carry them out, provide greater insight on this issue.

[12] If, however, an occupational exposure mo[illegible] COPD is used, one could entertain the possibility of short-term intense exposures causing COPD that might be detected after only a short period of follow-up.

Constrictive Bronchiolitis

The diagnostic category of bronchiolitis contains several small airway diseases, which are defined by the presence of bronchiolar inflammation, fibrosis, or both (Singer et al., 2016). Further classification is based on the location of the fibrosis and inflammation within the bronchiole (e.g., luminal, mural, or peribronchiolar) and the cellular components of the inflammatory infiltrate (e.g., neutrophilic, lymphocytic, histiocytic) (Singer et al., 2016). Prior to the ATS/ERS classification in 2001, the term "bronchiolitis obliterans" occasionally referred to cases of bronchiolitis obliterans organizing pneumonia, which were characterized by intraluminal polyps of granulation tissue (ATS and ERS, 2002). These cases are now classified as the small airway component of organizing pneumonia. Obliterative bronchiolitis, also called bronchiolitis obliterans or constrictive bronchiolitis, is defined histopathologically by the presence of subepithelial fibrosis (Colby, 1992; Epler and Colby, 1983). This fibrotic constrictive lesion develops externally to the airway lumen, constricting the airway by encircling it with eventual obliteration of the lumen. This is distinct from the inflammatory proliferative lesion that develops internally from the airway wall, filling the lumen with an inflammatory polypoid lesion or buds of granulation tissue, and which is referred to as proliferative bronchiolitis and also as cryptogenic organizing pneumonia and, previously, bronchiolitis obliterans organizing pneumonia (Epler, 2010).

Studies of constrictive bronchiolitis are difficult to conduct because the disease is difficult to diagnose, both on clinical testing and on lung biopsy. Noninvasive diagnostic tests often have low sensitivity (true positive rate), so the diagnosis of constrictive bronchiolitis often requires thoracoscopic lung biopsy. Histologic diagnosis is dependent on the proper inflation and staining of pathologic samples. Otherwise the condition may be misdiagnosed due to tissue artifact. The lesions of constrictive bronchiolitis may be patchy and occupy only a short segment of a longer bronchiole. Because of this patchy nature, there may be false negatives on lung biopsy, and specific techniques should be used to increase sensitivity for diagnosis. These methods include performing multiple "step" sections from the paraffin-embedded tissue block and performing elastic stains (e.g., Voerhoff von Giesson, Movatt pentachrome) to highlight the presence of increased fibrosis occupying the space between the epithelial basement membrane and the small airway elastica. There are other histologic clues that may aid in diagnosis due to their frequent association with constrictive bronchiolitis. These clues include foamy macrophage accumulation within terminal bronchioles, cholesterol granuloma formation (stasis granulomas), smooth muscle hypertrophy, and proximal bronchiolectasis and bronchiectasis with chronic inflammation. These additional histologic features are non-specific and should not be used to diagnose constrictive bronchiolitis in the absence of subepithelial fibrosis. For example, bronchiolar smooth muscle hyperplasia has been described in asthma and COPD (Colby, 1998).

Further diagnostic challenges arise from a histologic artifact that occurs secondarily to post-biopsy ex vivo smooth muscle contraction in lung tissue (and other types of tissues) (Thunnissen et al., 2016). In these biopsies the bronchiolar smooth muscle tends to show circumferential constriction, which results in a decrease in airway diameter. This constriction results in accentuated differences when the airway is compared with the paired pulmonary artery, as the arteries tend to show longitudinal constriction and do not show significant diminution of luminal diameter. This effect is less commonly observed in lobectomy and pneumonectomy specimens in which formalin is perfused through the airways, resulting in inflation of the bronchioles and alveoli. The histologic appearance of decreased bronchiole luminal diameter, bronchiolar epithelial scalloping, and prominence of the smooth muscle layer all can indicate possible side effects of this ex vivo smooth muscle contraction. Figure 4-1 consists of three panels. Panel 4-1a (left) displays a normal bronchiole with a typical airway wall anatomy. Panel 4-1b (middle) depicts the pathology seen in constrictive bronchiolitis in which fibrous tissue (scarring) is deposited between the epithelial basement membrane and the elastic tissue layer, resulting in a narrowing of the bronchiolar lumen and subsequent airflow obstruction. Panel 4-1c (right) shows how, if a biopsy specimen is not inflated, it can create an artificial narrowing of the airway, which may be misdiagnosed as constrictive bronchiolitis. In light of the above issues in diagnosis, a recognition of subepithelial fibrosis is necessary to differentiate authentic cases of constrictive bronchiolitis from histologic mimics.

Both constrictive bronchiolitis and proliferative bronchiolitis can be caused by environmental and occupational inhalation exposures. Historically, constrictive bronchiolitis was caused by accidental exposures to high concentrations of toxic gases, such as chlorine and oxides of sulfur and nitrogen. More recently, diacetyl-containing food

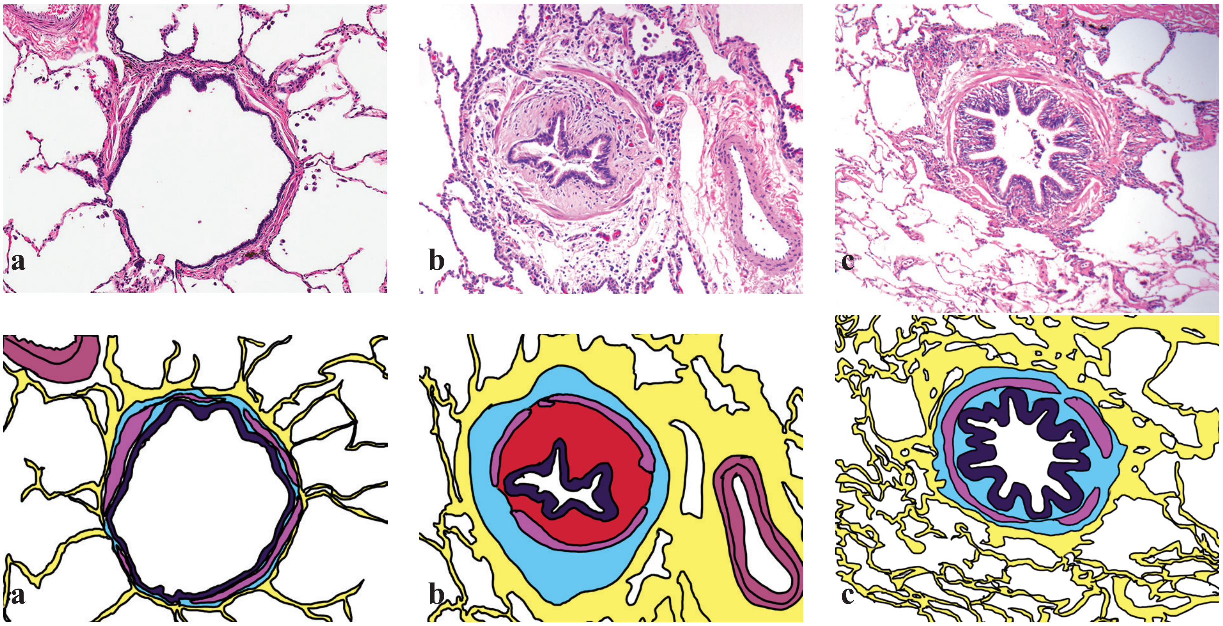

FIGURE 4-1 Histology photomicrographs and diagrams illustrating a normal bronchiole (left), a bronchiole exhibiting narrowing consistent with constrictive bronchiolitis (middle), and a bronchiole exhibiting narrowing due to an artifact from lack of inflation (right).
4-1a (top left): A normal bronchiole from a resected inflated lung shows a typical airway wall with layers of ciliated respiratory epithelium, subepithelial basement membrane, elastica, and smooth muscle, all in close continuity.
4-1a (bottom left): A corresponding line drawing highlights the close apposition of smooth muscle (pink), elastica and subepithelial connective tissue (light blue), and epithelium (purple).
4-1b (top middle): In constrictive bronchiolitis there is a deposition of fibrous tissue between the epithelial basement membrane and the elastic tissue layer. This scarring results in a narrowing of the bronchiolar lumen.
4-1b (bottom middle): A corresponding line drawing shows the separation of the smooth muscle (pink) and the elastica and subepithelial connective tissue (light blue) from the epithelium (purple) due to the presence of dense fibrosis (red).
4-1c (top right): In specimens that are not inflated with formalin through the airway (including most surgical wedge biopsies and all transbronchial biopsies) it is common to have smooth muscle contraction, resulting in an artifactual narrowing of the airway. This can be mistaken for constrictive bronchiolitis but can be differentiated from it by the lack of scar tissue between the epithelial basement membrane and the elastic tissue layer.
4-1c (bottom right): A corresponding line drawing shows that the smooth muscle (pink) has contracted and the lumen of the airway has narrowed, but the epithelium (purple) is still in close continuity with the subepithelial connective tissue and elastica (light blue) and smooth muscle.

flavorings and other flavoring chemicals have been shown to cause constrictive bronchiolitis (Kreiss, 2013). A 2013 review of the literature on occupational causes of constrictive bronchiolitis that focused on literature published between 2009 and 2012 highlighted the difficulties with the pathologic description of constrictive bronchiolitis (Kreiss, 2013). Whereas constrictive bronchiolitis following high-dose acute exposures often results in fixed airflow limitation without a response to bronchodilator on spirometry testing, a more indolent form of bronchiolitis associated with exertional dyspnea and cough, with more subtle lung function abnormalities, and without a recognized hazardous exposure is a more common presentation. The review included studies of biopsy-confirmed case series of constrictive bronchiolitis from U.S. soldiers, Iranian survivors of sulfur mustard gassing, hospital-based studies, and flavoring-related cases, all documenting that indolent cases of constrictive bronchiolitis can have normal spirometry or either restrictive or obstructive abnormalities. High-resolution CT studies can be normal or can reflect air trapping and mosaic attenuation on expiratory films. Constrictive bronchiolitis is a rare disease without required surveillance, so prevalence estimates in the general U.S. population are unknown.

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports

Volumes 4, 8, and 10 of the *Gulf War and Health* series have discussed respiratory symptoms as a group, but none of the studies reviewed in these previous volumes reported on outcomes of constrictive bronchiolitis. The 2011 report on long-term health consequences of burn pit exposure in Iraq and Afghanistan identified constrictive bronchiolitis as a disease that warranted further study as to whether burn pit exposure is associated with development of the disease (IOM, 2011). That determination was based on reports of several cases among soldiers deployed to bases with burn pits (Bartoo, 2010; King et al., 2008; Miller, 2009) and on a study by King et al. (2011). However, because constrictive bronchiolitis is one of the outcomes specifically included in this committee's Statement of Task, it is included in the update of the scientific literature.

In response to these cases of chronic bronchiolitis, the U.S. Army Surgeon General requested a further study by the Center for Health Promotion and Preventive Medicine at Fort Campbell, Kentucky (APHC, 2010). The exploratory analysis of chronic or recurring lung disease among veterans exposed to the Mosul sulfur fire in 2003 (191 Army firefighters and 6,341 soldiers located within 50 km of the fire) compared with unexposed deployed troops found no association between exposure to the fire and chronic bronchiolitis, but the possibility of health effects could not be ruled out. Follow-up was conducted through June 2007.

One of the questions included in VA's Airborne Hazards and Open Burn Pit Registry asks if a participant has ever been told by a health care professional that he or she had constrictive bronchiolitis. The question was restricted to those who had answered that they had been told by a health care professional that they had a lung disease or condition other than asthma, emphysema, chronic bronchitis, or COPD. Among the 4,333 participants eligible to answer this question, 501 (11.6%) reported yes, 2,984 (68.9%) said no, and 848 (19.6%) did not respond (NASEM, 2017). No additional analyses were conducted for constrictive bronchiolitis in the report.

Update of the Scientific Literature on Constrictive Bronchiolitis

There is some evidence that constrictive bronchiolitis may be more common among military personnel who have been deployed to Southwest Asia. The committee identified four studies of constrictive bronchiolitis in U.S. service members deployed in support of OEF/OIF (King et al., 2011; Krefft et al., 2020; Madar et al., 2017; Morris et al., 2020). Studies that grouped outcomes of constrictive bronchiolitis with other diagnoses (Krefft et al., 2017) were not included in this section. Although less robust and of limited value compared with full published analyses, four abstracts that were published as conference posters at the American Thoracic Society's 2017 annual meeting are included for completeness because constrictive bronchiolitis is an outcome of special focus in the committee's Statement of Task.

In the first study from February 2004 through December 2009, King et al. (2011) evaluated 80 soldiers at Fort Campbell, Kentucky, who had respiratory symptoms and who were referred to the clinic because of exercise intolerance resulting from exertional dyspnea. All the soldiers had been deployed to Iraq or Afghanistan, and all underwent extensive evaluation of occupational and environmental exposures. Of the 80 soldiers, 49 were referred for video-assisted thoracoscopic lung biopsy, and 38 of the referred 49 were diagnosed with constrictive bronchiolitis. Constrictive bronchiolitis was defined as an increase in wall thickness of more than 20% as compared with normal thickness, and this thickness could be due to subepithelial fibrosis, smooth muscle hypertrophy, or both. The airway thickening was due to smooth muscle (7 cases), fibrous tissue (3 cases), and mixed smooth muscle and fibrous tissue (28 cases). Other small airway findings included respiratory bronchiolitis, bronchiolar inflammation, pigment deposition with polarizable material, and bronchial-associated lymphoid tissue. Results on pulmonary function and cardiopulmonary exercise testing for the soldiers with constrictive bronchiolitis were compared with results for historical military control subjects (69 asymptomatic active-duty soldiers who were evaluated at an army tertiary care center in 2002). The 38 soldiers with constrictive bronchiolitis had a variety of military jobs; 35 were men; 25 were lifetime nonsmokers, 7 were active smokers, and 6 were former smokers; and 28 had served in northern Iraq in 2003 and reported having been exposed to smoke from the Mosul sulfur-mine fire. Other reported exposures included dust storms (n = 33), incinerated solid waste in burn pits (n = 24), and incinerated human waste (n = 18). However, 11 of the soldiers who underwent biopsy reported having had no exposure to the sulfur-mine fire or any other exposure. Physical chest examinations were normal in all the soldiers. High-resolution CT tests were performed on 37 soldiers, and 25 of them had normal results. PFT showed some decreased values when compared with military controls, but results were generally within normal limits. Letters to the editor regarding this analysis included questions regarding other exposures, particularly to chlorine gas (Zarogiannis and Matalon, 2011); pre-biopsy workups for asthma, exercise-induced bronchospasm, and vocal-cord dysfunction (Morris and Zacher, 2011); and questions regarding the histopathologic diagnosis of constrictive bronchiolitis (Kuschner, 2011). The authors responded, offering additional details of the testing protocol. The committee finds this case series to be relevant to its charge but notes that a non-standard, broad definition of constrictive bronchiolitis was used, which may have overdiagnosed the condition due to tissue artifact (Thunnissen et al., 2016).

Following the publication by King et al. (2011), there was interest in whether other populations of service members that had undergone biopsies would show a similar high prevalence of constrictive bronchiolitis. Madar et al. (2017) retrospectively reviewed a series of biopsies of non-neoplastic lung disease that were evaluated at the Armed Forces Institute of Pathology or the Joint Pathology Center from January 2005 through December 2012 in 391 service members (137 had deployed to Southwest Asia prior to biopsy [deployed] and 254 had not deployed before the biopsy [nondeployed]). According to electronic medical records, 41% of the deployed and 56% of the nondeployed personnel were prior smokers; whether changes in smoking habits occurred during deployment or at the time of biopsy is not documented. Histologic diagnoses were categorized into 10 major histologic groups, one of which was small airways disease, which would include diagnoses of constrictive bronchiolitis; no cases of constrictive bronchiolitis were found in those who had deployed to Southwest Asia either prior to or after biopsy. In addition to the limitations of this study noted in Chapter 3, the identification of constrictive bronchiolitis was limited by the relatively small sample size, which was underpowered for detecting rare outcomes.

Krefft et al. (2020) aimed to describe deployment-related respiratory disease and the diagnostic utility of resting and exercise PFT with a retrospective study of 127 military personnel, veterans, and civilian contractors who supported military operations in Southwest Asia and who presented with new-onset respiratory symptoms between 2009 and 2017 and referred to a single occupational lung disease clinic. Detailed medical, occupational, and smoking histories were collected. Of the 127 patients, 113 underwent PFT as described in the summary of this study in the Pulmonary Function Testing section of this chapter. Chest CT scans were available for 118 of 127 symptomatic patients. Lung biopsies were performed in 52 patients. Deployment-related respiratory diseases were classified as proximal and/or distal. Distal lung disease included any one or more of the following on surgical lung biopsy: emphysema under low- or high-power magnification, histopathologic findings of hyperinflation/emphysema, bronchiolitis, non-necrotizing granulomatous inflammation, small airways inflammation, peribronchiolar fibrosis, or granulomatous pneumonitis. Bronchiolitis as a broad category was observed in 60% of biopsies. The non-specific terminology resulting from combining all forms of bronchiolitis into a broad category limited the inferences that could be made regarding constrictive bronchiolitis specifically. Although at least one case of constrictive bronchiolitis was described, the total number of cases was not given. The authors noted that the histologic abnormalities in symptomatic deployers represent a broader spectrum of distal lung injury than just constrictive bronchiolitis. Comparisons were made between those with and those without histologic findings of distal lung disease, which is not specific to constrictive bronchiolitis. Thus, this study is limited for the committee's purposes because it is essentially descriptive, and it groups cases of interest into a larger category of distal lung disease and does not include a nondeployed or elsewhere-deployed control group.

Morris et al. (2020) reported the initial results of a detailed investigation of clinical lung diseases in military personnel deployed to the Southwest Asia theater under the auspices of the STAMPEDE III research initiative described in Chapter 3. STAMPEDE participants with chronic respiratory symptoms (n = 380) underwent a comprehensive cardiopulmonary evaluation that included a history and physical examination. Laboratory tests, radiographic imaging, and PFTs were performed, and the participants completed a questionnaire that elicited information on their deployment history, airborne exposures, smoking, and pulmonary symptoms before, during, and after deployment. Obstructive lung disease was observed in 11 (2.9%) patients; one case was diagnosed as bronchiolitis. Seven of the 11 obstructive lung disease patients indicated that they were smokers, and no lung biopsies were performed.

In an identified conference poster, Jani et al. (2017b) examined whether service members participating in VA's Airborne Hazards and Open Burn Pit Registry who self-reported a diagnosis of constrictive bronchiolitis have unique identifiable risk factors compared with those not reporting this diagnosis. Using a case–control design, 433 cases (affirmative response to the question of having ever been told they had constrictive bronchiolitis by a health care professional) were matched in a 1:2 ratio on age ± 1 year and sex with service members who responded no to that question. Potential risk factors were compared between the groups. Of those reporting a diagnosis of constrictive bronchiolitis, 90.1% were male, 45.2% were overweight, and 60.6% never smoked (9.4% reported current smoking and 25.5% reported past smoking). Cases reported comorbid respiratory conditions more frequently than controls, including chronic bronchitis (61.5% vs 19.3%, respectively), COPD (24.1% vs 0.2%), and asthma (47.0% vs 12.2%). The authors concluded that registry participants who self-reported a diagnosis of constrictive bronchiolitis self-reported other respiratory conditions more frequently than controls and that this may reflect uncertainty or confusion about diagnosed conditions. Given that participation in the registry is voluntary and no comparisons were made with nonregistry participants, self-selection bias is a concern. Using logistic regression, a diagnosis of constrictive bronchiolitis was found to increase with increasing levels of exposure to smoke from burn pits.

The lung biopsies from the King et al. (2011) cohort have been evaluated using various histologic, morphologic, and immunochemical methods in three studies presented in abstract form at international conferences (Gutor et al., 2019; Polosukhin et al., 2017, 2018). In the first study, Polosukhin et al. (2017) examined lung parenchymal tissue specimens from 12 veterans with confirmed constrictive bronchiolitis and 10 veterans without lung disease and who had never smoked to evaluate the hypothesis that constrictive bronchiolitis in service members may be the result of direct damage to the airway epithelium by airborne toxins due to incomplete epithelial regeneration, leading to long-term impairment of the epithelial barrier in distal airways. A mouse model of constrictive bronchiolitis was also developed and tested. Histologic sections were evaluated with hematoxylin and eosin, trichrome (for fibrosis), alpha-tubulin (for localization of cilia), immunoglobulin A (IgA) and polymeric immunoglobulin, or IgA and p65 subunit of nuclear factor kappa B (NF-κB) (looking for evidence of decreased immune capacity) or were hybridized to a bacterial 16s rRNA gene probe (to look for evidence of bacterial infection). The specimens from veterans with constrictive bronchiolitis showed the histologic presence of inflammation and subepithelial fibrosis and a loss of multi-ciliated cells in the bronchioles. Additional findings included decreased polymeric immunoglobulin receptor (pIgR) expression and reduced secretory IgA on the bronchiolar surface, evidence of bacterial invasion across the epithelium barrier, and NF-κB activation in epithelial cells. Significance testing was not reported. The reported findings suggest that airborne toxins may result in long-term epithelial remodeling resulting in decreased immune capacity and increased susceptibility to infection.

In the second study, Polosukhin et al. (2018) examined lung parenchymal tissue from 26 soldiers with constrictive bronchiolitis, 8 civilians with nondeployment constrictive bronchiolitis, 50 smokers with COPD, 24 lifelong nonsmokers, and 15 former smokers without lung disease. Tissue sections were evaluated with H&E, trichrome (for fibrosis), alpha-tubulin (for localization of cilia), IgA and polymeric immunoglobulin, or IgA and p65 subunit of NF-κB (looking for evidence of decreased immune capacity), or neutrophil elastase (for identification of neutrophils) or CD68 (for identification of macrophages), or else they were hybridized to a bacterial 16s rRNA gene probe (to look for evidence of bacterial infection). The abstract text did not indicate whether the pathologist conducting the examination was blinded as to exposure status. The COPD patients showed goblet cell metaplasia and stratification. A loss of multi-ciliated cells was the most common abnormality in constrictive bronchiolitis. Both diseases showed reduced secretory IgA, and 19% of small airways in constrictive bronchiolitis contained bacterial DNA within the epithelium. Significance testing was not reported. The results of constrictive bronchiolitis cases combined both the soldiers and the civilians, so it is unclear whether differences in constrictive bronchiolitis may be due to factors of deployment. The results suggested that there were different pathways for airway remodeling in COPD and constrictive bronchiolitis.

In the third study abstract, Gutor et al. (2019) described examining lung parenchymal tissue from 27 soldiers with constrictive bronchiolitis, 55 smokers with COPD, 8 lifelong nonsmokers, and 10 former smokers without lung disease. Histologic sections were evaluated with H&E, PAS (for mucus identification), PicroSirius Red (for fibrosis evaluation), CD19, CD4, and CD8 (for B, T-helper, and T-cytotoxic cells). Airways were examined for inflammation, wall thickening, collagen content, and the number of alveolar attachments. The lungs of patients with COPD showed inflammation, wall remodeling and thickening, and a loss of alveolar attachments. Airways in patients with constrictive bronchiolitis showed wall fibrosis and inflammation. Significance testing was not reported. Fibrosis of small airways in constrictive bronchiolitis was found to be insufficient to cause airflow obstruction. This finding is supportive of the claim that the diagnostic criteria used in making the original diagnoses in King et al. (2011) were too sensitive and have resulted in a group of mixed small airway diseases and normal lung biopsies being called constrictive bronchiolitis.

Synthesis

Constrictive bronchiolitis is a rare disorder, the prevalence of which is not established in the general population. Diagnosis requires a biopsy, and the disease may be misdiagnosed if samples are not properly inflated. It was not identified with any frequency in the military population until 2008, when the cohort that underwent surgical lung biopsy from King et al. (2011) was published. Subsequent studies (Krefft et al., 2020; Madar et al., 2017; Morris et al., 2020) and analyses published as conference abstracts, some of which lacked lung biopsies, have described rare additional cases of constrictive bronchiolitis. Although participants in VA's Airborne Hazards and Open Burn Pit Registry have self-reported high numbers of diagnoses (Jani et al., 2017b; NASEM, 2017), these cases are unconfirmed (responses to health questions were not verified with medical records) and may have been indicated due to uncertainty or confusion about diagnosed conditions. Three conference abstracts that evaluated the lung biopsies from the King et al. (2011) cohort using different histologic, morphologic, and immunochemical methods (Gutor et al., 2019; Polosukhin et al., 2017, 2018) found evidence of different pathways for airway remodeling in COPD and in constrictive bronchiolitis and indicated that the diagnostic criteria used in making the original diagnoses in King et al. (2011) were too sensitive, resulting in false-positive diagnoses of constrictive bronchiolitis. Therefore, the available published information on the relationship between deployment to Southwest Asia and subsequent development of constrictive bronchiolitis is lacking, which limits the inferences that can be made.

Conclusions

Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and the subsequent development of constrictive bronchiolitis.

Interstitial Lung Diseases

Diseases that involve the parenchymal or gas exchanging units of the lung are referred to collectively as the interstitial lung diseases. Interstitial lung diseases can be divided into those that are associated with known causes and those that are idiopathic. Known causes include occupational and environmental exposures to inorganic dusts (e.g., asbestos, crystalline silica, and coal mine dust, which all cause pneumoconiosis), organic dusts (which cause hypersensitivity pneumonitis), drugs (such as some anticancer agents), and radiation therapy–induced lung injury. Alveolar-filling diseases, including pulmonary alveolar proteinosis (PAP) and acute eosinophilic pneumonia (AEP), are often grouped under the rubric of interstitial lung diseases. Autoimmune interstitial lung diseases commonly occur in association with connective tissue diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, and scleroderma). Interstitial lung diseases without known causes include sarcoidosis and the idiopathic interstitial pneumonias. The major idiopathic interstitial pneumonias are further characterized as respiratory bronchiolitis–interstitial lung disease, desquamative interstitial pneumonia, idiopathic pulmonary fibrosis (or usual interstitial pneumonia), idiopathic nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, and acute interstitial pneumonia (ATS and ERS, 2013). All the interstitial lung diseases are diagnosed based on a typical constellation of clinical findings, including medical and exposure histories, lung function testing, chest imaging abnormalities, and targeted laboratory testing, often but not always with lung biopsy. The following sections review the epidemiologic literature on interstitial lung diseases that were examined in relation to deployment to Southwest Asia.

Sarcoidosis

Sarcoidosis is an inflammatory disease that most commonly affects the lung but may involve any other organ system as well. Localized collections of white blood cells (called granulomas) are characteristic of the lung inflammation in sarcoidosis and may progress to permanent scarring. This inflammation may cause symptoms of dyspnea, cough, chest tightness, and fatigue and may lead to lung function and gas exchange abnormalities. The diagnosis of sarcoidosis is based on three major criteria: a compatible clinical presentation, finding nonnecrotizing granulomatous inflammation in one or more tissue samples, and the exclusion of alternative causes of granulomatous lung disease (Crouser et al., 2020). Although environmental factors are suspected, the causes of sarcoidosis are unknown (NHLBI, 2015). Sarcoidosis closely resembles chronic beryllium disease, which is caused by exposure and immunologic sensitization to beryllium dust and fumes. Beryllium is a lightweight metal used in airplane and other types of metal parts. A careful exposure history in combination with specialized laboratory testing for beryllium sensitization is necessary to distinguish chronic beryllium disease from sarcoidosis. A recent study using the U.S. Optum database estimated the overall sarcoidosis incidence in the U.S. population to be 7.6–8.4 cases per 100,000 population per year and the prevalence to be 59.0–60.1 cases per 100,000 population, or 0.6% (Gerke et al., 2017). Following the September 11, 2001, World Trade Center attack, an increase in sarcoidosis was found in populations who were exposed to the area, including fire department, rescue, and recovery workers (Hena et al., 2018). Population estimates of the number of sarcoidosis cases in veterans who have deployed to the Southwest Asia theater were not available; however, sarcoidosis is included in the estimates of interstitial lung disease in this population (estimated prevalence of 0.3%) (Pugh et al., 2016).

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports Previous reports have not addressed whether deployment to Southwest Asia is associated with sarcoidosis. Volumes 4, 8, and 10 of the *Gulf War and Health* series have discussed respiratory symptoms, conditions, and diseases as a group, but none of the studies reviewed in these previous volumes reported on the outcomes of sarcoidosis. However, *Gulf War and Health: Volume 3* reviewed the epidemiologic literature to determine whether sarcoidosis is associated with combustion byproducts, and that committee concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to combustion products and sarcoidosis. The 2011 report on the long-term health consequences of burn pit exposure in Iraq and Afghanistan used surrogate populations of individuals with exposures known to be associated with burn pit emissions (firefighters, incinerator workers, communities near incinerators) and relied on the assessments of studies of service members and veterans in *Gulf War and Health: Volume 8* (IOM, 2010) for conclusions on the association between exposure and health outcomes in service members and veterans, except when new studies were identified. Like the *Gulf War and Health* series, respiratory symptoms, conditions, and diseases were presented as a group, and no studies of sarcoidosis were identified in service members or veterans (IOM, 2011).

Update of the Scientific Literature on Sarcoidosis Four studies that examined sarcoidosis in post-9/11 veterans were identified (Banoei et al., 2019; Forbes et al., 2019; Madar et al., 2017; Morris et al., 2020). However, the analysis of STAMPEDE III (Morris et al., 2020) reported that only 6 people of the 380 in the study were diagnosed with interstitial lung diseases (which would include sarcoidosis), which does not help to inform knowledge about this outcome. One descriptive study that presented cases of sarcoidosis in 1990–1991 Gulf War veterans is also included for completeness (Hooper et al., 2008).

Post-9/11 Veterans Banoei et al. (2019) conducted a small case–control study to evaluate whether veterans (n = 13) with sarcoidosis exhibited different plasma metabolomic and metallomic profiles than civilians (n = 30) with sarcoidosis. Sarcoidosis was defined as the presence of clinical signs and symptoms of pulmonary sarcoidosis or the presence or history of bilateral hilar lymphadenopathy on chest imaging, along with biopsy-proven sarcoid-like granulomas in pulmonary samples, with the exclusion of other granulomatous conditions, including mycobacterial infection. To further analyze the metabolomic profiles of veterans without sarcoidosis who had similar exposure histories, 35 veterans with COPD were selected as controls, matched by race, gender, and deployment history. Civilians were recruited from the University of Miami Sarcoidosis Program and veterans from the Miami Veterans Administration Sarcoidosis Program. Proton nuclear magnetic resonance spectroscopy, hydrophilic interaction liquid chromatography mass spectrometry, and inductively coupled plasma mass spectrometry were used to quantify metabolites and metal elements in plasma samples. Multivariate data analysis was applied to reduce the complexity of metabolomics data and for data mining. Principal component analysis was performed to find outliers, trends, and similarities, using data sets derived from the plasma samples for the evaluation of interrelations and groupings of metabolomics data between veterans and civilians with pulmonary sarcoidosis and veterans with COPD. There were no significant differences in age, race, or lung function between veterans and civilians with sarcoidosis. Veterans with sarcoidosis differed from civilians, according to metabolic and metallomics profiles, but metabolomics and metallomics profiles were similar for veterans with sarcoidosis and veterans with COPD. The authors concluded that environmental risk factors may be important in the development of different molecular phenotypic responses of sarcoidosis.

Forbes et al. (2019) conducted a retrospective chart review using ICD-9-coded medical encounter data from the Defense Medical Surveillance System of all active-duty military personnel who were diagnosed with sarcoidosis from 2005 to 2010. Deployment dates and locations were obtained through the Armed Forces Health Surveillance Branch. Electronic medical records were reviewed for dates of diagnosis, temporal relationships between diagnosis and deployment, symptoms pre- and post-deployment, spirometry, diffusing capacity, radiographic staging, and treatment course. A total of 478 cases of pulmonary sarcoidosis were identified (determined by an inpatient encounter coded with both ICD-9 135 in any diagnostic position or two or more outpatient encounters with both codes ICD-9 135 and ICD-9 517.8 in any diagnostic position within 90 days). Of the identified cases, 400 (83.6%) had tissue biopsies showing granulomatous inflammation consistent with sarcoidosis, and the remaining 78 cases were diagnosed based on clinical findings without tissue confirmation. The diagnosis of sarcoidosis was established with a tissue diagnosis in 68% of the deployed cohort. Of the cases, 80% were male, 38.7% were never deployed, 11.7% were diagnosed prior to deployment, and 50.2% were diagnosed post-deployment. In the pre- and post-deployment cohorts, 76% had documented lung involvement. Overall differences in spirometry and in the radiographic stage of sarcoidosis were not identified. Annual incidence rates were assessed; the authors calculated an annual incidence rate of pulmonary sarcoidosis to be 11.19 per 100,000 person-years. The annual rates of sarcoidosis decreased significantly over the 6-year study period ($p = 0.025$) for all service branches combined. Army personnel were assessed separately because their rate was found to be twice that of all other services combined (IRR = 2.07, 95%CI 1.81–2.36), but the decrease in rates of sarcoidosis observed among active-duty Army personnel over the 2005–2010 time period was not statistically significant ($p = 0.560$). No statistically significant linear trend was observed for annual rates of pulmonary sarcoidosis among service members who had deployed in support of OEF/OIF/OND ($p = 0.674$), but the annual rate was statistically significant for those who did not deploy ($p = 0.006$). The authors concluded that their data did not suggest that military deployment to Southwest Asia is associated with any increase in disease severity based on spirometric or radiographic findings, but that there is a correlation between nondeployment and the development of sarcoidosis. The findings were limited by the retrospective analysis of data collected based on ICD codes from electronic health records, which may not be representative or completely clinically documented. Furthermore, asymptomatic sarcoidosis cases would not have been identified since there is no routine pre- or post-deployment radiographic screening of military personnel. In addition, a diagnosis of active sarcoidosis may preclude deployment, contributing to a finding of higher rates of disease in nondeployers and resulting in substantial detection bias.

Madar et al. (2017) retrospectively reviewed a series of biopsies of non-neoplastic lung disease that were evaluated at the Armed Forces Institute of Pathology or Joint Pathology Center from January 2005 through December 2012 in 391 service members (137 had deployed to Southwest Asia prior to biopsy [deployed] and 254 had not deployed before the biopsy [nondeployed]). According to electronic medical records, 41% of the deployed and 56% of the nondeployed personnel were prior smokers; whether changes in smoking habits occurred during deployment or at the time of biopsy is not documented. Histologic diagnoses were categorized into 10 major histologic groups, one of which was granulomatous disease, which would include diagnoses of sarcoidosis. The major histologic group granulomatous disease (which includes sarcoidosis) had no association with deployment status (16.1% vs 9.1%; p = 0.21), but within this group, the histologic category of non-necrotizing granulomas was more common among deployed participants (22 vs 23; p = 0.038); this was the only one of the 38 histologic categories that was more common in deployed participants. Logistic regression estimates indicate that non-necrotizing granuloma diagnosis was predicted by deployment status, with deployed individuals 2.4 times more likely to have this diagnosis than nondeployed individuals, an effect constant across age groups, gender, ethnicity, and tobacco use. In addition to the limitations of this study noted in Chapter 3, the inclusion of non-surgical samples may have enhanced the ability to diagnose sarcoidosis, if it had been present, and the several cases of non-necrotizing granulomas would have been lost from the study had these small tissue samples been excluded from analysis.

1990–1991 Gulf War Veterans Hooper et al. (2008) used DoD administrative data to examine the long-term hospitalization experience based on ICD-9-CM codes of regular active-duty U.S. Gulf War veterans (n = 211,642) still on active duty between 1994 and 2004 (presented at 3-year intervals) compared with veterans who had separated from military service (n = 321,806). For the 10-year combined observation period, there were 43,346 hospitalizations for those who remained on active duty after 1994. Of those hospitalizations, 12.2% (n = 2,872) were coded as related to the respiratory system. For each diagnostic category, the top five primary diagnoses over the entire follow-up period were presented. Sarcoidosis ranked fifth at 7.1% (n = 79) of inpatient hospitalizations under the category of infectious and parasitic diseases (n = 1,115 for the category). However, sarcoidosis is not known to be an infectious or parasitic disease, and hospitalization data likely underrepresent those with chronic pulmonary sarcoidosis where treatment rarely requires hospitalization, limiting the generalizability of this study. This descriptive study is further limited by the lack of comparisons with the separated veteran group and the fact that no information was presented on hospitalizations stratified by Gulf War exposures.

Synthesis Sarcoidosis is a multi-system inflammatory disorder that most commonly affects the lung. The clinical presentation ranges from asymptomatic disease to a progressive relapsing form. There is substantial variability in the number of organs involved with sarcoidosis, and the disease can be difficult to distinguish from others with similar clinical and histologic features, further contributing to diagnostic uncertainty. Sarcoidosis was not examined as an independent outcome in many of the previous reports of the *Gulf War and Health* series, and Volume 3 of the series found inadequate/insufficient evidence to determine whether an association exists between exposure to combustion products and sarcoidosis.

A small set of studies was identified that specifically examined sarcoidosis in relation to deployment to Southwest Asia. In a small case–control study (Banoei et al., 2019), according to metabolic and metallomics profiles, veterans with sarcoidosis were similar to veterans with COPD but differed from civilians with sarcoidosis. Forbes et al. (2019) performed chart reviews of the 478 cases of sarcoidosis diagnosed among all active-duty personnel from 2005 to 2010 using ICD-9-coded medical encounter data from the Defense Medical Surveillance System. Of the identified cases, 38.7% never deployed, 11.7% were diagnosed prior to deployment, and 50.2% were diagnosed post-deployment. Overall differences in spirometry and in radiographic stage of sarcoidosis were not identified between those who had deployed and those who did not. The annual rates of sarcoidosis decreased significantly over the 6-year study period for all service branches combined, but the rate for Army personnel was found to be twice that of all other services combined. These data do not suggest that military deployment to Southwest Asia is associated with any increase in disease severity based on spirometric or radiographic findings, but there does appear to be a correlation between nondeployment and the development of sarcoidosis. Asymptomatic sarcoidosis cases would not have been identified since there is no routine pre- or post-deployment radiographic screening of military personnel. In addition, a diagnosis of active sarcoidosis may preclude deployment, contributing to a finding of higher rates of disease in nondeployers and resulting in a substantial detection bias. Among the 391 biopsies of non-neoplastic lung disease among service members who were evaluated at the Armed Forces Institute of Pathology or Joint Pathology Center from January 2005 through December 2012, Madar et al. (2017) found that 35.0% had deployed to Southwest Asia prior to the biopsy. The major histologic group granulomatous disease (which includes sarcoidosis) had no association with deployment status, but within this group, the histologic category of non-necrotizing granulomas was significantly more common among deployed participants. Logistic regression estimates indicate that non-necrotizing granuloma diagnosis was predicted by deployment status, with deployed individuals 2.4 times more likely to have this diagnosis than nondeployed individuals, an effect constant across age groups, gender, ethnicity, and tobacco use. The inclusion of non-surgical samples may have enhanced the ability to diagnose sarcoidosis and would have led to an underestimation of other diagnoses, such as bronchiolitis and idiopathic interstitial lung diseases, that require surgical lung biopsy for diagnostic confirmation. The other two studies identified that reported on sarcoidosis (Hooper et al., 2008; Morris et al., 2020) were descriptive and thus cannot be used to inform inferences about an association between deployment to Southwest Asia and sarcoidosis.

Conclusions Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and subsequent development of sarcoidosis.

Hypersensitivity Pneumonitis

"Pneumonitis" is a general term that refers to inflammation of the gas-exchanging part of lung tissue. Hypersensitivity pneumonitis, sometimes included under the more generic term of "granulomatous pneumonitis," is a disease in which the lungs become inflamed due to an immunologic reaction to an inhaled dust, or a chemical or biologic agent. Pereira et al. (2016) assert that "the disease is best classified as acute and chronic." Environmental and occupational causes of hypersensitivity pneumonitis include exposure to particulates from bird droppings and feathers, to airborne bacteria and molds, and to several low-molecular-weight chemicals, which cause specific types of the disease, such as bird fancier's lung, farmer's lung, hot tub lung, and isocyanate hypersensitivity pneumonitis (Mayo Clinic, 2018b). The prevalence of hypersensitivity pneumonitis is unknown due to the challenges in identifying causal exposures and in clinical diagnosis. The difficulty in determining prevalence is compounded by the lack of standardized epidemiologic criteria for diagnosis. The estimated prevalence of hypersensitivity pneumonitis varies by industry, region, and work practices. Interstitial lung disease registries consistently show that hypersensitivity pneumonitis is in the top five most commonly occurring interstitial lung diseases worldwide and represents up to 15% of all interstitial lung diseases (Quirce et al., 2016).

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports Volumes 4, 8, and 10 of the *Gulf War and Health* series have discussed respiratory symptoms, conditions, and diseases as a group, but none of the studies reviewed in these previous volumes reported on the outcomes of hypersensitivity pneumonitis. The 2011 report on the long-term health consequences of burn pit exposure in Iraq and Afghanistan used surrogate populations with exposures known to be associated with exposures to burn pit emissions (firefighters, incinerator workers, communities near incinerators) and relied on the assessments of studies of service members and veterans in *Gulf War and Health: Volume 8* (IOM, 2010) for conclusions on the association between exposure and health outcomes in service members and veterans, except when new studies were identified. As with the *Gulf War and Health* series, respiratory symptoms, conditions, and diseases were presented as a group, and hypersensitivity pneumonitis was not one of the outcomes mentioned (IOM, 2011).

Update of the Scientific Literature on Hypersensitivity Pneumonitis Krefft et al. (2020) aimed to describe deployment-related respiratory disease and the diagnostic utility of resting and exercise PFTs with a retrospective study of 127 military personnel, veterans, and civilian contractors who supported military operations in Southwest Asia, who presented with new-onset respiratory symptoms between 2009 and 2017, and who were referred to a single occupational lung disease clinic. Detailed medical, occupational, and smoking histories were collected, and 113 of the 127 underwent PFT, as described previously in the Pulmonary Function Testing section of this chapter, chest CT scans were available for 118 of 127 symptomatic patients, and lung biopsies were performed in 52 patients. Deployment-related respiratory diseases were classified as proximal and/or distal. Distal lung disease included any one or more of the following: emphysema under low- or high-power magnification, histopathologic findings of hyperinflation/emphysema, bronchiolitis, non-necrotizing granulomatous inflammation, small airways inflammation, peribronchiolar fibrosis, or granulomatous pneumonitis on surgical lung biopsy. Granulomatous pneumonitis (50%) accompanied by lymphocytic interstitial inflammation was identified in half of the biopsies. Detailed descriptions of the histologic findings were not discussed. The study design precluded an assessment of the prevalence of granulomatous pneumonitis in symptomatic personnel who had deployed to Southwest Asia. This was primarily a descriptive case series that focused on describing the clinical spectrum of proximal and distal respiratory diseases found in those with persistent respiratory symptoms following deployment, and there was no comparison group. Comparisons were made between those with and without histologic findings of distal lung disease, which is not specific to pneumonitis. Thus, this study is limited for the committee's purposes of inferences that can be made between deployment to Southwest Asia and hypersensitivity pneumonitis.

Synthesis Hypersensitivity pneumonitis is an immune-mediated interstitial lung disease that occurs in susceptible individuals following exposure to one or more environmental antigens. Although hypersensitivity pneumonitis is one of the more common interstitial lung diseases, variability in disease definitions and in clinical presentation and challenges in antigen-exposure recognition limit assessments of incidence and prevalence in military populations. Only one study, Krefft et al. (2020), examined outcomes of hypersensitivity pneumonitis in a small group of personnel who supported military operations in Southwest Asia over a 9-year period, but because no comparisons were made, this study is of limited use for making inferences.

Conclusions Based on the results of the one available study of military personnel and veterans reviewed in this report, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and subsequent development of hypersensitivity pneumonitis.

Idiopathic Interstitial Pneumonias

The idiopathic interstitial pneumonias (IIPs) are a heterogeneous group of diffuse pulmonary diseases resulting from inflammation and fibrosis of lung tissue. Diagnosis relies on an integrated approach using multidisciplinary discussion among clinicians, radiologists, and, when appropriate, pathologists (ATS and ERS, 2002). Clinical data including symptom presentation, exposures, smoking status, associated diseases, lung function, and laboratory and imaging findings, sometimes with surgical lung biopsy, are needed for diagnosis. There are six major idiopathic interstitial pneumonias: respiratory bronchiolitis–interstitial lung disease and desquamative interstitial pneumonia (both of which are smoking related), idiopathic pulmonary fibrosis (or usual interstitial pneumonia) and idiopathic nonspecific interstitial pneumonia, grouped as chronic fibrosing IIPs; and cryptogenic organizing pneumonia and acute interstitial pneumonia, grouped as acute/subacute IIPs. Additionally, there are two rare idiopathic interstitial pneumonias, idiopathic lymphoid interstitial pneumonia and pleuroparenchymal fibroelastosis, and a category of IIPs termed unclassifiable (ATS and ERS, 2013). IIPs linked to smoking and the very rare or unclassifiable IIPs are not discussed.

Acute interstitial pneumonia is an idiopathic interstitial lung disease that is clinically characterized by a sudden onset of dyspnea and the rapid development of respiratory failure. It is histologically characterized by diffuse alveolar damage, often with organizing pneumonia or fibrosis. The definition of acute interstitial pneumonia excludes patients with acute respiratory distress syndrome (ARDS) attributable to an identifiable cause as well as patients with underlying fibrotic lung disease or systemic disorders known to be associated with lung involvement, such as connective tissue disease (Miller et al., 2019). Acute interstitial pneumonia is a rare illness in the U.S. general population (Vourlekis, 2004).

Idiopathic pulmonary fibrosis (IPF) occurs when the air sacs (alveoli) of the lungs become damaged and scarred. This scarred tissue can interfere with the exchange of oxygen from the lungs into the bloodstream. In the United States, IPF is a rare disease affecting about 100,000 people (roughly 0.03%), with 30,000 to 40,000 new cases diagnosed each year. Familial pulmonary fibrosis is less common than the sporadic form of the disease. Only a small percentage of cases of IPF appear to run in families (NLM, 2019). Data on pulmonary fibrosis in Southwest Asia theater veterans are unknown; one study estimated that 0.3% of OEF/OIF veterans who received care at VA hospitals and clinics had interstitial lung disease, including pulmonary fibrosis (Pugh et al., 2016).

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports Previous reports have not addressed whether deployment to Southwest Asia is associated with idiopathic interstitial pneumonias. Volumes 4, 8, and 10 of the *Gulf War and Health* series have discussed respiratory symptoms, conditions, and diseases as a group, but none of the studies reviewed in these previous volumes reported on outcomes of idiopathic interstitial pneumonias.

Update of the Scientific Literature on Idiopathic Interstitial Pneumonias As summarized under Sarcoidosis in this section, Madar et al. (2017) retrospectively reviewed a series of biopsies of non-neoplastic lung disease that were evaluated at the Armed Forces Institute of Pathology or Joint Pathology Center over a 7-year period (2005–2012) in 391 service members (35% had deployed to Southwest Asia prior to biopsy [deployed] and 65% had not deployed before the biopsy [nondeployed]). According to electronic medical records, the deployed and nondeployed personnel differed by several demographic factors and by smoking status. Histologic diagnoses were categorized into 10 major histologic groups, of which idiopathic interstitial pneumonia was one group. This histologic group had the most cases, totaling 118 (30.2%) of all individuals. This histologic group was statistically significantly more common in the nondeployed participants ($n = 90$, 35.4%) than in the deployed group ($n = 28$, 20.4%), and it was the only major histologic group to show a statistically significant difference between deployed and nondeployed participants, $p < 0.01$. Multivariable logistic regression models indicated that deployment did not significantly predict the diagnosis of the idiopathic interstitial pneumonia group, but increasing age was a significant predictor ($p < 0.001$), as would be expected since idiopathic interstitial pneumonias typically occur in older age groups. Within the idiopathic interstitial pneumonia group, two histologic categories were significantly more common in the nondeployed than in the deployed individuals: organizing pneumonia ($n = 45$, 17.7% vs 14, 10.2%, respectively; $p = 0.015$) and usual interstitial pneumonia ($n = 18$, 7.1% vs $n = 3$, 2.2%, respectively; $p = 0.040$).

Pugh et al. (2016) conducted a retrospective cohort study to examine the prevalence of chronic lung diseases, including COPD, based on ICD-9-CM codes and military deployment using VA health care data from 760,621 U.S. veterans deployed to combat operations in Iraq or Afghanistan who received care from VA between October 1, 2002, and September 30, 2011. Interstitial lung diseases, including pneumoconiosis (500–508), postinflammatory pulmonary fibrosis (515), pulmonary eosinophilia (518.3), and pulmonary interstitial/infiltrative disorders (518.89), were grouped for analysis. A total of 2,372 diagnoses (0.3% of the study population) of interstitial lung disease were found over the study period, with the majority of cases being male (89.8%), white (57.5%), having served in the Army (70.0%), and enlisted (89.3%). Just over one-third (36.3%) used tobacco, and 15.7% had a diagnosed TBI. The prevalence of interstitial lung disease was calculated for each year between 2003 and 2011, and the data were examined for any changes in prevalence during that time; no differences were reported compared with 2011 (calculated using log-odds and controlling for demographics, multiple deployments, smoking, and the presence of TBI). Compared with individuals 30 years of age or younger, older age was statistically significantly associated with interstitial lung disease, as was African American race (compared with white) and females compared with males. Moreover, both smoking ($OR = 1.83$, 95%CI 1.66–2.02) and TBI ($OR = 1.88$, 95%CI 1.62–2.19) were statistically significantly associated with increased odds of a diagnosis of interstitial lung disease. No difference in the odds of interstitial lung diseases was found for individuals who had multiple deployments compared with those who had a single deployment ($OR = 0.98$, 95%CI 0.89–1.09). The nature of exposures during deployment could not be assessed, and the temporal sequence between deployment and diagnosis of interstitial lung disease is unknown. Because the veterans studied may have been too young for many to have developed symptoms of chronic pulmonary diseases, these results may be subject to both selection and ascertainment biases.

Synthesis The heterogeneous group of idiopathic interstitial pneumonias comprises, by definition, pneumonias of unknown etiology. Idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, and respiratory bronchiolitis are more common in smokers and occur mainly in older age groups (>50 years of age). Previous National Academies reports have not addressed whether deployment to Southwest Asia is associated with idiopathic interstitial pneumonias. Two studies of post-9/11 service members were identified that examined the outcomes of IIPs. In their retrospective review of biopsies that were evaluated at the Armed Forces Institute of Pathology or Joint Pathology Center, Madar et al. (2017) identified a total of 118 cases of interstitial pneumonias (30.2% of all biopsies). This diagnosis was statistically significantly more common in the nondeployed than in the deployed group. Within the IIP group, two histologic categories were significantly more common in the nondeployed than in deployed individuals: organizing pneumonia and usual interstitial pneumonia. Pugh et al. (2016) examined the prevalence of chronic lung disease and military deployment using health care system data from 760,621 U.S. veterans deployed to combat operations in Iraq or Afghanistan who received care from VA. A total of 2,372 interstitial lung diseases were identified and grouped for analysis. Compared with individuals 30 years of age or younger, older age was statistically significantly associated with interstitial lung disease, as was African American race (compared with white), and females compared with males. No statistically significant difference was found between those who served in the Army and members of each of the other service branches or between individuals who experienced multiple deployments and individuals with a single deployment. Both smoking and TBI were statistically significantly associated with a diagnosis of interstitial lung disease.

Conclusions Based on the results of the two available studies of military personnel and veterans reviewed in this report, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and the subsequent development of idiopathic interstitial pneumonias.

Acute Eosinophilic Pneumonia

Eosinophilic pneumonias are a heterogeneous group of non-infectious lung disorders where the percentage of eosinophils (a type of white blood cell) is increased in lung and peripheral blood. Eosinophilic pneumonia is characterized by the infiltration of eosinophils into lung tissue. The disease can be either acute or chronic, and both are rare. Environmental and occupational exposures that have been associated with AEP include smoking (active and passive, particularly new-onset smoking); toxins, including the inhalation of cocaine and heroin, vaping, or water pipe use of tobacco or marijuana; and inhaled dusts, such as from the World Trade Center smoke (Rom et al., 2002; Sine et al., 2018). There are no reported AEP incidence rates in the general population of U.S. adults (De Giacomi et al., 2018). One study estimates the incidence rate of AEP among U.S. military personnel deployed to Iraq to be 9.1 per 100,000 person-years over the study period (Shorr et al., 2004).

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports Previous reports have not addressed whether deployment to Southwest Asia is associated with eosinophilic pneumonia. Volumes 4, 8, and 10 of the *Gulf War and Health* series have discussed respiratory symptoms, conditions, and diseases as a group, but none of the studies reviewed in these previous volumes reported on outcomes of eosinophilic pneumonia.

Update of the Scientific Literature on Acute Eosinophilic Pneumonia As summarized in Chapter 3 and under Sarcoidosis and IIPs in this section, Madar et al. (2017) retrospectively reviewed a series of biopsies of non-neoplastic lung disease that were evaluated at the Armed Forces Institute of Pathology or the Joint Pathology Center from January 2005 through December 2012 in 391 service members (137 had deployed to Southwest Asia prior to biopsy [deployed] and 254 had not deployed before the biopsy [nondeployed]). According to electronic medical records, 41% of the deployed and 56% of the nondeployed personnel were prior smokers; whether changes in smoking habits occurred during deployment or at the time of biopsy is not documented. Histologic diagnoses were categorized into 10 major histologic groups, of which eosinophilic pneumonia was one group. One case of AEP was identified in the nondeployed group, and one case of chronic eosinophilic pneumonia was identified in the deployed group. No statistically significant association was found with deployment status when multivariable binary logistic regression models were conducted on this outcome. In addition to the limitations of this study noted in Chapter 3 and other outcome-specific limitations discussed in other sections, eosinophilic pneumonia is rare and does not typically require lung biopsy for clinical diagnosis, resulting in substantial detection bias.

The Operation Iraqi Freedom Severe Acute Pneumonitis Epidemiology Group reported bilateral pneumonitis requiring intubation and mechanical ventilation in 19 U.S. military personnel deployed in the U.S. Central Command area of operations during March–August 2003 (OIF SAPEG, 2003). Two patients died. Of the 19 patients, 18 were men (median age 25 years; range 19–47 years), 12 were full-time active duty personnel, and 7 were in the reserves/National Guard. Service branches included Army (17), Navy (1), and Marine Corps (1); 11 were junior enlisted personnel, 7 were noncommissioned officers, and 1 was an officer. Military specialties included combat arms (8), engineering (3), transportation (2), signal corps (2), medical services (2), and military police (1). At the time they became ill, the individuals were located in Iraq (13), Kuwait (3), Djibouti (1), Qatar (1), and Uzbekistan (1). Other than two patients from the same unit with an onset of illness 4 months apart, no apparent geographic or unit-level clustering was identified. Of the 19 patients, the majority (15) smoked cigarettes or cigars, including the 10 patients whose cases were either confirmed or probable (based on the finding of eosinophilia). Nine of these 10 patients had begun smoking tobacco during deployment, compared with none of the 9 patients whose cases were suspected (based on respiratory failure from pneumonitis but without eosinophilia). All had been exposed to heat, dust, and varying amounts of environmental pollution (e.g., smoke). This was the first description of military deployment associated with AEP and included some with "possible" AEP before additional clinical and epidemiologic investigation was available.

In a follow-up to the 2003 report, Shorr et al. (2004) reported an expanded case series of morbidity and mortality from AEP in U.S. service members who were deployed in or near Iraq. Between March 2003 and March 2004, 18 definite or probable cases of AEP were identified prospectively from combat support hospitals in the U.S. Central Command area of responsibility and retrospectively using military records among a population of 183,000 service members. The incidence was 9.1 per 100,000 person-years (95%CI 4.3–13.3). Of the 18 identified cases, 2 died (1 definite and 1 probable), resulting in a case-fatality rate of 11%. A standardized questionnaire was used to interview surviving patients and capture demographic, exposure, and clinical data. The cases were heterogeneous with respect to military occupation, specific location of deployment, and the timing of the onset of illness. A shorter version of the standardized questionnaire (absent the clinical collection tool) was self-administered in Iraq to a convenience sample of 72 members of the respective military units of the two soldiers who died (termed controls). Exposure questions included questions on the use of tobacco products (cigarettes and cigars); dust; sleeping location and duration; petroleum products; bulk ammunition; solvents or other chemicals; medical waste; close contact with the local population or prisoners of war; local sources of water; burning vehicles or buildings; human waste or other refuse; local foods; animals or animal droppings; insects; over-the-counter and prescription medications; insect repellants; and pesticide, fungicide, or herbicide application. Smoking status was categorized as nonsmoker, new-onset smoker, or chronic smoker. New-onset smoking was defined as initiation of smoking in the theater or immediately preceding deployment among former nonsmokers or prior smokers (who restarted after at least 1 year of cessation). Of the 16 surviving patients, 12 received follow-up evaluations that included a complete history and physical examination, allergen testing, clinical screening for the presence of atopy, repeat chest radiography, and PFT. Eosinophil cationic protein levels were measured, and many of the initial laboratory and serologic tests were repeated. The exams were specifically looking for evidence of recurrence, development of chronic eosinophilic pneumonia, or evolution of some new collagen vascular disease. The surviving patients were also re-interviewed using a standardized questionnaire. A detailed tobacco product analysis of samples of cigarettes and cigars available in the theater region was undertaken to test for several potential environmental agents. There was no evidence of a common source of exposure, person-to-person transmission, or similar time of disease onset. The most frequently reported exposures among patients were smoking tobacco (100%), fine airborne sand or dust (94%), convoy operations (76%), and close contact with the local population (71%). Tobacco smoking was the only exposure that was more common among patients than controls. All the patients in the theater reported smoking tobacco, and 14 (78%) were new-onset smokers. In contrast, 48 controls (67%) in the theater reported smoking tobacco, and only 2 reported that they started during this deployment. Military personnel who were new-onset smokers had a statistically significantly increased risk of AEP compared with controls ($p < 0.001$). No other toxin or exposure was identified to account for the high incidence of acute eosinophilic pneumonia.

Sine et al. (2018) performed a retrospective chart review of 43 cases of AEP contained in the Army Public Health Center registry of military cases from March 2003 to March 2010 and treated at Landstuhl Regional Medical Center, Germany, after evacuation from the Southwest Asia theater. Because the intention of the study was to compare these cases with those of other case series in order to make recommendations regarding changes in the diagnostic criteria for AEP, the inferences that can be made regarding AEP and possible exposures are limited. However, it was reported that 91% of the 43 were smokers, and 77% had recently started or restarted smoking. The cases include the same 18 cases as reported by Shorr et al. (2004) supplemented with additional cases for an additional 6 years (until 2010).

Synthesis Previous National Academies reports have not addressed whether deployment to Southwest Asia is associated with eosinophilic pneumonia. AEP is a rare and potentially severe febrile respiratory disease that was first described in military personnel in a case series in 2003 (OIF SAPEG, 2003), then expanded to encompass a total of 18 cases deployed in or near Iraq over a 13-month period between 2003 and 2004 (Shorr et al., 2004). The majority were men, all used tobacco, and nearly all reported exposure to airborne dust. Epidemiologic investigation pointed to smoking, particularly new-onset smoking, as the most likely risk factor, though data were limited by similarities in environmental exposures between cases and controls and the lack of individual exposure characterization. An additional case series was identified that included the same cases as presented in Shorr et al. (2004) and identified 25 more cases through March 2010, but no comparisons of risk factors were made, limiting the usefulness of this study for the committee's purposes. In their review of lung biopsies evaluated at the Armed Forces Institute of Pathology or Joint Pathology Center, Madar et al. (2017) reported that there was one case of AEP in the deployed group and one case in the nondeployed group. Because of the small number of cases and the fact that AEP does not typically require biopsy, this study is not informative for examining AEP.

Conclusions Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and subsequent development of acute eosinophilic pneumonia.

Pulmonary Alveolar Proteinosis

PAP is a diffuse lung disease in which lipoproteinaceous material composed principally of surfactant proteins accumulates in alveoli and blocks oxygen from diffusing into the blood, resulting in a feeling of breathlessness (dyspnea). PAP can be grouped into three major categories: primary PAP, secondary PAP, and congenital PAP (more accurately called disorders of surfactant production and clearance). Primary PAP is characterized by reduced granulocyte-macrophage colony-stimulating factor stimulation of alveolar macrophages, which reduces the ability of the macrophages to remove surfactant from alveoli (NORD, 2017). Secondary PAP has been associated mainly with exposure to high concentrations of respirable crystalline silica but has also been described in association with other hazardous exposures, including metal fumes (indium, aluminum) and several organic and inorganic dusts (Hwang et al., 2017; Ishii et al., 2011). PAP is a rare syndrome in the United States. One study using a large insurance claims database estimated the prevalence to be 6.87 per million in the general population, similar in males and females, and increasing with age (McCarthy et al., 2018). The pooled occupational exposure prevalence of PAP (i.e., the percentage of the total prevalence linked to workplace exposures) has been estimated at 29% (95%CI 21–37%) (Blanc et al., 2019).

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports Previous reports have not addressed whether deployment to Southwest Asia is associated with PAP. Volumes 4, 8, and 10 of the *Gulf War and Health* series have discussed respiratory symptoms, conditions, and diseases as a group, but none of the studies reviewed in these previous volumes reported on outcomes of PAP.

Update of the Scientific Literature on Pulmonary Alveolar Proteinosis As summarized in several outcomes in this section, Madar et al. (2017) retrospectively reviewed a series of biopsies of non-neoplastic lung disease that were evaluated at the Armed Forces Institute of Pathology or Joint Pathology Center over a 7-year period (2005–2012) in 391 service members (35% had deployed to Southwest Asia prior to biopsy [deployed] and 65%

had not deployed before the biopsy [nondeployed]). According to electronic medical records, the deployed and nondeployed personnel differed by several demographic factors and smoking status. Histologic diagnoses were categorized into 10 major histologic groups, and PAP was included under the category of "other." There was one case of PAP in the nondeployed group. This outcome was not included in regression analyses.

Synthesis All forms of PAP are rare disorders of surfactant production and clearance. Secondary causes of PAP, such as exposure to high concentrations of dust from respirable crystalline silica, aluminum, titanium, or indium-tin oxide, have not been described in association with Southwest Asia military deployment. Only one study (Madar et al., 2017) identified a case of PAP, and no comparisons were made.

Conclusions Based on the results of the one available study of military personnel and veterans reviewed in this report, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and subsequent development of pulmonary alveolar proteinosis.

Infectious Lower Respiratory Diseases

The terms "bronchitis," "acute bronchitis," "pharyngitis," "acute respiratory infection," and even "cold" are nonspecific and overlapping, which makes them problematic for analyzing findings from epidemiologic investigations. Acute respiratory infections are common in the military population, especially among recruits and in other military environments, where close and crowded living conditions, physical and psychological stresses, environmental challenges, and demanding physical training all lead to more intense exposure as well as a state of relative immune compromise (Sanchez et al., 2015). In their review of respiratory infections in the U.S. military, Sanchez et al. (2015) stated that the incidence of hospitalizations for respiratory disease among recruits exceeds that among comparable civilian adults by 3- to 4-fold. Respiratory infections represent the most commonly diagnosed medical condition in recruits and personnel involved in advanced individual training phases, and they are estimated to account for 36,000 to 100,000 medical encounters affecting an estimated 25,000 to 80,000 recruits each year. Among non-recruit active-duty personnel, respiratory infections were estimated to account for 300,000–400,000 medical encounters and to affect 200,000–600,000 service members each year during the influenza seasons in 2012–2014. Exposure to novel respiratory pathogens may occur during deployments in areas where these diseases are endemic. During military deployments in the 1990–1991 Gulf War and Balkan peacetime engagements in the 1990s, novel respiratory infections accounted for 14% of all medical encounters. Wartime respiratory illness rates were estimated to be approximately 15% per month in Iraq and Afghanistan in 2003–2004 and in 2005–2006.

In a cross-sectional survey of 15,459 U.S. military personnel deployed to Iraq or Afghanistan during 2003–2004 who were participating in a rest-and-recuperation program, Sanders et al. (2005) found that respiratory illness, specifically cough or cold experienced during deployment, was self-reported by 69.1% of the personnel and that of these, 17.1% of cases were reported to be severe enough to seek medical care. An additional 2.6% reported that they had developed pneumonia. Of those reporting respiratory illness, 38.9% smoked (at least half a pack of cigarettes per day), and of the smokers, 47.6% had started or restarted smoking during deployment. Similarly, Riddle et al. (2008) found that 24% of 3,374 troops who were deployed to Afghanistan, Iraq, or Kuwait between April 2006 and March 2007 and completed deployment questionnaires reported that they had experienced at least one acute respiratory illness episode while deployed. Half of those who reported an acute respiratory illness episode sought care for it.

Acute Bronchitis

Acute bronchitis is an inflammation of the lining of the tracheobronchial tree, typically in association with a respiratory infection. Cough is the most common symptom; although the cough may initially be non-productive, it typically evolves to where it is producing thickened mucus. Acute bronchitis usually improves within 1 week to 10 days without lasting effects, though the cough may linger for several weeks. Acute bronchitis is usually caused by viral infection. The environmental and occupational exposures that increase the risk of acute infectious bronchitis include smoking (passive and active) and airborne irritants, such as vapors or metal fumes (Mayo Clinic, 2017).

Acute bronchitis is common in the general U.S. population, and it is estimated that about 5% of the general population reports an episode of acute bronchitis per year (Singh et al., 2020). Similarly, acute bronchitis and other respiratory infections are common in the U.S. military serving in Southwest Asia, as noted above. Being in the military increases the risk of acute infections owing to environmental and lifestyle factors, such as living in barracks, close proximity, and stress, but whether deployment to Southwest Asia specifically increases the risk has not been systematically studied.

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports Although several studies of bronchitis were identified in 1990–1991 Gulf War veterans, only one specified acute bronchitis (Smith et al., 2002). As described under other outcomes in this chapter, Smith et al. (2002) used DoD hospitalization data (ICD-9-CM codes) from August 1991 through July 1999 to retrospectively examine associations between respiratory diseases, including acute bronchitis, and modeled exposure to oil-well fires among 405,142 active-duty service members who served in the 1990–1991 Gulf War at the time of the oil-well fires. Service members were categorized as exposed (n = 337,077) and nonexposed (n = 68,065) to oil-well fires, and no statistically significant difference in risk was found for acute bronchitis between exposed (n = 93) and nonexposed (n = 16) service members (RR = 1.09, 95%CI 0.62–1.90). These estimates were stated to be adjusted for demographic and military characteristics, but it was not clear which factors were adjusted for; smoking status was not collected. Analyses were limited to morbidity severe enough to require admission to a DoD hospital for inpatient care, a major limitation for an analysis of acute bronchitis, which rarely requires hospitalization, as is evident by the relatively few cases identified over the 8-year follow-up period.

As cited throughout this chapter, the AFHSC (2010) collected data on acute respiratory infections (ICD-9 460–466), which include acute bronchitis. The analysis examined medical encounters at military facilities by Army and Air Force personnel within 36 months of April 2006, after deployment to Joint Base Balad or Camp Taji (with burn pits), Camp Buehring or Camp Arifjan (without burn pits), or the Republic of Korea (urban air pollution and PM exposure) from 2005 to 2007. Poisson models that were adjusted for sex, birth year, marital status, race/ethnicity, education, smoking status, physical activity, service branch, military rank, pay grade, and occupation were used to calculate IRRs. Although several hundred cases of acute respiratory infections were reported for personnel in the Army and Air Force across all locations combined, acute respiratory infections were statistically significantly lower for service members deployed at all bases except Camp Arifjan (which showed no difference) than for service members who remained in the United States.

Update of the Scientific Literature on Acute Bronchitis Five studies of acute bronchitis in post-9/11 service members and veterans were identified. Three of these were in U.S. personnel. The other two were descriptive studies of Polish coalition forces (Korzeniewski and Brzozowksi, 2011; Korzeniewski et al., 2013) that reported on the incidence of acute respiratory infections experienced in theater; since neither of these compared incidence rates in the deployed forces to rates among nondeployed service members or another appropriate comparison group, they provide no information to contribute to inferences that can be made regarding deployment to Southwest Asia and acute bronchitis.

Baird et al. (2012) examined the post-deployment respiratory health status of U.S. Army personnel potentially exposed to emissions from the fire at the Al-Mishraq sulfur plant near Mosul, Iraq, in 2003. Two were groups potentially exposed to the sulfur fire smoke plume—personnel involved in fighting the fire (n = 191) and personnel presumably downwind during the time of the fire (n = 6,341). These were compared with two unexposed groups: those who deployed to the area after the fire was extinguished (n = 2,284), and those who deployed to other Southwest Asia locations contemporaneously with the time of the fire (n = 1,869). Acute respiratory infection encounters (ICD-9-CM 460–466, inclusive) included acute bronchitis, although this outcome was not examined separately. The age-adjusted standardized morbidity ratio for acute respiratory infection was not statistically significantly different from 1.0 when firefighters were compared with the contemporaneously deployed group (morbidity ratio = 1.25, 95%CI 0.93–1.63) but was statistically significantly decreased when firefighters were compared with the group deployed to the area before or after the fire (morbidity ratio = 0.74, 95%CI 0.54–0.96). Regarding the potentially exposed personnel who were deployed downwind of the fires, the standardized morbidity ratio for encounters for acute respiratory infections were statistically significantly increased when compared with the contemporaneously deployed group (morbidity ratio = 1.18, 95%CI 1.12–1.24), and statistically significantly decreased compared with the group deployed to the area before or after the fire (morbidity ratio = 0.70, 95%CI 0.66–0.73). Confounding due to potential uncharacterized differences in risk factors, such as smoking behavior and other environmental or occupational exposures, between the sulfur fire exposed and unexposed groups cannot be ruled out.

Sharkey et al. (2015) used the same deployed and nondeployed populations as the AFHSC (2010) analysis described previously but used a larger U.S.-based reference population and included an additional 12 months of data. This retrospective cohort study used Poisson models that were adjusted for age, pay grade, sex, race, and service branch to calculate IRRs for acute respiratory infections (ICD-9-CM 460–466)—which includes acute bronchitis—at two time periods: up to 36 months after the baseline data were gathered and up to 48 months afterward. The risks of acute respiratory infections at the four Southwest Asia bases and Korea sites examined were all statistically significantly lower (with the exception of Arifjan, which did not meet statistical significance) than the risks for personnel who remained in the United States. Similar results were found at the 48-month follow-up, with all groups except Arifjan again showing statistically significantly lower adjusted incidence rates of acute respiratory infections compared with the U.S. cohort. No observed association between acute respiratory infections and locations with burn pits was found.

Soltis et al. (2009) analyzed incidence and risk factors for self-reported acute respiratory illness in 2,872 troops deployed to Iraq, Afghanistan, and Kuwait who completed a self-reported questionnaire and a clinic health questionnaire between February 2005 and February 2006. Overall, 39.5% reported having at least one acute respiratory infection while deployed, with a rate of 15.0 episodes per 100 person-months among those who completed the voluntary deployment questionnaire and 24.8 episodes (95%CI 23.2–26.5) per 100 person-months among those who completed the clinic health screening form. Of these, 18.5% sought medical care and 33.8% reported having decreased job performance. Negative binomial regression analysis found female sex, service in the Navy, and a lack of flush toilets to be independently associated with increased rates of acute respiratory illness. Deployment to OIF, increasing age, and higher rank were also associated with an increased risk of acute respiratory illness. The study allowed a broad sampling of deployed U.S. troops at three sites during a defined time period with two different data sources for comparison. The study was limited by the self-reported data that lacked medical confirmation, by possible recall bias of those who were symptomatic, and by possible selection bias due to an under-representation of certain ranks and branches.

Synthesis Acute respiratory illnesses (including acute bronchitis) are among the most commonly reported diagnoses during U.S. military deployments to Southwest Asia (Sanchez et al., 2015). Morbidity from acute infectious respiratory illnesses is particularly notable during the combat phase of operations, where there may be limited access to adequate hygiene and where the effects on individual and unit effectiveness may be substantial (Sanders et al., 2005). The contributions of exposure to either acute airborne hazards, such as the al-Misraq sulfur mine fire, or chronic daily PM, in addition to factors such as close and crowded living quarters, physical and psychologic stresses, and demanding physical training—causing more intense exposure and potentially having effects on immune status—are difficult to characterize except in aggregate from available published studies.

Conclusions Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and the subsequent development of acute bronchitis.

Pneumonia

Pneumonia is caused by an infection that inflames the lung air sacs. The air sacs fill with fluid or pus (purulent material), causing cough with phlegm, fever, chills, decreased oxygen saturation, and difficulty breathing. A variety of organisms, including bacteria, viruses, and fungi, can cause pneumonia (Mayo Clinic, 2018c). Pneumonia is a common illness in the U.S. general population and is the primary diagnosis for an estimated 527,000 emergency department visits per year (CDC, 2016).

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports Few studies reviewed in previous *Gulf War and Health* volumes reported on pneumonia as an outcome. In their follow-up study of the health of Australian Gulf War veterans, conducted in 2011–2013, Sim et al. (2015) found 38 (5.5%) of the Gulf War–deployed and 17 (2.6%) of the comparison era veterans self-reported doctor-diagnosed or treated pneumonia since January 2001, resulting in a statistically significantly increased risk of pneumonia for veterans who had deployed to the Gulf War (RR = 1.87, 95%CI 1.03–3.39) after adjusting for age group, service branch, and rank estimated as of August 1990 and for any atopy at baseline and current smoking status (never, former, current smoker).

The AFHSC (2010) collected data on pneumonia and influenza (ICD-9 480-488). The analysis examined medical encounters at military facilities by Army and Air Force personnel within 36 months of April 2006, after deployment to Joint Base Balad or Camp Taji (with burn pits), Camp Buehring or Camp Arifjan (without burn pits), or the Republic of Korea (urban air pollution and PM exposure) from 2005 to 2007. Fewer than 30 cases were reported for both service branches and across all locations combined. Given this small number, the differences in incidence rates were not calculated.

Update of the Scientific Literature on Pneumonia Eight studies of pneumonia in post-9/11 service members were identified (five in U.S. personnel and three among foreign personnel). However, the three studies of foreign coalition forces (Aoun et al., 2014; Korzeniewski and Brzozowksi, 2011; Korzeniewski et al., 2013) were descriptive studies that reported on the incidence of pneumonia infections experienced in the Southwest Asia theater but did not compare incidence rates among deployed groups or between deployed groups and a nondeployed or other appropriate comparison group, and thus they could not provide information to contribute to inferences that can be made regarding deployment to Southwest Asia and pneumonia. Two studies of post-9/11 U.S. service members were also excluded because they do not inform the evidence base of whether deployment to Southwest Asia is associated with differences in infectious respiratory diseases. Sanders et al. (2005) only reported on the self-reported prevalence of conditions without making any comparisons to nondeployed or other groups of deployed personnel, and Riddle et al. (2008) reported on grouped acute respiratory illness compared with historical data.

Post-9/11 Veterans Abraham and Baird (2012) conducted a case-crossover study of short-term, for example, 0- and 1-day lagged, exposures to ambient $PM_{2.5}$ and PM_{10} and cardiovascular and respiratory medical encounters (ICD-9 460–519) among 2,838 U.S. military personnel deployed to Southwest Asia. PM exposure was assessed using data collected over a period of approximately 1 year at 15 military bases. Of the qualifying health encounters, 83.5% were acute respiratory infections (n = 2,495), with an additional 1.6% (47) attributable to pneumonia and influenza. Ambient levels were routinely high at the bases assessed, but no statistically significant associations between PM and respiratory outcomes were observed in the young, relatively healthy, deployed military population. In addition to the several potential sources of bias detailed in Chapter 3, the statistical power of the assessment was limited by both the short (1-year) duration of the study and the small population under study—and likely also by the small magnitude of the effect of PM exposure on the risk of acute respiratory events in this population.

Eick et al. (2011) conducted a retrospective cohort study of 1,000 service members deployed between June 30, 2004, and June 30, 2007. The authors tested pre- and post-deployment sera for the presence of antibodies to different pathogens, including *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. The DoD Serum Repository, which maintains serum specimens collected from service members, was asked to identify service members who had at least two serum specimens available, collected within the 60 days preceding and following the deployment start and end dates, respectively. If multiple specimens met the requirements, the specimens collected closest to the deployment start and end dates were selected. From an original cohort of 14,360 personnel with appropriate samples, 1,000 were chosen randomly. Characteristics were similar between the study subjects and the total deployed cohort; most were white men. However, the study sample was more likely to be female (12.0% vs

9.4%, p = 0.0046) and in the Air Force (46.0% vs 24.7%, p <0.0001) compared with the total deployed cohort. Additionally, study subjects were more likely to have deployed in 2005 and 2006 than the total deployed cohort (p <0.0001). Pre-deployment seroprevalence for *C. pneumonia* was observed in 651 personnel (65.1%; 95%CI 62.2–68.1), and seroconversion during deployment was observed in 33 (10.2% of susceptibles; 95%CI 6.9–13.5). Pre-deployment seroprevalence for *M. pneumonia* was observed in 219 personnel (21.9%; 95%CI 19.4–24.5), and seroconversion during deployment was observed in 29 (3.7% of susceptibles; 95%CI 2.4–5.0). Seroprevalence and seroconversion percentages were stratified by demographic (age category, gender, and race) and military (service, component, year of deployment, length of deployment, number of previous deployments, and time since entry into military service) risk factors. Seroprevalence and seroconversion were compared among categories within these specific demographic, service, and deployment categories. The characteristics that were significantly associated with seroprevalence or seroconversion were included in a multivariate analysis to calculate adjusted ORs. Trends in seroprevalence and seroconversion percentages by these categories were assessed when appropriate. Self-reported symptoms (cough, runny nose, fever, weakness, headache, chest pain, trouble breathing, diarrhea, and vomiting) occurring during the deployment and reported on the post-deployment health assessment forms were compared between seroconverters and nonseroconverters overall and for each pathogen. Overall, 14.2% of service members seroconverted to at least one of six pathogens not including influenza; when influenza seroconversion was included, the rate increased to 30.1%. Pre-deployment seropositivity for *C. pneumoniae* and *M. pneumoniae* was different by race, and it was higher in black individuals than in white individuals (OR = 1.9, 95%CI 1.2–2.9 and OR = 1.7, 95%CI 1.1–2.5, respectively). After adjustment black participants still had higher odds of seropositivity to these pathogens compared with white participants. Black participants also had higher odds of *M. pneumoniae* seroconversion during the deployment than white participants (11.1% vs 2.3%, respectively; OR = 5.0, 95%CI 2.2–11.7). There was a decreasing trend of *M. pneumoniae* seropositivity with increasing year of deployment (29.3% in 2004 to 10.4% in 2007, z-statistic = 0.0012), a trend that held after adjustment for age and race. Overall, serologically confirmed respiratory infections were common among 2004–2007 OEF deployers, sometimes at higher rates than found in the overall U.S. population. Limitations of the study include a lack of information on smoking status, recall bias on the post-deployment health assessment, and possible false-positive and false-negative seroconversion tests.

1990–1991 Gulf War Veterans One study of long-term hospitalization experience based on ICD-9-CM codes of DoD administrative data, which has been described throughout this chapter, of regular active-duty U.S. 1990–1991 Gulf War veterans still on active duty between 1994 and 2004 (n = 211,642) compared with veterans who had separated from military service (n = 321,806) was also identified (Hooper et al., 2008). For the 10-year combined observation period, the top five primary diagnoses of respiratory system diseases (n = 2,872) were presented, and pneumonia (organism unspecified) ranked second at 12.1% (n = 347). Although the number of pneumonia diagnoses was presented for the entire follow-up period for the active-duty group, no comparisons with the separated group were presented, thereby limiting the informativeness of this study.

Synthesis Respiratory infections are common in deployed military personnel, but data linking lower respiratory infections, especially pneumonia, to hazardous inhalational exposures are limited. Only one study that reported on outcomes of pneumonia (Sim et al., 2015) was reviewed in the *Gulf War and Health* series; 1990–1991 Australian Gulf War–deployed veterans had a statistically significantly increased risk of self-reported doctor-diagnosed or treated pneumonia 10 years after service compared with Gulf War–era veterans. Conclusions regarding associations between respiratory outcomes and deployment to Southwest Asia in the *Gulf War and Health* series grouped all respiratory health outcomes and did not make separate conclusions for any infectious respiratory disease. Three new studies were identified that examined outcomes of pneumonia, two among post-9/11 veteran populations and one follow-up of 1990–1991 Gulf War veterans. Abraham and Baird (2012) examined pneumonia, among other respiratory health outcomes, and high ambient PM levels among U.S. service members deployed to Southwest Asia post-9/11 and found no statistically significant associations for pneumonia. Eick et al. (2011) conducted a retrospective cohort study of 1,000 deployed service members and found that serologically confirmed respiratory infections were common, with 30.1% of deployed service members having seroconverted to at least one of seven respiratory pathogens. While black race was associated with higher odds of *M. pneumoniae* seroconversion during the deployment compared with white race, there was a decreasing trend of *M. pneumoniae* seropositivity with increasing years of deployment, and this decreasing trend remained after adjustment for age and race. In the study of long-term hospitalizations of 1990–1991 Gulf War veterans (Hooper et al., 2008), the number of cases of pneumonia was presented but no comparisons of effect estimates were presented.

Conclusions Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and the subsequent development of pneumonia.

Tuberculosis

Tuberculosis (TB), caused by infection with the organism *Mycobacterium tuberculosis*, tends to be a chronic illness; left untreated, particularly in immunocompromised hosts, TB infection can lead to death. TB most commonly infects the lungs but can involve other organ systems, including the skin, kidney, spine, and brain. Exposure occurs primarily from person-to-person transmission, although rare cases of iatrogenic transmission through contaminated medical equipment have occurred. Not everyone infected with TB bacteria becomes sick. Asymptomatic TB infection, which generally is not transmissible, is referred to as latent TB infection (LTBI). People with an active TB lung infection are usually symptomatic and can be contagious. The time course for disease onset following exposure is quite variable as disease may occur soon after infection (within weeks). Others develop a re-activated illness years later, especially if they develop a disease associated with a weakening of their immune system (Mayo Clinic, 2016). Environmental contributions to TB infections include crowded living conditions, exposures to tobacco smoke (Schmidt, 2008), and indoor air pollution from biomass stoves (Lin et al., 2007) in settings where active disease is more prevalent. In 2018 there were 9,029 TB cases or 2.8 cases of TB per 100,000 persons in the United States.

TB is not common in U.S. military populations. LTBI affects between 3.1% and 5.0% of the U.S. population, but the figure is 1% in military-aged groups. Although countries in the Southwest Asia theater are TB endemic, the prevalence of TB disease among military populations remains lower—0.4 cases per 100,000 in 2012—than in the U.S. population, largely because of the healthy warrior effect. Deployment to TB endemic areas is estimated to be responsible for 24% of cases in the active component military, but the activation of untreated LTBI existing prior to entry into military service is still the most important source of subsequent TB disease. However, one study, which may have excluded groups with the highest risk of LTBI, estimated that LTBI prevalence among deployed service members was the same as in the nondeployed population (Mancuso, 2017).

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports Volumes 4, 8, and 10 of the *Gulf War and Health* series have discussed respiratory symptoms, conditions, and diseases as a group, and infectious diseases were generally either excluded entirely or grouped in the studies reviewed. However, *Gulf War and Health: Volume 5* reviewed the epidemiologic literature on associations between deployment to the Gulf War and infectious diseases. No cases of active TB lung infection were recognized in military personnel who served in either Operation Desert Storm or Operation Desert Shield (Hyams et al., 1995). In many soldiers in some units, however, tuberculin skin tests were negative before the Gulf War and positive afterward (Oster and Sanford, 1992), indicating LTBI. Among the military personnel deployed to OEF and OIF, approximately 2.5% of those given pre- and post-deployment TB skin tests converted from negative to positive. TB skin test conversion is pathognomonic of relatively recent exposure to *Mycobacterium tuberculosis*; thus, transmission of *M. tuberculosis* occurred within some military units deployed to Southwest Asia.

Update of the Scientific Literature on Tuberculosis Only one study that reported on outcomes of tuberculosis was identified. Khalil et al. (2018) described the study design for the Gulf War Era Cohort and Biorepository and provided preliminary results from the pilot phase of the effort, which had enrolled 1,275 veterans, 900 of whom had deployed to Southwest Asia. Self-reported health outcomes of symptoms (in the past year) and health care provider–diagnosed conditions were reported stratified by users (n = 584) and nonusers (n = 679) of VA health care in the past year. A supplemental table for the paper that was posted to the web reported that of the 1,275 subjects who responded to the survey question asking whether a doctor or other health care provider had ever told them that they had tuberculosis, 28 (2.2%) answered yes (2.2% of both VA users and nonusers). No formal assessment of differences in the frequency of tuberculosis between VA users and nonusers was made nor were comparisons made between deployed and nondeployed veterans and, hence, these results do not inform questions about the role of Gulf War deployment on increased risk of TB.

Synthesis The prevalence of both latent and active tuberculosis lung infection is low in U.S. military populations compared with the general U.S. population. Only one new study of TB was identified. Khalil et al. (2018) showed that approximately 2.5% of military personnel deployed to the 1990–1991 Gulf War who were given pre- and post-deployment TB skin tests converted from negative to positive, indicating that transmission of *M. tuberculosis* occurred within some military units deployed to Southwest Asia. The study did not compare rates of conversion between those who deployed and those who did not, limiting the conclusions that can be made from it regarding the role of deployment exposures and risk for TB.

Conclusions Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and the subsequent development of tuberculosis.

RESPIRATORY CANCERS

The committee's Statement of Task directed it to pay particular attention to cancer in its examination of respiratory health outcomes associated with airborne exposures in the Southwest Asia theater. It considered the following cancers as relevant to their charge: lung cancer (carcinoma of the lung or bronchus), cancer of the esophagus, and oral, nasal, and pharyngeal cancers. In addition to studies that examined these cancers individually, studies that grouped these outcomes as "respiratory system cancers" were also reviewed.

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports

Studies of respiratory cancers were summarized in Volumes 2, 3, 4, 8, and 10 of the National Academies *Gulf War and Health* series (IOM, 2003a, 2005, 2006, 2010; NASEM, 2016). The statements of task for these committees shaped their approach to these summaries. The committees responsible for Volumes 2 and 3 were charged with evaluating the scientific evidence that addressed whether a statistical association existed between exposure to specific agents and illnesses. The epidemiologic literature considered was thus different than what has been examined here, including not just studies of active duty personnel and veterans who served in the Southwest Asia theater but also studies of civilian cohorts that were exposed to the same or similar agents under different circumstances, for different durations, and at different exposure levels than the military populations. Volume 2, which evaluated the evidence regarding insecticides and solvents, reported that there was inadequate or insufficient evidence to determine whether an association existed between exposure to these agents and the cancers of interest.[13] The committee responsible for Volume 3 concluded that there was sufficient evidence of an association between exposure to combustion products and lung cancer as well as limited or suggestive evidence of an association between exposure to combustion products and cancers of the nasal cavity and nasopharynx, cancers of the oral cavity and oropharynx, and laryngeal cancer. Inadequate or insufficient evidence existed to draw a conclusion about an association between exposures to fuels and these outcomes.

[13] The committee could not reach consensus on whether the association between tetrachloroethylene exposure and lung cancer was inadequate or insufficient, or whether there was limited or suggestive evidence of an association.

Volumes 4 and 8—which addressed the health effects of serving in the 1990–1991 Gulf War—did not report a specific conclusion regarding any respiratory cancer. Both noted that many veterans were still too young for cancer diagnoses and that for most cancers the follow-up period after the Gulf War was probably too short to expect the onset of cancer. The Volume 10 committee concluded that "there is insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and any form of cancer, including lung cancer" (NASEM, 2016, p. 95).

Neither *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan* (IOM, 2011) nor *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry* (NASEM, 2017) drew conclusions about respiratory cancers.

In the summaries presented below, studies are categorized by country, beginning with those addressing U.S. veterans, and are listed in the order in which they were published. The text is largely derived from the earlier National Academies reports.

1990–1991 Gulf War Veterans

As summarized under other outcomes in this chapter, Smith et al. (2002) used DoD hospitalization data (ICD-9-CM codes) from August 1991 through July 1999 to retrospectively examine associations between modeled exposure to oil-well fires and respiratory diseases, including respiratory cancers, among 405,142 active-duty service members who served in the 1990–1991 Gulf War at the time of the oil-well fires. Service members were categorized as exposed (n = 337,077) and nonexposed (n = 68,065) to oil-well fires, and no difference in the risk of malignant neoplasms of the respiratory and intrathoracic organs was found between the exposed (n = 49) and unexposed (n = 10) groups (RR = 1.10, 95%CI 0.56–2.17), adjusted for demographic and military characteristics (not specified). The relatively short observation period (8 years) was identified as a limitation of this study for assessing cancer risk, and no information on smoking was included in models of effect estimates.

Young et al. (2010) examined proportional cancer incidence among all 621,902 U.S. veterans deployed to the Gulf War and 746,248 era veterans. Era veterans were a stratified random sample of veterans from all services who served during the conflict but were not deployed to the Persian Gulf region. Veterans diagnosed with cancer between 1991 and 2006 were identified using data from the DMDC, which was linked to central cancer registries in 28 states and the VA Central Cancer Registry. The 28 state registries captured 84% of the U.S. population, based on the 2000 U.S. Census; cancer cases were grouped into 30 categories. Logistic regression models that controlled for age, race, and sex were used to determine whether the proportion of veterans with a diagnosed cancer differed between deployed and era veterans. Crude and adjusted proportional incidence ratios (PIRs) were calculated to determine differences by specific cancer type; adjustments were made for sex, diagnosis age, diagnosis age squared, diagnosis year, race, branch of service, unit type, and registry group. For cancer types with statistically significant adjusted PIRs, standardized incidence ratios (SIRs) were calculated. SIRs compared the Gulf War veterans and era veterans with the general population, adjusted for sex, race, and age. A total of 21,075 incident cancer diagnoses were identified—8,211 among the deployed veterans and 12,864 among the era veterans—and of these, 2,796 were identified from the VA Central Cancer Registry. Lung cancer was the only site-specific cancer examined that was found to have a significantly higher proportion among deployed veterans than among era veterans (PIR = 1.15, 95%CI 1.03–1.29). It remained statistically significant when further analysis compared the proportional incidence of lung cancer in Army and Marine (ground troop) veterans with era veterans (PIR = 1.21, 95%CI 1.07–1.38). SIRs comparing deployed and era veterans with the general U.S. population were also calculated. Neither deployed nor era veterans showed significantly increased risks of lung cancer compared with the general population. Three additional respiratory cancer outcomes were also examined; none yielded statistically significant outcomes for either the comparison between all Gulf War veterans and era veterans or for that between Gulf War ground troop veterans and era veterans. For "oral cavity and pharynx" cancer, the adjusted PIRs were 0.97 (95%CI 0.83–1.13) and 0.98 (95%CI 0.81–1.17), respectively; for esophageal cancer they were 0.85 (95%CI 0.63–1.15) and 0.82 (95%CI 0.57–1.18), respectively; and for "other respiratory system" cancers they were 1.01 (95%CI 0.78–1.30) and 1.07 (95%CI 0.79–1.45, respectively). The investigators adjusted for some demographic, diagnostic, and military factors, but no data on smoking status were available so this factor was not included in the adjusted models.

The length of follow-up was, at most, 15 years, which may not be enough time for certain cancers, such as lung cancer, to develop if there was a Gulf War etiologic factor. Additionally, the numbers of incident cancer diagnoses are likely to be underestimated because 22 states were not represented, which may alter the PIR as it is affected by the relative frequencies of other cancer types. Also, of the 28 state cancer registries that were included, not all covered the full time period. Major strengths of the study are that it used the entire population of deployed Gulf War veterans and a large and representative sample of era veterans and that it used cancer registry data—as opposed to mortality, hospitalization, or self-reported diagnoses—to assess cancer incidence outcomes. The sample size was large enough to provide adequate statistical power to detect relatively small differences in lung cancer between veteran groups and between each veteran cohort and the general U.S. population. However, data on smoking were not available, and the analyses could thus not be adjusted for this potential confounder.

Other 1990–1991 Gulf War Coalition Forces Veterans As part of the Australian Gulf War Veterans' Follow Up Health Study, cancer incidence rates were examined through 2008 in the entire cohort of 1,871 Australian Gulf War veterans and a comparison group of 2,922 veterans who were frequency matched based on age, sex, rank category, and service branch (Sim et al., 2015). Incident cancers were identified and linked to the cohort using the Australian Cancer Database. Its data include the date of cancer diagnosis, site, histology, the Australian state in which the cancer was diagnosed, date of death (if applicable), and the ICD-10 codes for the type of cancer. Hazard ratios (HRs) were used to make comparisons between the two veteran groups, and standardized incidence ratios were used to make comparisons between each veteran group and the Australian population. Because women veterans composed only 2% of the Australian deployed cohort and no deployed women developed cancer in the 18-year follow-up, women were excluded from the cancer incidence analyses. There were fewer than five lung, trachea, and bronchus cancers in both the Gulf War veterans and the comparison group. The calculated standardized incidence rate was 4.2 (95%CI 0.06–3.00) in the veterans cohort and 5.2 (95%CI 0.13–2.07) in the comparison group. While the study adjusted for some factors, such as age, service branch, and rank, it did not adjust for other important potential confounders, such as smoking, BMI, and alcohol use.

Macfarlane et al. (2003) assessed all first diagnoses of malignant cancer using the UK National Health Service Central Register in UK service member and veterans. The deployed group consisted of all military personnel who served in the Persian Gulf in the period September 1990–June 1991 (n = 51,721). The comparison group was randomly selected from members of the armed services who were in service on January 1, 1991, but not deployed in the Persian Gulf and was stratified to match the deployed cohort on age, sex, service branch, rank, and level of fitness for active service (n = 50,755). Follow-up was from April 1, 1991, until a diagnosis of cancer, emigration, death, or July 31, 2002, whichever came first. The IRR for bronchus, lung, and trachea cancer was 0.41 (95%CI 0.10–1.73) after adjusting for sex, age, service branch, rank, smoking, and alcohol consumption. This result was based on a very small number of cases—three in the deployed cohort and five in the comparison group—which raises concerns about its reliability.

The Canadian Department of National Defence used the national mortality database and the national cancer registry to examine mortality rates and cancer incidence among Canadian Gulf War veterans from 1991 through 1999 (Statistics Canada, 2005). Two cohorts were established—the deployed cohort of 5,117 service members who served in the Persian Gulf between August 24, 1990, and September 30, 1991, and the nondeployed cohort of 6,093 service members who were eligible for deployment but who were not deployed. During the follow-up period, three deaths from respiratory cancers were identified in the deployed cohort and "a number less than 3" in the nondeployed cohort. The incidence density ratio was 2.36 (95%CI 0.39–14.2), adjusted for age and sex. In addition to the small sample size (and therefore low statistical power to detect associations if they exist), the limitations of this study include the relatively short follow-up (which would not allow the identification of long-term effects of deployment) and the lack of information on potential confounding factors, such as smoking and other lifestyle factors.

Post-9/11 Veterans

The committee responsible for the 2017 National Academies report *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry* carried out an analysis of the initial months of data gathered from respondents to the registry's questionnaire (NASEM, 2017). The data were derived from the first 13 months of completed questionnaires (n = 46,404), representing approximately 1.0% of the 1990–1991 Gulf War veterans and 1.7% of post-9/11 veterans who met the registry's eligibility criteria. While data were collected on self-reported esophageal and lung cancer, the committee determined that these were unlikely to be informative because the questions were too general, insufficient time had elapsed since the exposures for effects to manifest, and the population was too young for most cancers to have developed; for these reasons the committee did not analyze them.

Update of the Scientific Literature on Respiratory Cancers

The committee identified nine studies (Díaz Santana et al., 2017; Dursa et al., 2016a,b; Hooper et al., 2008; Khalil et al., 2018; Rohrbeck et al., 2016; Smith et al., 2006, 2008; Zundel et al., 2019) that addressed cancer outcomes in theater veterans that had not previously been summarized in earlier National Academies reports. However, only two specifically presented data for respiratory cancers (Khalil et al., 2018; Rohrbeck et al., 2016). Studies that only report on cancers or malignant neoplasms as a group without distinguishing respiratory cancers do not contribute to informing the evidence base on the association between deployment to Southwest Asia and respiratory-specific outcomes, including cancer. The studies that examined mortality from respiratory cancers are summarized under the Mortality section.

Post-9/11 Veterans

Rohrbeck et al. (2016) conducted a limited cohort study that compared U.S. service members deployed to Iraq (2006–2008, n = 163) and Afghanistan (2011–2012, n = 37) with matched nondeployed service members (n = 200) to examine the association between exposure to burn pits and the occurrence of ICD-coded respiratory outcomes, including neoplasms of the oral cavity and neoplasms of the respiratory organs, after return from deployment. Service members were recruited using data from the Defense Medical Surveillance System. Data from medical encounters in military treatment facilities, both hospitalizations and outpatient visits, were used to capture information on neoplasms; however, no encounters for these outcomes were observed.

1990–1991 Gulf War Veterans

Khalil et al. (2018) described the study design for the Gulf War Era Cohort and Biorepository and provided preliminary results from the pilot phase of the effort, which had enrolled 1,275 veterans, 900 of whom had deployed to Southwest Asia. Self-reported health outcomes of symptoms (in the past year) and health care provider–diagnosed conditions were reported, stratified by users (n = 584) and nonusers (n = 679) of VA health care in the past year. A supplemental table for the paper that was posted to the web notes that none of the 1,256 subjects who responded to the survey question indicated that a doctor or other health care provider had ever told them that they had lung cancer. As the study participants consented to further contact and analyses of the data and biospecimens they provided, this cohort may be useful in future studies of respiratory cancer and other outcomes.

Synthesis

The only studies of respiratory cancer outcomes in theater veterans that have been published to date address the military personnel who participated in the 1990–1991 Gulf War. As is true for all the outcomes reviewed by the committee, the studies are plagued by poor exposure characterization, with self-reports or location information being used as proxies for measured exposure levels. Several report such a small number of respiratory cancer outcomes that the risk estimates have large confidence intervals. Some, although not all, fail to account for potential confounding by cigarette smoking—the most important risk factor for lung cancer. And the earlier studies summarized by previous National Academies committees note that cancers associated with environmental exposures may have long latency periods and that too little time may have passed since in-theater exposures to see their effects. As a consequence, no conclusions can be drawn from this body of literature.

Smith et al. (2008), who performed an analysis of data obtained as part of the Millennium Cohort Study, found that military deployment was associated with smoking initiation among never smokers and with smoking resumption among those who had stopped. This finding, among others, led Krefft et al. (2015) to argue that tobacco smoking should be considered a deployment-related exposure that contributes to lung cancer risk. There is no question that cigarette smoking is an important risk factor for a number of cancers of interest. However, lacking sufficiently representative data on either the quantitative excess of smoking associated with deployment or its continuation post-deployment, the attributable risk associated with this change in smoking behavior cannot be estimated.

Conclusions

Based on the epidemiologic studies of military personnel and veterans reviewed in this and previous National Academies reports, the committee concludes that there is inadequate or insufficient evidence of an association between airborne hazards exposures in the Southwest Asia theater and the subsequent development of respiratory cancers. While data exist on 1990–1991 Gulf War veterans, the committee notes that no studies have been published concerning those who participated in the post-9/11 conflicts and that—even if such studies were available—the amount of time since exposure may only now be long enough to justify new incidence studies of respiratory cancers in this cohort.

MORTALITY

The committee's Statement of Task directed it to pay particular attention to excess mortality in military personnel who served in the Southwest Asia theater. This section evaluates the results of epidemiologic studies of overall mortality and, where the information is available, respiratory disease–related causes of death among service members and veterans in the 1990–1991 Gulf War and post-9/11[14] cohorts.

The section begins with a brief summary of the mortality studies evaluated in previous *Gulf War and Health* volumes, with an emphasis on findings regarding mortality from respiratory disease–related causes and the conclusions those committees drew from that evidence. Next, a description of each of the newly identified studies of mortality is presented along with each study's salient results. Studies of overall mortality, of cancers of the respiratory system, and of non-cancerous respiratory conditions are considered separately.

Summary of Epidemiologic Studies Reviewed in Previous Gulf War and Health and Related Reports

Periodically throughout the *Gulf War and Health* series, committees have examined mortality overall and, when possible, by cause (Volumes 4, 8, and 10). Through Volume 10, 19 studies of mortality among 1990–1991 Gulf War veterans have been reviewed and assessed (Barth et al., 2009; Bossarte, 2014; Bullman et al., 2005; DASA, 2005, 2009; Gackstetter et al., 2006; Gray et al., 2000; Haley, 2003; Kang and Bullman, 1996, 2001; Knapik et al., 2009; Lincoln et al., 2006; Macfarlane et al., 2000, 2005; Shaw et al., 1991; Sim et al., 2015; Statistics Canada, 2005; UK Ministry of Defence, 2014; Zwerling et al., 2000). These studies examined mortality for veterans from Australia, Canada, the United Kingdom, and the United States who were deployed to Iraq or in the surrounding theater of operations in support of Operation Desert Shield or Operation Desert Storm. Some of these veterans may also have been deployed in the post-9/11 conflicts, but they were selected for inclusion in the study cohorts based on their 1990–1991 Gulf War service. Some studies examined overall mortality or specific causes that did not include respiratory diseases (e.g., Barth et al. [2009], which examined mortality from neurologic conditions only). Most comparisons were made between the deployed Gulf War veterans and nondeployed era veterans, although some studies were able to make comparisons between deployed veterans who were exposed and those who were nonexposed to a particular agent (such as nerve agents at Khamisiyah). In general, the popula-

[14] The primary post-9/11 U.S. military operations in the Southwest Asia theater were Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND).

tions examined in the Australian, Canadian, and UK studies were small, reflecting the relatively limited number of personnel deployed from these countries.

Empirical analyses reviewed by prior Gulf War and Health committees that examined all disease-specific causes of mortality found either no difference (Bullman et al., 2005; DASA, 2009; Kang and Bullman, 1996; Macfarlane et al., 2000, 2005) or lower mortality rates for deployed 1990–1991 Gulf War veterans compared with nondeployed veterans, a finding consistent with studies of U.S. (Bossarte, 2014), UK (UK Ministry of Defense, 2014), and Australian (Sim et al., 2015) veterans. For the purposes of this report, the only relevant mortality studies were those that reported on respiratory-specific conditions (Bossarte, 2014; Bullman et al., 2005; DASA, 2009; Kang and Bullman, 1996, 2001; Macfarlane et al., 2000, 2005; Sim et al., 2015; Statistics Canada, 2005; UK Ministry of Defence, 2014).

Non-Cancerous Respiratory Conditions

Mortality from respiratory conditions in Gulf War veterans has been examined in veterans from Canada (Statistics Canada, 2005), the United Kingdom (DASA, 2009; Macfarlane et al., 2000, 2005; UK Ministry of Defence, 2014), and the United States (Bossarte, 2014; Bullman et al., 2005; Kang and Bullman, 1996, 2001). None of these studies adjusted for smoking status.

The first mortality study of U.S. 1990–1991 Gulf War veterans covered 1991–1993 and included the entire deployed cohort (n = 695,515) and a nondeployed era cohort (n = 746,291). The study found an elevated difference in respiratory system disease mortality that included the null (mortality rate ratio [MRR] = 1.27, 95%CI 0.60–2.70) (Kang and Bullman, 1996). However, when compared with the U.S. population, both Gulf War veterans (SMR = 0.14, 95%CI 0.07–0.23) and era veterans (SMR = 0.11, 95%CI 0.06–0.18) had a statistically significantly lower risk of death due to respiratory illness. An updated mortality study of the same cohort through December 31, 1997 (Kang and Bullman, 2001), found no statistically significant differences between the deployed and nondeployed veteran groups, stratified by sex, for respiratory mortality; both deployed and nondeployed veterans had statistically significant lower respiratory mortality than the general U.S. population.

In a study of cause-specific mortality through December 31, 2000, of deployed U.S. veterans considered to be exposed or not exposed to nerve agents released from the destruction of the Khamisiyah munitions storage facility in 1991, no increase in mortality due to respiratory conditions was seen in the putatively exposed veterans (RR = 1.03, 95%CI 0.62–1.72; adjusted for age) (Bullman et al., 2005). Similarly, no difference in risk for respiratory disease mortality was observed when the investigators divided the exposed group into persons exposed for 1 day only or for 2 days compared with people who were not exposed (exposure based on the 2000 plume model), adjusted for age, race, sex, rank, and unit component. VA's presentation to the Volume 10 committee (Bossarte, 2014) included mortality rates for respiratory conditions for both deployed and nondeployed Gulf War veterans over a 20-year period (1991–2011). No statistically significant differences were found between the two groups (MRR = 0.96, 95%CI 0.86–1.06) adjusted for race, sex, age, branch of service, and unit component.

Other 1990–1991 Gulf War Coalition Forces Veterans In the first UK study to assess mortality, conducted through March 31, 1999, Macfarlane et al. (2000) found no excess deaths due to conditions of the respiratory system in either deployed or nondeployed veterans after adjusting for age only (MRR = 1.0, 95%CI 0.13–7.47). An update of the same cohort through 2004 (Macfarlane et al., 2005) also found no statistically significant excess of deaths related to respiratory disease (MRR = 1.64, 95%CI 0.58–4.66), after adjusting for age only. In the analysis conducted by the Defence Analytical Services and Advice, 13 deaths due to respiratory diseases were reported among deployed UK veterans and 12 deaths among comparable age-adjusted era veterans, resulting in no difference for age-adjusted mortality (MRR = 1.06, 95%CI 0.47–2.39). An update of that analysis conducted by the UK Ministry of Defence (2014), again found few deaths due to respiratory diseases (34 of 1,506 total deaths among the deployed veterans and 36 [adjusted] of 1,583 total deaths among the nondeployed veterans), and the difference remained not statistically significant (MRR = 0.93, 95%CI 0.58–1.49; adjusted for age). Specific types of respiratory system conditions were not presented for either UK analysis. Standardized mortality ratios for respiratory diseases comparing deployed and nondeployed veterans with the age- and gender-adjusted UK population were not calculated.

Statistics Canada (2005) conducted a mortality follow-up study of Canadian Gulf War veterans and compared them with randomly selected Canadian veterans who were eligible but not deployed to the Gulf War and to the general Canadian population. There were too few deaths from respiratory disease to make meaningful comparisons between the veteran cohorts and the general population, and smoking status was not available.

Given that, in the mortality studies reviewed, few deaths due to respiratory causes were reported and no statistically significant excess of mortality due to respiratory disease was found among Gulf War veterans compared with nondeployed era veterans or the general, country-specific population, the Volume 10 committee concluded that there was limited or suggestive evidence of *no* association between deployment to the Gulf War and mortality from respiratory disease. Notably, in all these studies of 1990–1991 Gulf War veterans, the populations are relatively young, and a large number of deaths from chronic respiratory diseases would not be expected.

Cancers

Studies that assessed mortality from all types of cancers in previous *Gulf War and Health* volumes did not find an increased risk in deployed versus nondeployed veterans (Barth et al., 2009; Bullman et al., 2005; DASA, 2009; Kang and Bullman, 2001; Macfarlane et al., 2000, 2003, 2005; Sim et al., 2015; Statistics Canada, 2005; UK Ministry of Defence, 2014). Given the maximum follow-up period of about 10 years for most of these studies, prior committees concluded that, in general, many veterans were still too young to have developed the most common forms of cancer and that, for most cancers, the follow-up period after the Gulf War was probably too short to expect the onset of any exposure-related cancers, let alone death from such cancers. Smoking status was not available or included in any of these studies of cancer mortality.

In a study of cause-specific mortality through December 31, 2000, of deployed U.S. veterans considered to be exposed or not exposed to nerve agents as a result of the Khamisiyah munitions destruction in 1991, no increase in mortality due to lung cancer was observed in the exposed veterans overall (RR = 0.72, 95%CI 0.47–1.10) when adjusted for age, race, sex, rank, and unit component or when stratified by days of exposure (1 day or 2 or more days), compared with the nonexposed (Bullman et al., 2005). The Volume 10 committee considered a presentation of an original data analysis from VA to the committee that included mortality rates for all cancers and, specifically, for lung cancer over a 20-year period (1991–2011) (Bossarte, 2014), but it was given less weight than the published epidemiologic studies. No statistically significant difference was observed between the deployed and nondeployed veterans with regard to death from any cancer (MRR = 0.99, 95%CI 0.95–1.03) when adjusted for race, sex, age, branch of service, and unit component). Mortality rates for lung cancer were calculated for each veteran group but were only compared with the general U.S. population, not to each other. The lung cancer mortality rates for both deployed and nondeployed veterans were statistically significantly lower than those for the general U.S. population (SMR deployed = 0.60, 95%CI 0.57–0.64; SMR nondeployed = 0.59, 95%CI 0.56–0.62).

Other 1990–1991 Gulf War Coalition Forces Veterans The UK statistical report (DASA, 2009), which had a follow-up period of 16 years, found no difference in the number of malignant neoplasms of respiratory and intrathoracic organs in deployed versus nondeployed UK Gulf War veterans (MRR = 0.75, 95%CI 0.48–1.18). A subset of that category—malignant neoplasms of the bronchus and lung, which formed a majority of the malignant respiratory neoplasms—similarly exhibited no differences between deployed and era veterans (MRR = 0.71, 95%CI 0.45–1.13). An updated analysis of this cohort (UK Ministry of Defence, 2014) included an additional 6 years of follow-up. Between April 1, 1991, and December 31, 2013 (approximately 22 years), 404 neoplasm deaths out of 911 disease-related deaths were reported among deployed veterans and 455 (adjusted) neoplasm deaths out of 1,035 disease-related deaths in nondeployed veterans (MRR = 0.89, 95%CI 0.78–1.02; adjusted for age). Site-specific malignant neoplasm deaths were reported for respiratory and intrathoracic organs (54 vs 87 [adjusted] in deployed and era veterans, respectively); bronchus and lung cancers were reported as a subset of these. Lung cancer mortality was statistically significantly lower for deployed Gulf War veterans (n = 49) compared with nondeployed veterans (n = 82, adjusted) (MRR = 0.60, 95%CI 0.42–0.85) after adjustment for age. The nondeployed comparison group was similar to the deployed group in age, gender, service, regular/reservist status, and rank. Standardized mortality ratios for respiratory cancers comparing deployed and nondeployed veterans with the age- and gender-adjusted UK population were not calculated.

Whereas the Volume 8 committee did not reach any conclusions regarding the association between deployment to the Gulf War and mortality from any cancer, the Volume 10 committee concluded that there was insufficient or inadequate evidence of an association between deployment to the Gulf War and mortality from any form of cancer. No conclusions were made for specific cancers, such as lung cancer.

Update of the Scientific Literature on Mortality

Eight studies of mortality that had not been previously summarized in the *Gulf War and Health* series were identified by the committee in its literature search (Barth et al., 2016b; Belenkiy et al., 2014; Bollinger et al., 2015; Gray and Kang, 2006; Hooper et al., 2010; Maynard et al., 2018a,b; Shorr et al., 2004). Some of these studies were conducted in post-9/11 populations (Belenkiy et al., 2014; Bollinger et al., 2015; Hooper et al., 2010; Shorr et al., 2004), which were considered to be outside the population of interest in some of these earlier reports. Of the eight studies, six were excluded from further consideration because one was a review that did not offer any new or original information (Gray and Kang, 2006), one was a case series of AEP that included deaths but was not designed to assess population-level mortality (Shorr et al., 2004), one assessed mortality related to trauma rather than to disease (Belenkiy et al., 2014), two publications by Maynard et al. (2018a,b) examined the association between disability rating for veterans with service-connected conditions and either cause of death or 1-year mortality rates, and Hooper et al. (2010) conducted a mortality analysis using the participants of Panel 1 of the Millennium Cohort Study and different sources of death data to compare the all-cause mortality experience. Bollinger et al. (2015) is summarized for completeness, but it reported on overall deaths, not on deaths from respiratory conditions or other conditions.

Using the same population of 621,901 Gulf War–deployed veterans and 746,247 nondeployed veterans originally studied by Kang and Bullman (2001) and summarized in Volume 4, Barth et al. (2016b) continued their mortality follow-up of all causes and disease-specific causes through 2004. The total follow-up period was 13 years, and several comparisons were made: deployed Gulf War veterans who were potentially exposed to nerve agents at Khamisiyah versus those who were not; deployed Gulf War veterans versus nondeployed era veterans; and deployed and nondeployed veterans versus the standardized U.S. population. To be eligible for inclusion, Gulf War–deployed veterans must have served in the Persian Gulf between August 1, 1990, and March 1, 1991; troops that arrived in the region after March 1, 1991, were excluded. Vital status was determined using VA's Beneficiary Identification and Records Locator Subsystem in combination with the Social Security Administration Death Master File. Cause of death data were determined from death certificates in VA claim files or from the National Death Index Plus, which is part of the National Center for Health Statistics. Deaths were coded using ICD-9 codes. Data on demographics and military characteristics were from DoD's DMDC. Over the 13-year period, 10,869 deaths among deployed Gulf War veterans and 14,716 deaths among nondeployed era veterans were reported. Adjusted RRs were presented that were derived from a Cox proportional hazard model after controlling for age, race, sex, service branch, type of unit, and length of follow-up. Smoking status was not ascertained or included in the models. Although both estimates were statistically significant, a slightly lower rate of death from all causes was found for deployed versus nondeployed males (RR = 0.94, 95%CI 0.95–0.99) and a slightly higher rate of death was found for deployed versus nondeployed females (RR = 1.15, 95%CI 1.03–1.28). When mortality from all disease-related causes was examined, the adjusted RR was statistically significantly lower for deployed versus nondeployed males (RR = 0.93, 95%CI 0.90–0.97), and the difference for deployed versus nondeployed females was higher but did not reach statistical significance (RR = 1.10, 95%CI 0.96–1.27). The data on cause of death were missing for 770 (7.1%) deceased Gulf War veterans and for 1,090 (7.4%) deceased era veterans. With respect to deaths from respiratory system disorders (ICD-9 460–519), which do not include cancers, there were 192 deaths in the deployed veterans (180 males and 12 females) and 318 deaths in the nondeployed veterans (291 males and 27 females). No statistically significant differences were found for deployed versus nondeployed males (RR = 0.95, 95%CI 0.78–1.15) or females (RR = 1.07, 95%CI 0.54–2.11). Comparisons with the U.S. population were presented for respiratory system disorders, stratified by sex and age adjusted. SMRs comparing deployed veterans to this population showed that deaths from respiratory system disorders were statistically significantly lower for deployed veterans overall (SMR = 0.30, 95%CI 0.26–0.34) and for both males (SMR = 0.30, 95%CI 0.25–0.34) and females (SMR = 0.33, 95%CI 0.17–0.57), separately. Similar findings of a statistically significantly lower risk of death from respiratory system disorders were found among the nondeployed veterans compared with the U.S. population for both males (SMR = 0.32, 95%CI 0.28–0.35) and females (SMR = 0.30, 95%CI 0.20–0.44). The deficits in mortality rates compared with the general U.S. population support the "healthy soldier effect."

Mortality risks and adjusted RRs (derived from a Cox proportional hazards model after controlling for sex, race, type of unit, age, and oil-well fire smoke exposure) for lung cancer and non-cancer respiratory system conditions, and for COPD (ICD-9 490–492, 494, 496) specifically, were also estimated for the subset of the deployed population who were exposed to nerve agents from the Khamisiyah demolition for 1 day or ≥2 days compared with nonexposed deployed veterans. Exposure at Khamisiyah was based on the 2000 plume model from Winkenwerder (2002), the limitations of which have been discussed in other reports. Among those exposed to nerve agents from Khamisiyah, 58 deaths from lung cancer occurred among the 1-day-exposed group, 10 deaths in the ≥2 days-exposed group, and 163 in the nonexposed deployed group. Compared with the nonexposed deployed, adjusted RRs were not statistically significant for the 1-day exposed (RR = 0.78, 95%CI 0.57–1.06) or the ≥2 days exposed (RR = 0.78, 95%CI 0.39–1.53). For non-cancer respiratory system conditions, there were 32 deaths among 1-day exposed, 7 deaths among the ≥2 days exposed, and 77 deaths among the nonexposed deployed veterans. Similar to the case with lung cancer, the adjusted RRs for non-cancer respiratory system conditions showed no statistically significant differences between 1-day exposed (RR = 1.00, 95%CI 0.65–1.55) or the ≥2 days exposed (RR = 1.60, 95%CI 0.73–3.55) and the nonexposed deployed veterans. For COPD there were 11, 3, and 21 deaths, respectively, in the 1-day exposed, ≥2 days exposed, and nonexposed deployed veterans. Comparisons with the nonexposed deployed veterans showed no statistically significant differences for COPD for 1-day exposed (RR = 1.23, 95%CI 0.57–2.65) or the ≥2 days exposed (RR = 2.45, 95%CI 0.69–8.76) veterans. Although there appears to be an exposure–response effect, the point estimates are imprecise because the number of events is small.

Bollinger et al. (2015) evaluated mortality rates for post-9/11 veterans using several different comparison populations—the general U.S. population; enrollees in the VA health care system, users of VA health care, and nonusers of VA health care[15]; and an active-duty military cohort (which included activated National Guard and Reserve members)—to determine whether the "healthy soldier effect" and "healthy warrior survivor effect" contributed to different rates of mortality. The intention was to determine whether the mortality experience of post-9/11 veterans differed from that of previous veteran cohorts by examining the ways in which the healthy soldier effect operates in VA enrollees and DoD active duty service members compared with the U.S. population. Data sources were the VA OEF/OIF/OND Roster file, VA "mini" vital status file of mortality data, and DoD's DMDC Reporting System. For inclusion in the VA cohort, individuals had to have contact with the VA health care system at least once between October 2001 and September 30, 2011 (most veterans do complete an initial assessment check-in); individuals were excluded if their ages were missing or their deaths were combat related. The final VA cohort was 899,737 individuals consisting of 765,029 (85%) veterans who had used VA health care and 134,708 (15%) veterans who did not use VA health care in the 10-year period. The DoD active-duty military cohort consisted of persons deployed in support of OEF/OIF/OND from January 2002 through December 2011 (n = 4,619,178); deaths that were combat related were excluded. Mortality rates for the U.S. population were calculated using 2002–2010 data from the Centers for Disease Control and Prevention (CDC) Wonder system that was sex, age, and race/ethnicity adjusted for people aged 18–72 years. The total numbers of included deaths were 4,055 for VA health care users, 193 for non-VA health care users, 10,390 for the DoD active-duty cohort, and 7,890,897 for the U.S. population. Standardized mortality ratios using indirect standardization were calculated to control for the different age structures of VA, DoD, and U.S. populations. Mortality rates were standardized to U.S. age-, race-, and sex-specific mortality and applied to the age structure of VA and DoD populations to get an expected number of deaths. These rates standardized to DoD age-, rank-, component-, and branch-specific

[15] VA health system enrollees, VA health care users, and non-VA health care users were broken out because these groups have different demographic characteristics that influence mortality.

mortality were applied to VA cohorts' age, rank, component, and branch structure to get an expected number of deaths in order to evaluate whether mortality differences between VA and DoD cohorts were due to military-specific characteristics. Smoking status was not available. SMRs cannot be compared across populations with different age distributions, so Bollinger et al. (2015) estimated a directly standardized relative risk (DSRR) using the standardized mortality rate and the population standard for each age group to allow for comparisons between groups. The DoD population was statistically significantly younger than the VA cohorts of health care users and nonusers (34.2 years vs 34.4 years and 33.1 years, respectively). Compared with the U.S. population, VA health care users had a statistically significantly higher risk of all-cause mortality (SMR = 3.15, 95%CI 3.1–3.25; DSRR = 2.86), as did the DoD active-duty cohort (SMR = 1.47, 95%CI 1.44–1.49; DSRR = 1.19), but there was no difference for nonusers of VA health care (SMR = 0.92, 95%CI 0.79–1.05; DSRR = 0.79). When the VA cohort was compared with the DoD cohort, VA health care users had a statistically significantly increased risk of all-cause mortality (SMR = 2.34, 95%CI 2.26–2.41; DSRR = 2.28), but nonusers of VA health care had a statistically significantly decreased risk of all-cause mortality (SMR = 0.63, 95%CI 0.55–0.72; DSRR = 0.62). The results of these analyses suggest that overall OEF/OIF/OND veterans who use VA have higher-than-expected mortality compared with the general U.S. population. When the results were stratified by demographic characteristics, the SMRs and DSRRs were similar for males and females in VA and DoD cohorts. The SMRs varied by race and age groups for VA and DoD populations. Mortality ratios were highest in the youngest veterans (<24 years); SMR = 5.29, 1.43, and 2.47 for VA users, VA nonusers, and DoD cohort, respectively, compared with the U.S. population. Mortality rates were lowest in the oldest veterans (40–72 years), SMR = 1.37, 0.38, and 0.38, respectively, compared with the U.S. population. When VA users were stratified by race, SMRs were 3.75, 3.13, and 1.64 for white non-Hispanic, Hispanic, and black non-Hispanic, respectively. By contrast, in the DoD population, the SMRs for white non-Hispanic, Hispanic, and black non-Hispanic were 1.09, 1.87, and 2.33, respectively. The OEF/OIF/OND cohort of 4.6 million individuals differs from previous military cohorts in that the conflicts have continued longer than any other war or conflict and have resulted in multiple deployments and longer durations for more individuals. In addition, survival from battlefield injuries has improved, which results in higher rates of disability among this cohort of veterans.

This study is not directly relevant to the question of increased mortality from respiratory conditions associated with exposures in the OEF/OIF/OND conflicts; however, it does provide a context for evaluating mortality and potential inferences to respiratory conditions. Given the relatively short follow-up of relatively young populations (55% of the VA cohort and 59.3% of the DoD cohort were younger than 24 years), most of the deaths are likely due to causes other than chronic disease, although the cause-specific information was not presented. The SMRs were highest for the younger age groups across the two VA and the DoD cohorts. The observed lower SMRs for older veterans with longer military service is consistent with a healthy soldier survivor effect, reflecting the fact that healthier soldiers tend to have longer military service. These trends in SMRs are also consonant with patterns observed for certain occupational cohorts, such as chemical workers. The elevated SMR in the active DoD population may be a consequence of relaxed eligibility standards—higher weight, lower scores on aptitude tests, criminal and medical waivers, and lack of a high school diploma—applied to meet recruitment goals for the Afghanistan and Iraq conflicts, which would lead to service members being more comparable with the general U.S. population. An alternate explanation may be that these military personnel faced serious non-combat-related health hazards during deployment to OEF/OIF/OND. Without being able to distinguish between these two explanations, SMRs are not interpretable as measures of excess mortality risk related to respiratory hazards in theater. Moreover, because only all-cause mortality was considered, the higher mortality rates in the youngest age group are more likely driven by external causes (e.g., motor vehicle accidents, suicide, drug overdose) than disease—particularly respiratory disease—specific causes. These findings suggest that the health advantage typically observed in military populations (the "healthy warrior effect") is mitigated for the post-9/11 cohort.

Limitations of Mortality Studies

Military personnel deployed to Afghanistan and the Southwest Asia theater and those serving in the armed forces but not deployed to that theater may offer reasonably comparable groups for examining many health outcomes, including death, but there are issues in the conduct and use of mortality studies that must be considered. A major limitation of the mortality studies discussed in this section is the short follow-up period. In general, more time is required for the potential contributory effects of aging on the development of putative risk of exposure resulting in death before investigators will be able to assess whether deployed veterans are experiencing increased mortality compared with their nondeployed counterparts, particularly for conditions with established risk factors and long latencies, such as cancer, or conditions that have deteriorating and protracted courses, such as chronic respiratory diseases.

Most of the mortality studies discussed here relied on data from the National Death Index. Although the information in these indexes is taken from death certificates, which are completed by different types of health professionals with varying levels of expertise in assessing cause of death, there are stringent requirements and rules that likely minimize misclassification. Misclassification of the cause of death is more likely when the cause is more specific (e.g., all-cause deaths versus deaths from COPD). Large sample sizes can compensate for bias toward the null caused by nondifferential misclassification. The most reliable cause of death information is typically provided by medical examiners and physician providers; those records are less likely to have nondifferential misclassification bias, especially for causes of death that may have links to specific exposures or require knowledge of underlying pathology (IOM, 2003b). Furthermore, knowledge of or review of the decedent's medical and exposure history is known to improve the accuracy of death certificate data.

Finally, few studies have been published with enough power to assess cause-specific mortality rates among deployed and nondeployed Gulf War veterans from the United States or any coalition country (e.g., Australia, Canada, United Kingdom). In addition to large cohort studies comparing deployed and nondeployed veterans, nested case–control studies among the deployed may yield efficient and more suitable comparisons between deceased or "sick" veterans (cases) and "non-sick" veterans (controls). Another factor to consider is competing risks of death, which is especially problematic when the competing causes of death are not independent of each other (such as when they are both associated with the exposure, as in the case of silicosis and lung cancer in a mortality study of silica exposure). Completeness of follow-up information is also an important consideration between veterans who use VA medical care and those who do not. For example, veterans using VA medical care are likely to be more easily traced and to have more available information on underlying medical conditions and behaviors, such as smoking.

Synthesis

Based on the mortality studies of 1990–1991 Gulf War veterans summarized previously in *Gulf War and Health* Volumes 4, 8, and 10 and the one new study of deaths from non-cancer respiratory conditions in post-9/11 veterans over 10 years of follow-up (Barth et al., 2016b), the committee found no statistically significant excess of mortality due to respiratory disease among either the post-9/11 or Gulf War veteran cohorts. There do not appear to be differences in mortality between deployed and nondeployed veterans for the studies that looked at short-term follow-up (up to 13 years for 1990–1991 Gulf War veterans), but whether there are longer-term mortality differences is uncertain. Given the decades that have passed since the last mortality study of 1990–1991 Gulf War veterans was conducted, the committee does not believe continued confidence in those finding is warranted. The inferences possible from future studies of mortality would be improved by using internal analyses that compare higher- and lower-exposed veterans (assuming adequate exposure assessment measures) rather than analyses comparing all veterans to the general population. For mortality studies of 1990–1991 Gulf War or post-9/11 veterans, this requires that a retrospective exposure assessment be conducted as a necessary component of any future mortality study if it is to produce useful unbiased estimates of mortality risk. Taken altogether, the existing literature supports the need to examine effect modification of respiratory outcomes associated with burn pit and other exposures by education, income, race, and other measures of socioeconomic status in future studies of veterans and service members. To be informative, future studies of service members and veterans should ascertain smoking habits and adjust for them.

Conclusions

The current committee concurs with previous committees and concludes that there is inadequate or insufficient evidence of an association between deployment to the Southwest Asia theater during the 1990–1991 Gulf War and subsequent mortality from respiratory disease. The committee further concludes that there is inadequate or insufficient evidence of an association between deployment to the post-9/11 conflicts and subsequent mortality from respiratory disease; it notes that no studies of mortality have separated respiratory disease from other causes. Chapter 5 notes that data are readily available to fill the knowledge gaps identified in the existing mortality literature and offers a recommendation on future research that would address them.

FINAL OBSERVATIONS

In the course of its review, the committee assessed more than 55 epidemiologic studies that met its inclusion criteria, which included that the study address a respiratory health outcome in service members who were deployed to Southwest Asia, examine outcomes with relation to a comparison group, and present an empirical analysis of the data rather than simply list descriptive statistics. The committee also considered the results of previous evaluations of respiratory outcomes contained in the National Academies *Gulf War and Health* series and other related reports that examined epidemiologic evidence in military and veteran populations, and exposure to burn pits specifically.

Although most of the committee's conclusions fall under the category of "inadequate or insufficient evidence to determine an association," it wishes to emphasize that this should not be interpreted as meaning that there is no association between respiratory health outcomes and deployment to Southwest Asia, but rather that the available data are, on the whole, of insufficient quality to make a scientific determination. Notably, most of the studies reviewed by the committee did not perform objective exposure assessment, and the majority relied on deployment as a surrogate for exposure. As noted several times throughout this report, many studies make the implicit assumption that all deployed veterans had the same exposures to airborne hazards, which likely leads to bias of the effect estimate toward the null due to nondifferential exposure misclassification. More plainly stated, if an epidemiologic study of an adverse exposure combines data from subjects with high exposure together with data from subjects with low or no exposure, any effect of that exposure will be diluted.

Given these limitations in the current body of literature, the committee concludes that a new approach is needed that will allow researchers to better examine and answer the question of whether certain respiratory outcomes are associated with deployment to Southwest Asia. This new approach is not one that is intended to reprise a common theme in academia of "more research is needed" or to suggest that the only alternative is to undertake work that will take many years to bear fruit. While new data collection may be necessary in some circumstances, well conducted epidemiologic studies are possible today using retrospective designs that are able to account for confounding factors, such as smoking habits; to combine and analyze existing data in innovative ways; to standardize outcome ascertainment methods to allow for better comparability of results; and to improve estimation of exposure.[16]

The report's next chapter (Chapter 5) offers a number of suggestions for how to move forward. It identifies data sources, potential methods, and collaborating organizations that could be used to leverage available exposure and health outcomes information to address the question of the impact of deployment to Southwest Asia on respiratory health.

REFERENCES

Abraham, J. H., and C. P. Baird. 2012. A case-crossover study of ambient particulate matter and cardiovascular and respiratory medical encounters among U.S. military personnel deployed to Southwest Asia. *Journal of Occupational and Environment Medicine* 54(6):733–739.

Abraham, J. H., S. F. DeBakey, L. Reid, J. Zhou, and C. P. Baird. 2012. Does deployment to Iraq and Afghanistan affect respiratory health of US military personnel? *Journal of Occupational and Environmental Medicine* 54(6):740–745.

[16] For example, American Thoracic Society/European Respiratory Society consensus statement on standardizing endpoints for clinical asthma trials and clinical practice (Reddel et al., 2009).

Abraham, J. H., A. Eick-Cost, L. L. Clark, Z. Hu, C. P. Baird, R. DeFraites, S. K. Tobler, E. E. Richards, J. M. Sharkey, R. J. Lipnick, and S. L. Ludwig. 2014. A retrospective cohort study of military deployment and postdeployment medical encounters for respiratory condition. *Military Medicine* 176(5):540–546.

AFHSC (Armed Forces Health Surveillance Center), the Naval Health Research Center, and the U.S. Army Public Health Command. 2010. *Epidemiological studies of health outcomes among troops deployed to burn pit sites*. Silver Spring, MD: Defense Technical Information Center.

Aoun, O., C. Roqueplo, and C. Rapp. 2014. Spectrum and impact of health problems during deployment: A prospective, multicenter study of French soldiers operating in Afghanistan, Lebanon and Côte d'Ivoire. *Travel Medicine and Infectious Disease* 12(4):378–384.

APHC (Army Public Health Command). 2010. *Screening health risk assessments, Joint Base Balad, Iraq, 11 May–19 June 2009*. Aberdeen Proving Ground, MD: Army Public Health Command. July.

ATS and ERS (American Thoracic Society and European Respiratory Society). 2002. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *American Journal of Respiratory Critical Care Medicine* 165(2):277–304.

ATS and ERS. 2013. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *American Journal of Respiratory Critical Care Medicine* 188:733–748.

Baird, C. P., S. DeBakey, L. Reid, V. D. Hauschild, B. Petruccelli, and J. H. Abraham. 2012. Respiratory health status of U.S. Army personnel potentially exposed to smoke from 2003 Al-Mishraq Sulfur Plant Fire. *Journal of Occupational and Environment Medicine* 54(6):717–723.

Banoei, M. M., I. Lupe, R. Dowlatabadi Bazaz, M. Campos, H. J. Vogel, B. W. Winston, and M. Mirsaeidi. 2019. Metabolomic and metallomic profile differences between veterans and civilians with pulmonary sarcoidosis. *Scientific Reports* 9:19584.

Barth, S. K., H. K. Kang, T. A. Bullman, and M. T. Wallin. 2009. Neurological mortality among U.S. Veterans of the Persian Gulf War: 13-year follow-up. *American Journal of Industrial Medicine* 52(9):663–670.

Barth, S. K., E. K. Dursa, M. R. Peterson, and A. Schneiderman. 2014. Prevalence of respiratory diseases among veterans of Operation Enduring Freedom and Operation Iraqi Freedom: Results from the National Health Study for a New Generation of U.S. Veterans. *Military Medicine* 179(3):241–245.

Barth, S. K., E. K. Dursa, R. Bossarte, and A. Schneiderman. 2016a. Lifetime prevalence of respiratory diseases and exposures among veterans of Operation Enduring Freedom and Operation Iraqi Freedom Veterans: Results from the National Health Study for a New Generation of U.S. Veterans. *Journal of Occupational and Environmental Medicine* 58(12):1175–1180.

Barth, S. K., H. K. Kang, and T. Bullman. 2016b. All-cause mortality among U.S. veterans of the Persian Gulf War: 13-year follow-up. *Public Health Reports* 131(6):822–830.

Bartoo, C. 2010. Soldiers' mysterious lung disease identified. *The Reporter* (Vanderbilt University Medical Center's Weekly Newspaper), February 12. https://www.mc.vanderbilt.edu/reporter/index.html?ID=8270 (accessed May 2, 2020).

Bascom, R., and P. Raford. Upper airway disorders. 1994. In L. Rosenstock and M. Cullen, eds., *Textbook of clinical occupational and environmental medicine*. Philadelphia, PA: W.B. Saunders Company. Pp. 322–326.

Belenkiy S. M., A. R. Buel, J. W. Cannon, C. R. Sine, J. K. Aden, J. L. Henderson, N. T. Liu, J. B. Lundy, E. M. Renz, A. I. Batchinsky, and L. C. Cancio. 2014. Acute respiratory distress syndrome in wartime military burns: Application of the Berlin criteria. *Journal of Trauma Acute Care Surgery* 76(3):821–827.

Blanc, P. D., I. Annesi-Maesano, J. R. Balmes, K. J. Cummings, D. Fishwick, D. Miedinger, N. Murgia, R. N. Naidoo, C. J. Reynolds, T. Sigsgaard, K. Toren, D. Vinnikov, and C. A. Redlich. 2019. The occupational burden of nonmalignant respiratory disease. An official American Thoracic Society and European Respiratory Society Statement. *American Journal of Respiratory and Critical Care Medicine* 199(11):1312–1334.

Bollinger, M. J., S. Schmidt, J. A. Pugh, H. M. Parsons, L. A. Copeland, and M. J. Pugh. 2015. Erosion of the healthy solider effect in veterans of U.S. military service in Iraq and Afghanistan. *Population Health Metrics* 13:8.

Bossarte, R. M. 2014. Presentation to the Institute of Medicine Committee on Gulf War: Veterans' Health. December 3, 2014. Department of Veterans Affairs Office of Public Health, Washington, DC.

Bullman T. A., C. M. Mahan, H. K. Kang, and W. F. Page. 2005. Mortality in U.S. Army Gulf War veterans exposed to 1991 Khamisiyah chemical munitions destruction. *American Journal of Public Health* 95(8):1382–1388.

Butzko, R. P., A. M. Sotolongo, D. A. Helmer, J. C. Klein-Adams, O. Y. Osinubi, A. R. Berman, R. Ortiz-Pacheco, and M. J. Falvo. 2019. Forced oscillation technique in veterans with preserved spirometry and chronic respiratory symptoms. *Respiratory Physiology and Neurobiology* 260:8–16.

CDC (Centers for Disease Control and Prevention). 2016. *National hospital ambulatory medical care survey: 2016 emergency department summary tables*. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2016_ed_web_tables.pdf (accessed August 4, 2020).

CDC. 2017. *Age-adjusted percentages (with standard errors) of selected respiratory diseases among adults aged 18 and over, by characteristics: United States, 2017*. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_A-2.pdf (accessed September 6, 2019).

CDC. 2018. *Summary health statistics tables for U.S. adults: National Health Interview Survey,* 2018. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_A-2.pdf (accessed August 21, 2020).

Chabra, R., and M. Gupta. 2019. Allergic and environmental induced asthma. In *StatPearls* [Internet]. Treasure Island, FL: StatPearls Publishing.

Cherry, N., F. Creed, A. Silman, G. Dunn, D. Baxter, J. Smedley, S. Taylor, and G. J. Macfarlane. 2001. Health and exposure of United Kingdom Gulf War veterans. Part I: The pattern and extent of ill health. *Journal of Occupational and Environment Medicine* 58:291–298.

Coates, A. L., J. Wanger, D. W. Cockcroft, B. H. Culver, K. H. Carlsen, Z. Diamant, G. Gauvreau, G. L. Hall, T. S. Hallstrand, I. Horvath, F. H. C. de Jongh, G. Joos, D. A. Kaminsky, B. L. Laube, J. D. Leuppi, and P. J. Sterk. 2017. ERS technical standard on bronchial challenge testing: General considerations and performance of methacholine challenge tests. *European Respiratory Journal* 49:1–17.

Colby, T. V. 1992. Pathologic aspects of bronchiolitis obliterans organizing pneumonia. *Chest* 102(1):38S–43S.

Colby, T. V. 1998. Bronchiolitis. Pathologic considerations. *American Journal of Clinical Pathology* 109(1):101–109.

Coombe, D., and S. Drydale. 1993. Assessment of the effects of atmospheric oil pollution in post war Kuwait. *Journal of the Royal Army Medical Corps* 139(3):95–97.

Cowan, D. N., J. L. Lange, J. Heller, J. Kirkpatrick, and S. DeBakey. 2002. A case–control study of asthma among U.S. Army Gulf War veterans and modeled exposure to oil well fire smoke. *Military Medicine* 167(9):777–782.

Crouser, E. D., L. A. Maier, K. C. Wilson, C. A. Bonham, A. S. Morgenthau, K. C. Patterson, E. Abston, R. C. Bernstein, R. Blankstein, E. S. Chen, D. A. Culver, W. Drake, M. Drent, A. K. Gerke, M. Ghobrial, P. Govender, N. Hamzeh, W. E. James, M. A. Judson, L. Kellermeyer, S. Knight, L. L. Koth, V. Poletti, S. V. Raman, M. H. Tukey, and Gloria E. Westney, on behalf of the American Thoracic Society Assembly on Clinical Problems. 2020. Diagnosis and detection of sarcoidosis: An official American Thoracic Society clinical practice guideline. *American Journal of Respiratory Critical Care Medicine* 201(8):e26–e51.

Culver, B. H. 2006. Interpretation of spirometry: We can do better than the GOLD standard. *Respiratory Care* 51(7):719–721.

Cypel, Y. S., K. Hamlett-Berry, S. K. Barth, D. E. Christofferson, V. J. Davey, S. Eber, A. I. Schneiderman, and R. M. Bossarte. 2016. Cigarette smoking and sociodemographic, military, and health characteristics of Operation Enduring Freedom and Operation Iraqi Freedom veterans: 2009–2011 National Health Study for a New Generation of US Veterans. *Public Health Reports* 131(5):714–727.

DASA (Defence Analytics Services and Advice). 2005. *1990/1991 Gulf Conflict—UK Gulf veterans mortality data: Causes of death*. Newport, South Wales, UK: National Statistics.

DASA. 2009. 1990/1991 *Gulf Conflict—UK Gulf veterans mortality data: Causes of death, 31 Dec 2008*. Bath, UK: National Statistics.

Davy, C., A. Dobson, E. Lawrence-Wood, M. Lorimer, K. Moores, A. Lawrence, K. Horsley, A. Crockett, and A. McFarlane. 2012. *The Middle East Area of Operations (MEAO) health study: Prospective study*. University of Adelaide, Centre for Military and Veterans Health, Adelaide, Australia. https://www.defence.gov.au/Health/Home/Docs/130318-MEAOProspectiveStudyReportVol1.pdf (accessed April 2, 2020).

De Giacomi, F., R. V. Eunhee, S. Yi, and J. H. Ryu. 2018. Acute eosinophilic pneumonia: Causes, diagnosis, and management. *American Journal of Respiratory and Critical Care Medicine* 197(6):728–736.

DelVecchio, S. P., J. F. Collen, L. L. Zacher, and M. J. Morris. 2015. The impact of combat deployment on asthma diagnosis and severity. *Journal of Asthma* 53(4):363–369.

Díaz-Sanchez, D., M. P, Garcia., M. Wang, M. Jyrala, and A. Saxon. 1999. Nasal challenge with diesel exhaust particles can induce sensitization to a neoallergen in the human mucosa. *Journal of Allergy and Clinical Immunology* 104(6):1183–1188.

Díaz Santana, M. V., S. Eber, S. Barth, Y. Cypel, E. Dursa, and A. Schneiderman. 2017. Health-related quality of life among U.S. veterans of Operations Enduring Freedom and Operation Iraqi Freedom: Results from a population-based study. *Military Medicine* 182(11/12):e1885–e1891.

Dion, G. R., C. L. Miller, R. G. Ramos, P. D. O'Connor, and N. S. Howard. 2013. Characterization of voice disorders in deployed and nondeployed U.S. Army soldiers. *Journal of Voice* 27(1):57–59.

Doebbeling, B. N.,W. R. Clarke, J. C. Torner, R. F. Woolson, M. D. Voelker, D. H. Barrett, and D. A. Schwartz. 2000. Is there a Persian Gulf War syndrome? Evidence from a large population-based survey of veterans and nondeployed controls. *American Journal of Medicine* 108(9):695–704.

Dunn, N. M., R. K. Katial, and F. C. L. Hoyte. 2015. Vocal cord dysfunction: A review. *Asthma Research and Practice* 1(1):1–8.

Dursa, E. K., S. K. Barth, R. M. Bossarte, and A. I. Schneiderman. 2016a. Demographic, military, and health characteristics of VA health care users and nonusers who served in or during Operation Enduring Freedom or Operation Iraqi Freedom, 2009–2011. *Public Health Reports* 131(6):839–843.

Dursa, E. K., S. K. Barth, A. I. Schneiderman, and R. M. Bossarte. 2016b. Physical and mental health status of Gulf War and Gulf Era Veterans. *Journal of Occupational and Environmental Medicine* 58(1):41–46.

Dursa, E. K., S. K. Barth, B. W. Porter, and A. I. Schneiderman. 2019. Health status of female and male Gulf War and Gulf Era veterans: A population-based study. *Womens Health Issues* 29(Suppl 1):S39–S46.

Eick, A. A., D. J. Faix, S. K. Tobler, R. L. Nevin, L. E. Lindler, Z. Hu, J. L. Sanchez, V. H. MacIntosh, and K. L. Russell. 2011. Serosurvey of bacterial and viral respiratory pathogen among deployed U.S. service members. *American Journal of Preventive Medicine* 41(6):573–580.

Eisen, S. A., H. K. Kang, F. M. Murphy, M. S. Blanchard, D. J. Reda, W. G. Henderson, R. Toomey, L. W. Jackson, R. Alpern, B. J. Parks, N. Klimas, C. Hall, H. S. Pak, J. Hunter, J. Karlinsky, M. J. Battistone, M. J. Lyons, and Gulf War Study Participating Investigators. 2005. Gulf War veterans' health: Medical evaluation of a U.S. cohort. *Annals of International Medicine* 142(11):881–890.

Epler, G. R. 2010. Diagnosis and treatment of constrictive bronchiolitis. *F1000 Medicine Reports* 2(32):1–5.

Epler, G. R., and T. V. Colby. 1983. The spectrum of bronchiolitis obliterans. *Chest* 83(2):161–162.

Falvo, M. J., J. H. Abraham, O. Y. Osinubi, J. Klein, A. M. Sotolongo, D. Ndirangu, L. A. Patrick-DeLuca, and D. A. Helmer. 2016a. Bronchodilator responsiveness and airflow limitation are associated with deployment length in Iraq and Afghanistan Veterans. *Journal of Occupational and Environment Medicine* 58(4):325–328.

Falvo, M. J., D. A. Helmer, J. C. Klein, O. Y. Osinubi, D. Ndirangu, L. A. Patrick-DeLuca, and A. M. Sotolongo. 2016b. Isolated diffusing capacity reduction is a common clinical presentation in deployed Iraq and Afghanistan veterans with deployment-related environmental exposures. *Clinical Respiratory Journal* 12:795–798.

Ferris, B. G. 1978. Epidemiology Standardization Project. II. Recommended respiratory disease questionnaires for use with adults and children in epidemiological research. *American Review of Respiratory Disease* 118:7–57.

Forbes, D. A., J. T. Anderson, J. A. Hamilton, F. A. Rawlins, C. Tinkelpaugh, J. H. Abraham, and M. J. Morris. 2019. Relationship to deployment on sarcoidosis staging and severity in military personnel. *Military Medicine* 185(5–6):e804–e810.

Gackstetter, G. D., T. I. Hooper, S. F. DeBakey, A. Johnson, B. E. Nagaraj, J. M. Heller, and H. K. Kang. 2006. Fatal motor vehicle crashes among veterans of the 1991 Gulf War and exposure to munitions demolitions at Khamisiyah: A nested case–control study. *American Journal of Industrial Medicine* 49(4):261–270.

Garshick, E. 2019. Service and Health Among Deployed Veterans (SHADE). Update: VA cooperative study #595: Pulmonary health and deployment to Southwest Asia and Afghanistan. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019.

Gerke, A. K., M. A. Judson, Y. C. Cozier, D. A. Culver, and L. L. Koth. 2017. Disease burden and variability in sarcoidosis. *Annals of the American Thoracic Society* 14(6):S421–S428.

GINA (Global Initiative for Asthma). 2019. *Global strategy for asthma management and prevention*. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf (accessed April 30, 2020).

GOLD (Global Initiative for Chronic Obstructive Lung Disease). 2018. *Global strategy for prevention, diagnosis and management of COPD (2018 Report)*. www.goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf (accessed March 28, 2020).

Goss Gilroy Inc. 1998. *Health study of Canadian forces personnel involved in the 1991 conflict in the Persian Gulf: Volume 1*. Ottawa, Canada: Goss Gilroy Inc. and Department of National Defence.

Graham, B. L., I. Steenbruggen, M. R. Miller, I. Z. Barjaktarevic, B. G. Cooper, G. L. Hall, et al. 2019. Standardization of spirometry: 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. *American Journal of Respiratory and Critical Care Medicine* 200(8):e70–e88.

Gray, G. C., and H. K. Kang. 2006. Healthcare utilization and mortality among veterans of the Gulf War. *Philosophical Transaction of the Royal Society B* 361:553–569.

Gray, G. C., K. S. Kaiser, A. W. Hawksworth, F. W. Hall, and E. Barrett-Connor. 1999. Increased postwar symptoms and psychological morbidity among U.S. Navy Gulf War veterans. *American Journal of Tropical Medicine and Hygiene* 60(5):758–766.

Gray, G. C., T. C. Smith, H. K. Kang, and J. D. Knoke. 2000. Are Gulf War veterans suffering war-related illnesses? Federal and civilian hospitalizations examined, June 1991 to December 1994. *American Journal of Epidemiology* 151(1):63–71.

Gray, G. C., R. J. Reed, K. S. Kaiser, T. C. Smith, and V. M. Gastanaga. 2002. Self-reported symptoms and medical conditions among 11, 868 Gulf War-era veterans: The Seabee Health Study. *American Journal of Epidemiology* 155(11):1033–1044.

Gutor, S., R.-H. Du, R. F. Miller, B. W. Richmond, P. P. Massion, T. S. Blackwell, and V. V. Polosukhin. 2019. The histopathological basis of airflow limitation in small airways disease. In C108. COPD: Phenotype, mechanism, and treatment. *American Journal of Respiratory and Critical Care Medicine* 199:A5784.

Gwini, S. M., H. L. Kelsall, J. F. Ikin, M. R. Sim, A. C. McFarlane, and A. B. Forbes. 2016. New onset of chronic diseases and changes in lifestyle risk factors among Gulf War veterans. *Journal of Occupational and Environmental Medicine* 58(8):770–777.

Haley, R. W. 2003. Excess incidence of ALS in young Gulf War veterans. *Neurology* 61(6):750–756.

Hena, K. M., J. Yip, N. Jaber, D. Goldfarb, K. Fullam, K. Cleven, W. Moir, Rachel Zeig-Owens, M. P. Webber, D. M. Spevack, M. A. Judson, L. Maier, A. Krumerman, A. Aizer, S. D. Spivack, J. Berman, T. K. Aldrich, and D. J. Prezant. 2018. Clinical course of sarcoidosis in World Trade Center–exposed firefighters. *Chest* 153(1):114–123.

Henneberger, P. K., C. A. Redlich, D. B. Callahan, P. Harber, C. Lemiere, J. Martin, S. M. Tarlo, O. Vandenplas, and K. Toren. 2011. An official American Thoracic Society statement: Work-exacerbated asthma. *American Journal of Respiratory and Critical Care Medicine* 184(3):368–378.

Higgins, T. S., and D. D. Reh. 2012. Environmental pollutants and allergic rhinitis. *Current Opinion in Otolaryngology & Head and Neck Surgery* 20(3):209–214.

Hines, S. E., P. Gucer, S. Kligerman, R. Breyer, J. Centeno, J. Gaitens, M. Oliver, S. Engelhardt, K. Squibb, and M. McDiarmid. 2013. Pulmonary health effects in Gulf War I service members exposed to depleted uranium. *Journal of Occupational and Environmental Medicine* 55(8):937–944.

Holley, A. B., M. Sobieszczyk, M. Perkins, B. M. Cohee, C. B. Costantoth, D. L. Mabe, R. Liotta, J. H. Abraham, P. R. Holley, and J. Sherner. 2016. Lung function abnormalities among service members returning from Iraq or Afghanistan with respiratory complaints. *Respiratory Medicine* 118:84–87.

Hooper, T. I., S. F. Debakey, B. E. Nagaraj, K. S. Bellis, B. Smith, T. C. Smith, and G. D. Gackstetter. 2008. The long-term hospitalization experience following military service in the 1991 Gulf War among veterans remaining on active duty, 1994–2004. *BMC Public Health* 8:60.

Hooper, T. I., G. D. Gackstetter, C. A. LeardMann, E. J. Boyko, L. A. Pearse, B. Smith, P. J. Amoroso, and T. C. Smith. 2010. Early mortality experience in a large military cohort and a comparison of mortality data sources. *Population Health Metrics* 8:15.

Hwang, J. A., J. H. Song, J. H. Kim, M. P. Chung, J. W. Song, Y. W. Kim, S. M. Choi, S. I. Cha, S. T. Uh, C-S Park, S. H. Jeong, Y. B. Park, H. L. Lee, J. W. Shin, E. J. Lee, Y. Jegal, H. K. Lee, J. S. Park, and M. S. Park. 2017. Clinical significance of cigarette smoking and dust exposure in pulmonary alveolar proteinosis: A Korean national survey. *BMC Pulmonary Medicine* 17(1):147.

Hyams, K. C., K. Hanson, F. S. Wignall, J. Escamilla, and E. C. Oldfield. 1995. The impact of infectious diseases on the health of U.S. troops deployed to the Persian Gulf during Operations Desert Shield and Desert Storm. *Clinical Infectious Disease* 20(6):1497–1504.

IOM (Institute of Medicine). 2003a. *Gulf War and health: Volume 2: Insecticides and solvents*. Washington, DC: The National Academies Press.

IOM. 2003b. *Medicolegal death investigation system*. Washington, DC: The National Academies Press.

IOM. 2005. *Gulf War and health: Volume 3: Fuels, combustions, products, and propellants*. Washington, DC: The National Academies Press.

IOM. 2006. *Gulf War and health: Volume 4: Health effects of serving in the Gulf War.* Washington, DC: The National Academies Press.

IOM. 2008. *Gulf War and health: Volume 6: Physiologic, psychologic, and psychosocial effects of deployment-related stress*. Washington, DC: The National Academies Press.

IOM. 2010. *Gulf War and health: Volume 8: Update of health effects of serving in the Gulf War*. Washington, DC: The National Academies Press.

IOM. 2011. *Long-term health consequences of exposure to burn pits in Iraq and Afghanistan*. Washington, DC: The National Academies Press.

IOM. 2014. *Gulf War and health: Volume 9: Long-term effects of blast exposure*. Washington, DC: The National Academies Press.

Iowa Persian Gulf Study Group. 1997. Self-reported illness and health status among Gulf War veterans. *JAMA* 277(3):238–245.

Ishii, H., R. Tazawa, C. Kaneko, T. Saraya. Y. Inoue, E. Hamano, Y. Kogure, K. Tomii, M. Terada, T. Takada, M. Hojo, A. Nishida, T. Ichiwata, B. C. Trapnell, H. Goto, and K. Nakata. 2011. Clinical features of secondary alveolar proteinsis: Pre-mortem cases in Japan. *European Respiratory Journal* 37:465–468.

Ishoy, T., P. Suadicani, B. Guldager, M. Appleyard, H. O. Hein, and F. Gyntelberg. 1999. State of health after deployment in the Persian Gulf: The Danish Gulf War Study. *Danish Medical Bulletin* 46(5):416–419.

Jackson, M., B. J. Bercerra, C. Marmolejo, R. M. Avina, N. Henley, and M. B. Becerra. 2017. Prevalence and correlates of sleep apnea among U.S. male veterans, 2005–2014. *Preventing Chronic Disease* 14(E46):1–5.

Jani, N., M. J. Falvo, A. Sotolongo, O. Y. Osinubi, C. Tseng, M. Rowneki, M. Montopoli, S. W. Morley, V. Mitchell, and D. A. Helmer. 2017a. Blast injury and cardiopulmonary symptoms in US veterans: Analysis of a national registry. *Annals of Internal Medicine* 167(10):753–755.

Jani, N., M. Falvo, A. Sotolongo, O. Osinubi, C. L. Tseng, M. Rowneki, M. Montopoli, S. Morley, V. Mitchell, and D. Helmer. 2017b. Self-reports of constrictive bronchiolitis among service members participating in the Veterans Administration and Department of Defense Airborne Hazards and Open Burn Pit Registry. *Chest* 152(4):A822.

Kang, H. K., and T. A. Bullman. 1996. Mortality among U.S. veterans of the Persian Gulf War. *New England Journal of Medicine* 335(20):1498–1504.

Kang, H. K., and T. A. Bullman. 2001. Mortality among U.S. veterans of the Persian Gulf War: 7-year follow-up. *American Journal of Epidemiology* 154(5):399–405.

Kang, H. K., C. M. Mahan, K. Y. Lee, C. A. Magee, and F. M. Murphy. 2000. Illnesses among United States veterans of the Gulf War: A population-based survey of 30,000 veterans. *Journal of Occupational and Environmental Medicine* 42(5):491–501.

Kang, H. K., B. Li, C. M. Mahan, S. A. Eisen, and C. C. Engel. 2009. Health of U.S. veterans of 1991 Gulf War: A follow-up survey in 10 years. *Journal of Occupational and Environmental Medicine* 51(4):401–410.

Karlinsky, J. B., M. Blanchard, R. Alpern, S. A. Eisen, H. Kang, F. M. Murphy, and D. J. Reda. 2004. Late prevalence of respiratory symptoms and pulmonary function abnormalities in Gulf War I veterans. *Archives of Internal Medicine* 164(22):2488–2491.

Kelsall, H. L., M. R. Sim, A. B. Forbes, D. P. McKenzie, J. F. Ikin, M. J. Abramson. 2004. Respiratory health status of Australian veterans of the 1991 Gulf War and the effects of exposure to oil fire smoke and dust storms. *Thorax* 59(10):897–903.

Kenn, K., and M. M. Hess. 2008. Vocal cord dysfunction: An important differential diagnosis of bronchial asthma. *Deutsches Ärzteblatt International* 105(41):699–704.

Khalil, L., R. B. McNeil, K. J. Sims, K. A. Felder, E. R. Hauser, K. M. Goldstein, C. I. Voils, N. G. Klimas, M. T. Brophy, C. M. Thomas, and R. L. Whitley. 2018. The Gulf War Era Cohort and Biorepository: A longitudinal research resource of veterans of the 1990–1991 Gulf War Era. *American Journal of Epidemiology* 187(11):2279–2291.

King, M. S., R. Miller, J. Johnson, M. Ninan, E. Lambright, A. F. Shorr, and J. Sheller. 2008. Bronchiolitis in soldiers with inhalation exposures in the Iraq War. Poster presented at the American Thoracic Society's 104th International Conference, Toronto, Canada, May 2008.

King, M. S., R. Eisenberg, J. H. Newman, J. J. Tolle, F. E. Harrell, Jr., H. Nian, M. Ninan, E. S. Lambright, J. R. Sheller, J. E. Johnson, and R. F. Miller. 2011. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. *New England Journal of Medicine* 365(3):222–230.

Klein-Adams, J. C., A. M. Sotolongo, J. M. Serrador, D. S. Ndirangu, and M. J. Falvo. 2019. Exercise-induced bronchoconstriction in Iraq and Afghanistan veterans with deployment-related exposures. *Military Medicine* 185(3–4):e389–e396.

Knapik, J. J., R. E. Marin, T. L. Grier, and B. H. Jones. 2009. A systematic review of post-deployment injury-related mortality among military personnel deployed to conflict zones. *BMC Public Health* 9:231–253.

Korzeniewski, K., and R. Brzozowski. 2011. Sickness profile among Polish troops deployed to Afghanistan in the years 2003–2005. *International Maritime Health* 62(1):63–70.

Korzeniewski, K., A. Nitsch-Osuch, M. Konarski, A. Guzek, E. Prokop, and K. Bieniuk. 2013. Prevalence of acute respiratory tract diseases among soldiers deployed for military operations in Iraq and Afghanistan. *Advances in Experimental Medicine and Biology* 788:117–124.

Krefft, S. D., M. Strand, J. Smith, C. Stroup, R. Meehan, and C. Rose. 2017. Utility of Kung clearance index testing as a noninvasive marker of deployment-related lung disease. *Journal of Occupational and Environmental Medicine* 59(8):707–711.

Krefft, S. D., J. Wolff, L. Zell-Baran, M. Strand, E. B. Gottschall, R. Meehan, and C. S. Rose. 2020. Respiratory diseases in post-9/11 military personnel following Southwest Asia deployment. *Journal of Occupational and Environmental Medicine* 62(5):337–343.

Kreiss, K. 2013. Occupational causes of constrictive bronchiolitis. *Current Opinion in Allergy Clinical Immunology* 13(2):167–172.

Kuschner, W. G. 2011. Constrictive bronchiolitis in soldiers: Reply. *New England Journal of Medicine* 365(18):1744.

Lange, J. L., D. A. Schwartz, B. N. Doebbeling, J. M. Heller, and P. S. Thorne. 2002. Exposures to the Kuwait oil fires and their association with asthma and bronchitis among Gulf War veterans. *Environmental Health Perspectives* 110(11):1141–1146.

Li, B., C. M. Mahan, H. K. Kang, S. A. Eisen, and C. C. Engel. 2011. Longitudinal health study of U.S. 1991 Gulf War Veterans: Changes in health status at 10-year follow-up. *American Journal of Epidemiology* 174(7):761–768.

Lin, H. H., M. Ezzati, and M. Murray. 2007. Tobacco smoke, indoor air pollution and tuberculosis: A systematic review and meta-analysis. *PLOS Medicine* 4 (1):e20.

Lincoln, A. E., T. I. Hooper, H. K. Kang, S. F. Debakey, D. N. Cowan, and G. D. Gackstetter. 2006. Motor vehicle fatalities among Gulf War Era veterans: Characteristics, mechanisms, and circumstances. *Traffic Injury Prevention* 7(1):31–37.

Lindheimer, J. B., D. B. Cook, J. C. Klein-Adams, W. Qian, H. Z. Hill, G. Lange, D. S. Ndirangu, G. R. Wylie, and M. J. Falvo. 2019. Veterans with Gulf War illness exhibit distinct respiratory patterns during maximal cardiopulmonary exercise. *PLOS ONE* 14(11):1–14.

Liu, J., N. Lezama, J. Gasper, J. Kawata, S. Morley, D. Helmer, and P. Ciminera. 2016. Burn pit emissions exposure and respiratory and cardiovascular conditions among Airborne Hazards and Open Burn Pit Registry participants. *Journal of Occupational and Environmental Medicine* 58(7):e249–e255.

Macfarlane, G. J., E. Thomas, and N. Cherry. 2000. Mortality among UK Gulf War veterans. *Lancet* 356(9223):17–21.

Macfarlane, G. J., A. M. Biggs, N. Maconochie, M. Hotopf, P. Doyle, and M. Lunt. 2003. Incidence of cancer among UK Gulf War veterans: Cohort study. *British Medicine Journal* 327(7428):1373–1375.

Macfarlane, G. J., M. Hotopf, N. Maconochie, N. Blatchley, A. Richards, and M. Lunt. 2005. Long-term mortality amongst Gulf War veterans: Is there a relationship with experiences during deployment and subsequent morbidity? *International Journal of Epidemiology* 34(6):1403–1408.

Madar, C. S., M. R. Lewin-Smith, T. J. Franks, R. A. Harley, J. S. Klaric, and M. J. Morris. 2017. Histological diagnoses of military personnel undergoing lung biopsy after deployment to Southwest Asia. *Lung* 195(4):507–515.

Mancuso, J. D. 2017. Tuberculosis screening and control in the U.S. military in war and peace. *American Journal of Public Health* 107(1):60–67.

Matthews, T., J. Abraham, L. L. Zacher, and M. J. Morris. 2014. The impact of deployment on COPD in active duty military personnel. *Military Medicine* 179(11):1273–1278.

Maule, A. L., P. A. Janulewicz, K. A. Sullivan, M. H. Krengel, M. K. Yee, M. McClean, and R. F. White. 2018. Meta-analysis of self-reported health symptoms in 1990–1991 Gulf War and Gulf War–era veteran. *BMJ Open* 8(e016086):1–12.

Maynard, C., R. Trivedi, K. Nelson, and S. D. Fihn. 2018a. Disability rating age at death, and cause of death in U.S. veterans with service-connected connections. *Military Medicine* 183(11–12):e371–e376.

Maynard, C., K. Nelson, and S. D. Fihn. 2018b. Disability rating and 1-year mortality among veterans with service-connected health conditions. *Public Health Reports* 133(6):692–699.

Mayo Clinic. 2016. *TB risk factors*. https://www.cdc.gov/tb/topic/basics/risk.htm (accessed August 5, 2019).

Mayo Clinic. 2017. *Bronchitis*. https://www.mayoclinic.org/diseases-conditions/bronchitis/symptoms-causes/syc-20355566 (accessed July 22, 2019).

Mayo Clinic. 2018a. *Asthma*. https://www.mayoclinic.org/diseases-conditions/asthma/symptoms-causes/syc-20369653 (accessed July 22, 2019).

Mayo Clinic. 2018b. *Pneumonitis*. https://www.mayoclinic.org/diseases-conditions/pneumonitis/symptoms-causes/syc-20352623 (accessed July 22, 2019).

Mayo Clinic. 2018c. *Pneumonia*. https://www.mayoclinic.org/diseases-conditions/pneumonia/symptoms-causes/syc-20354204 (accessed July 19, 2019).

Mayo Clinic. 2019a. *Chronic cough*. https://www. mayoclinic.org/diseases-conditions/chronic-cough/symptoms-causes/syc-20351575 (accessed August 5, 2019).

Mayo Clinic. 2019b. *Shortness of breath*. https://www.mayoclinic.org/symptoms/shortness-of-breath/basics/definition/sym-20050890 (accessed August 5, 2019).

Mayo Clinic. 2020. *Sleep apnea*. https://www.mayoclinic.org/diseases-conditions/sleep-apnea/symptoms-causes/syc-20377631 (accessed July 4, 2020).

McCarthy, C., R. Avetisyan, B. C. Carey, C. Chalk, and B. C. Trapnell. 2018. Prevalence and healthcare burden of pulmonary alveolar proteinosis. *Orphanet Journal of Rare Diseases* 13(129):1–5.

Meadows, S. O., C. C. Engel, R. L. Collins, R. L. Beckman, M. Cefalulu, J. Hawes-Dawson, M. Waymouth, A. M. Kress, L. Sontag-Padilla, R. Ramchand, and K. M. Williams. 2018. 2015 Department of Defense Health Related Behaviors Survey (HRBS). *RAND Health Quarterly* 8(2):5.

Meffert, B. N., D. M. Morabito, D. A. Sawicki, C. Hausman, S. M. Southwick, R. H. Pietrzak, and A. J. Heinz. 2019. U.S. veterans who do and do not utilize VA healthcare services: Demographic, military, medical, and psychosocial characteristics. *Primary Care Companion for CNS Disorders* 21(1):1–18.

Miller, D., S. Sazgar, and B. Natt. 2019. The Hamman Rich Syndrome: A case of recurrent acute interstitial pneumonia. In C65. Diffuse Parenchymal Lung Diseases: Basic and Clinical Studies. *American Journal of Respiratory and Critical Care Medicine* A5439. https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A5439 (accessed May 13, 2020).

Miller, R. 2009. Airway injury in U.S. soldiers following service in Iraq and Afghanistan. In U.S. Senate Committee on Veterans' Affairs Hearing. http://www.veterans.senate.gov/imo/media/doc/miller_100809.pdf (accessed August 31, 2020).

Morris, M. J., and L. L. Zacher. 2011. Constrictive bronchiolitis in soldiers: Reply. *New England Journal of Medicine* 365(18):1743–1744.

Morris, M. J., R. T. Oleszewski, J. B. Sterner, and P. F. Allan. 2013. Vocal cord dysfunction related to combat deployment. *Military Medicine* 178(11):1208–1212.

Morris, M. J., D. W. Dodson, P. F. Lucero, G. D. Haislip, R. A. Gallup, K. L. Nicholson, and L. L. Zacher. 2014. Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE). *American Journal of Respiratory and Critical Care Medicine* 190(1):78–84.

Morris, M. J., A. J. Skabelund, F. A. Rawlins III, R. A. Gallup, J. K. Aden, and A. B. Holley. 2019. Study of Active Duty Military Personnel for Environmental Deployment Exposures: Pre- and Post-Deployment Spirometry (STAMPEDE II). *Respiratory Care* 64(5):536–544.

Morris, M. J., R. J. Walter, E. T. McCann, J. H. Sherner, C. Murillo, B. Barber, J. C. Hunninghake, and A. B. Holley. 2020. Clinical evaluation of deployed military personnel with chronic respiratory symptoms: Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE) III. *Chest* 157(6):1559–1567.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2016. *Gulf War and health: Volume 10: Update of health effects of serving in the Gulf War, 2016*. Washington, DC: The National Academies Press.

NASEM. 2017. *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry*. Washington, DC: The National Academies Press.

NHLBI (National Heart, Lung, and Blood Institute). 2015. *Sarcoidosis*. https://www.nhlbi.nih.gov/health-topics/sarcoidosis (accessed July 22, 2019).

NHLBI. 2020a. *Alpha-1 antitrypsin deficiency*. https://www.nhlbi.nih.gov/health-topics/alpha-1-antitrypsin-deficiency (accessed March 28, 2020).

NHLBI. 2020b. *COPD*. https://www.nhlbi.nih.gov/health-topics/copd (accessed March 25, 2020).

Nisenbaum, R., K. Ismail, S. Wessely, C. Unwin, L. Hull, and W. C. Reeves. 2004. Dichotomous factor analysis of symptoms reported by U.K. and U.S. veterans of the 1991 Gulf War. *Population Health Metrics* 2(1):8.

NLM (National Library of Medicine). 2019. Idiopathic pulmonary fibrosis. https://ghr.nlm.nih.gov/condition/idiopathic-pulmonary-fibrosis#statistics (accessed August 5, 2019).

NORD (National Organization for Rare Disorders). 2017. *Pulmonary alveolar proteinosis*. https://rarediseases.org/rare-diseases/pulmonary-alveolar-proteinosis (accessed August 5, 2019)

O'Donnell, D. E., S. M. Revill, and K. A. Webb. 2001. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 164:770–777.

OIF SAPEG (Operation Iraqi Freedom Severe Acute Pneumonitis Epidemiology Group). 2003. Severe acute pneumonitis among deployed U.S. military personnel—Southwest Asia, March–August 2003. *Morbidity and Mortality Weekly Report* 52(36):857–859.

Oster, C. N., and J. P. Sanford. 1992. Febrile illness in a desert storm veteran. *Hospital Practice (Office Edition)* 27(11):145–148, 151, 155–160.

Peacock, M. D., M. J. Morris, M. A. Houghland, G. T. Anders, and H. M. Blanton. 1997. Sleep apnea–hypopnea syndrome in a sample of veterans of the Persian Gulf War. *Military Medicine* 162(4):249–251.

Pereira, C. A, A. Gimenez, L. Kuranishi, and K. Storrer. 2016. Chronic hypersensitivity pneumonitis. *Journal of Asthma and Allergy* 9:171–181.

Petruccelli, B. P., M. Goldenbaum, B. Scott, R. Lachiver, D. Kanjarpane, E. Elliott, M. Francis, M. A. McDiarmid, and D. Deeter. 1999. Health effects of the 1991 Kuwait Oil Fires: A survey of U.S. Army troops. *Journal of Occupational and Environment Medicine* 41(6):433–439.

Polosukhin, V. V., B. Richmond, R. Du, L. B. Ware, J. Lee, R. F. Miller, A. Harris, and T. S. Blackwell. 2017. Loss of multiciliated epithelium and impaired mucosal immunity in lungs of soldiers with constrictive bronchiolitis. Abstract, Session D98: Insights into environmental exposure in asthma, COPD, and constructive bronchiolitis. *American Journal Respiratory and Critical Care Medicine* 195:A7337. https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A7337 (accessed May 13, 2020).

Polosukhin, V. V., B. W. Richmond, R.-H. Du, L. B. Ware, J. W. Lee, A. L. Harris, R. F. Miller, and T. S. Blackwell. 2018. Comparative histological and morphometrical analysis of small conducting airways in constrictive bronchiolitis and chronic obstructive pulmonary disease. Abstract, Session B64: COPD: Lung Function, Imaging and Pathophysiology. *American Journal of Respiratory and Critical Care Medicine* 197:A3914. https://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A3914 (accessed May 13, 2020).

Proctor, S. P., T. Heeren, R. F. White, J. Wolfe, M. S. Borgos, J. D. Davis, L. Pepper, R. Clapp, P. B. Sutker, J. J. Vasterling, and D. Ozonoff. 1998. Health status of Persian Gulf War veterans: Self-reported symptoms, environmental exposures and the effect of stress. *International Journal of Epidemiology* 27(6):1000–1010.

Pugh, M. J., C. A. Jaramillo, K. Leung, P. Faverio, N. Fleming, E. Mortensen, M. E. Amuan, C. Wang, B. Eapen, M. Restrepo, and M. J. Morris. 2016. Increasing prevalence of chronic lung disease in veterans of the Wars in Iraq and Afghanistan. *Military Medicine* 181(5):476–481.

Quirce, S., O. Vandenplas, P. Campo, M. J. Cruz, F. de Blay, D. Koschel, G. Moscato, G. Pala, M. Raulf, J. Sastrem, A. Siracusa, S. M. Tarlo, J. Walusiak-Skorupa, and Y. Cormier. 2016. Occupational hypersensitivity pneumonitis: An EAACI position paper. *Allergy* 71(6):765–779.

Rawat, D., H. Basit, and S. Sharma. 2019. Dyspnea. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK499965 (accessed July 3, 2020).

Reddel, H. K., D. R. Taylor, E. D. Bateman, L. P. Boulet, H. A. Boushey, W. W. Busse, T. B. Casale, P. Chanez, P. L. Enright, P. G. Gibson, J. C. de Jongste, H. A. M. Kerstjens, S. C. Lazarus, M. L. Levy, P. M. O'Byrne, M. R. Partridge, I. D. Pavord, M. R. Sears, P. J. Sterk, S. W. Stoloff, S. D. Sullivan, S. J. Szefler, M. D. Thomas, and S. E. Wenzel. 2009. An official American Thoracic Society/European Respiratory Society Statement: Asthma control and exacerbations: Standardizing endpoints for clinical asthma trials and clinical practice. *American Journal of Respiratory and Critical Care Medicine* 180(1):59–99.

Redlich, C. A., S. M. Tarlo, J. L. Hankinson, M. C. Townsend, W. L. Eschenbacher, S. G. Von Essen, T. Sigsgaard, and D. N. Weissman. 2014. Official American Thoracic Society Technical Standards: Spirometry in the occupational setting. *American Journal of Respiratory and Critical Care Medicine* 189(8):984–994.

Riddle, M. S., D. R. Tribble, S. D. Putnam, et al. 2008. Past trends and current status of self-reported incidence and impact of disease and nonbattle injury in military operations in Southwest Asia and the Middle East. *American Journal of Public Health* 98(12):2199–2206.

Rivera, A. C., T. M. Powell, E J. Boyko, R. U. Lee, D. J. Faix, D. D. Luxton, and R. P. Rull. 2018. New-onset asthma and combat deployment: Findings from the Millennium Cohort Study. *American Journal of Epidemiology* 187(10):2136–2144.

Rohrbeck, P., Z. Hu, and T. M. Mallon. 2016. Assessing health outcomes after environmental exposures associated with open pit burning in deployed U.S. service members. *Journal of Occupational and Environmental Medicine* 58(85):S104–S110.

Rom, W. N., M. Weiden, R. Garcia, T. A. Yie, P. Vathesatogkit, D. B. Tse, G. McGuiness, V. Roggli, and D. Prezant. 2002. Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. *American Journal of Respiratory and Critical Care Medicine* 166(6):797–800.

Roop, S.A., A. S. Niven, B. E. Calvin, J. Bader, and L. L. Zacher. 2007. The prevalence and impact of respiratory symptoms in asthmatics and nonasthmatics during deployment. *Military Medicine* 172(12):1264–1269.

Sá-Sousa, A., T. Jacinto, L. Azevedo, M. Morais-Almeida, C. Robalo-Cordeiro, A. Bugalho-Almeida, et al. 2014. Operational definitions of asthma in recent epidemiological studies are inconsistent. *Clinical and Translational Allergy* 4(1):24.

Saers, J., L. Ekerljung, B. Forsberg, and C. Janson. 2017. Respiratory symptoms among Swedish soldiers after military service abroad: Association with time spent in a desert environment. *European Clinical Respiratory Journal* 4:1–6.

Sanchez, J. L., M. J. Cooper, C. A. Myers, J. F. Cummings, K. G. Vest, K. L. Russell, J. L. Sanchez, M. J. Hiser, and C. A. Gaydos. 2015. Respiratory infections in the U.S. military: Recent experience and control. *Clinical Microbiology Reviews* 28(3):743–800.

Sanders, J. W., S. D. Putnam, C. Frankart, R. W. Frenck, M. R. Monteville, M. S. Riddle, D. M. Rockbrand, T. W. Sharp, and D. R. Tribble. 2005. Impact of illness and non-combat injury during Operations Iraqi Freedom and Enduring Freedom (Afghanistan). *American Journal of Tropical Medicine and Hygiene* 73(4):713–719.

Scarupa, M. D., and M. A. Kaliner. 2009. Nonallergic rhinitis, with a focus on vasomotor rhinitis clinical importance, differential diagnosis, and effective treatment recommendations. *World Allergy Organization Journal* 2(3):20–25.

Schmidt, C. W. 2008. Linking TB and the environment: An overlooked mitigation strategy. *Environmental Health Perspectives* 116(11):A478–A485.

Sharkey, J. M., C. Baird, A. Eick-Cost, L. Clark, Z. Hu, S. Ludwig, and J. Abraham. 2015. Review of epidemiological analyses of respiratory health outcomes after military deployment to burn pit locations with respect to feasibility and design issues highlighted by the Institute of Medicine. In C. P. Baird and D. K. Harkins (eds.), *Airborne hazards related to deployment*. Fort Sam, TX: Borden Institute, U.S. Army Medical Department Center and School. Pp. 291–304.

Sharkey, J. M., J. H. Abraham, L. L. Clark, P. Rohrbeck, S. L. Ludwig, Z. Hu, and C. P. Baird. 2016. Postdeployment respiratory health care encounters following deployment to Kabul, Afghanistan: A retrospective cohort study. *Military Medicine* 181(3):265–271.

Shaw, E., L. Hermansen, W. Pugh, and M. White. 1991. *Disease and non-battle injuries among Navy and Marine Corps personnel during Operation Desert Shield/Desert Storm*. US Naval Health Research Center. https://apps.dtic.mil/dtic/tr/fulltext/u2/a250652.pdf (accessed June 18, 2020).

Shirtcliffe, P., M. Weatherall, S. Marsh, J. Travers, A. Hansell, A. McNaughton, S. Aldington, H. Muellerova, and R. Beasley. 2007. COPD prevalence in a random population survey: A matter of definition. *European Respiratory Journal* 30(2):232–239.

Shorr, A. F., S. I. Scoville, S. B. Cersovsky, C. D. Shanks, C. F. Ockenhouse, B. I. Smoak, W. W. Carr, and B. P. Petruccelli. 2004. Acute eosinophilic pneumonia among U.S. military personnel deployed in or near Iraq. *JAMA* 292(24):2997–3005.

Sim, M., D. Clarke, B. Forbes, D. Glass, S. Gwini, J. Ikin, H. Kelsall, D. McKenzie, B. Wright, A. McFarlane, M. Creamer, and K. Horsley. 2015. *Australian Gulf War Veterans' Follow Up Health Study technical report*. Canberra, Australia: Department of Veterans' Affairs. https://www.dva.gov.au/sites/default/files/files/consultation%20and%20grants/healthstudies/gulfwar/follow_up2015/aus_gulf_war_follow_up_tech_report2015.pdf (accessed June 18, 2020).

Simmons, R., N. Maconochie, and P. Doyle. 2004. Self-reported ill health in male UK Gulf War veterans: A retrospective cohort study. *BMC Public Health* 4(1):27.

Sine, C. R., P. D. Hiles, S. L. Scoville, R. L. Haynes, P. F. Allan, T. J. Franks, M. J. Morris, and E. C. Osborn. 2018. Acute eosinophilic pneumonia in the deployed military setting. *Respiratory Medicine* 137:123–128.

Singer, J. P., K. Jones, and S. C. Lazarus. 2016. Bronchiolitis and other intrathoracic airway disorders. In J. K. Stoller, V. C. Broaddus, R. J. Mason, J. D. Ernst, T. E. King, Jr., S. C. Lazarus, J. F. Murray, J. A. Nadel, and A. Slutsky (eds.), *Murray and Nadel's textbook of respiratory medicine*, 6th ed. Philadelphia, PA: Elsevier Saunders. Pp. 897–911.

Singh, A., A. Avula, and E. Zahn. 2020. Acute bronchitis. In: *StatPearls* [Internet]. Treasure Island, FL: StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK448067 (accessed June 18, 2020).

Smith, B., T. C. Smith, M. A. K. Ryan, and G. C. Gray. 2006. A comparison of the postdeployment hospitalization experience of U.S. military personnel following service in the 1991 Gulf War, Southwest Asia after the Gulf War, and Bosnia. *Journal of Occupational and Environmental Hygiene* 3(12):660–670.

Smith, B., L. K. Chu, T. C. Smith, P. J. Amoroso, E. J. Boyko, T. I. Hooper, G. D. Gackstetter, and M. A. K. Ryan. 2008. Challenges of self-reported medical conditions and medical records among members of a large military cohort. *BMC Medical Research Methodology* 8(37):1–10.

Smith, B., C. A. Wong, T. C. Smith, E. J. Boyko, G. D. Gackstetter, and M. A. K. Ryan for the Millennium Cohort Study Team. 2009. Newly reported respiratory symptoms and conditions among military personnel deployed to Iraq and Afghanistan: A prospective population-based study. *American Journal of Epidemiology* 170(11):1433–1442.

Smith, B., C. A. Wong, E. J. Boyko, C. J. Phillips, G. D. Gackstetter, M. A. Ryan, T. C. Smith, and Millennium Cohort Study Team. 2012. The effects of exposure to documented open-air burn pits on respiratory health among deployers of the Millennium Cohort Study. *Journal of Occupational and Environmental Medicine* 54(6):708–716.

Smith, T. C., J. M. Heller, T. I. Hooper, G. D. Gackstetter, and G. C. Gray. 2002. Are Gulf War veterans experiencing illness due to exposure to smoke from Kuwaiti oil well fires? Examination of Department of Defense hospitalization data. *American Journal of Epidemiology* 155(10):908–917.

Soltis, B. W., J. W. Sanders, S. D. Putnam, D. R. Tribble, and M. S. Riddle. 2009. Self reported incidence and morbidity of acute respiratory illness among deployed U.S. military in Iraq and Afghanistan. *PLOS ONE* 4(7):e6177.

Song, W., Y. Chang, S. Faruqi, J. Kim, M. Kang, S. Kim, E. Jo., M. Kim, J. Plevkova, H. Park, S. Cho, and A. H. Morice. 2015. The global epidemiology of chronic cough in adults: A systematic review and meta-analysis. *European Respiratory Journal* 45:1479–1481.

Statistics Canada. 2005. *The Canadian Persian Gulf Cohort Study: Detailed report*. http://www.veterans.gc.ca/pdf/about-us/research-directorate/gulf-war-linkage-project.pdf (accessed July 28, 2020).

Steele, L. 2000. Prevalence and patterns of Gulf War illness in Kansas veterans: Association of symptoms with characteristics of person, place, and time of military service. *American Journal of Epidemiology* 152(10):992–1002.

Szema, A. M., M. C. Peters, K. M. Weissinger, C. A. Gagliano, and J. J. Chen. 2010. New-onset asthma among soldiers serving in Iraq and Afghanistan. *Allergy and Asthma Proceedings* 31:e67–e71.

Szema, A. M., W. Salihi, K. Savary, and J. J. Chen. 2011. Respiratory symptoms necessitating spirometry among soldiers with Iraq/Afghanistan War lung injury. *Journal of Occupational and Environmental Medicine* 53(9):961–965.

Tarlo, S. M. 2006. Cough: Occupational and environmental considerations: ACCP evidence-based clinical practice guidelines. *Chest* 129(1):186S–196S.

Taylor, N., and D. Ross. 2019. Fumes and faeces in Kabul. *BMJ Military Health* 166(3):171–174.

Thunnissen, E., H. J. Blaauwgeers, E. M. de Cuba, C. Y. Yick, and D. B. Flieder. 2016. Ex vivo artifacts and histopathologic pitfalls in the lung. *Archives of Pathology & Laboratory Medicine* 140(3):212–220.

Tortora, G. J., and B. H. Derrickson. 2018. *Principles of anatomy and physiology*. New York: John Wiley & Sons.

UK (United Kingdom) Ministry of Defence. 2014. *National statistics notice: 1990/1991 Gulf conflict—UK Gulf veterans mortality data: Causes of death*. Bristol, UK: UK Ministry of Defence.

Unwin, C., N. Blatchley, W. Coker, S. Ferry, M. Hotopf, L. Hull, K. Ismail, I. Palmer, A. David, and S. Wessely. 1999. Health of UK servicemen who served in Persian Gulf War. *Lancet* 353:169–178.

VA (Department of Veterans Affairs). 2014a. *Diagnoses among deployed Gulf War veterans who used VA health care services, from 1st Qtr FY 2002 through 4th Qtr FY 2013*. Preliminary draft. Washington, DC: Veterans Health Administration.

VA. 2014b. *Diagnoses among non-deployed Gulf War veterans who used VA health care services, from 1st Qtr FY 2002 through 4th Qtr FY 2013*. *Preliminary draft*. Washington, DC: Veterans Health Administration.

VA. 2020. *Opportunities missed to contain spending on sleep apnea devices and improve veterans' outcomes*. Office of Inspector General, Office of Audits and Evaluations. Veterans Health Administration. Report #19-00021-41. https://www.va.gov/oig/pubs/VAOIG-19-00021-41.pdf (accessed August 20, 2020).

Vourlekis, J. S. 2004. Acute interstitial pneumonia. *Clinics in Chest Medicine* 25(4):739–747.

Weinstein, D. J., J. E. Hull, B. L. Ritchie, J. A. Hayes, and M. J. Morris. 2016. Exercise-associated excessive dynamic airway collapse in military personnel. *Annals of the American Thoracic Society* 13(9):1476–1482.

Winkenwerder, W. 2002. *U.S. demolition operations at Khamisiyah*. *Final report*. Washington, DC: Department of Defense. https://gulflink.health.mil/khamisiyah_iii (accessed June 17, 2020).

Woods, J., B. Barber, and M. J. Morris. 2018. *The effect of deployment on pulmonary function in active duty military members with asthma*. Abstract, Session C106: Occupational Lung Epidemiology. https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A6082 (accessed August 24, 2020).

Young, H. A., J. D. Maillard, P. H. Levine, S. J. Simmens, C. M. Mahan, and H. K. Kang. 2010. Investigating the risk of cancer in 1990–1991 U.S. Gulf War veterans with the use of state cancer registry data. *Annals of Epidemiology* 20(4):265–272.

Young, T., M. Palta, J. Dempsey, J. Skatrud, S. Weber, and S. Badr. 1993. The occurrence of sleep-disordered breathing among middle-aged adults. *New England Journal of Medicine* 328(17):1230–1235.

Zarogiannis, S. G., and S. Matalon. 2011. Constrictive bronchiolitis in soldiers: Reply. *New England Journal of Medicine* 365(18):1743.

Zundel, C. G., M. H. Krengel, T. Heeren, M. K. Yee, C. M. Grasso, P. A. Janulewicz Lloyd, S. S. Coughlin, and K. Sullivan. 2019. Rates of chronic medical conditions in 1991 Gulf War veterans compared to the general population. *International Journal of Environmental Research and Public Health* 16(6):949.

Zwerling, C., J. C. Torner, W. R. Clarke, M. D. Voelker, B. N. Doebbeling, D. H. Barrett, J. A. Merchant, R. F. Woolson, and D. A. Schwartz. 2000. Self-reported postwar injuries among Gulf War veterans. *Public Health Reports* 115(4):346–349.

5

Challenges and Opportunities for Advancing the Understanding of Respiratory Health Issues in Southwest Asia Theater Veterans

Previous chapters of the report identified putative airborne hazards present in the Southwest Asia Theater of Military Operations and Afghanistan,[1] described the respiratory health outcomes that might be associated with exposure to those hazards, and presented an evaluation of the scientific and medical evidence regarding the outcomes in military personnel who served in the theater. This chapter builds on the results of those efforts to offer insights on outstanding exposure and health questions and how the Department of Veterans Affairs (VA) could help to address them.

ISSUES IDENTIFIED FOR THE COMMITTEE'S ATTENTION

The committee's Statement of Task from VA directed it not only to evaluate the evidence regarding in-theater airborne exposures and adverse respiratory health effects but also to offer observations and recommendations on how VA might generate information that would help it to make better informed decisions in the future. Specifically, it requested that the committee "pay particular attention to hazards associated with burn pit exposures" and use the results of its comprehensive review to "identify knowledge gaps, research that could feasibly be conducted to inform the field and generate answers, newly emerging technologies that could aid in these efforts, and organizations that VA might partner with to accomplish this work."

The committee combined several sources of information to accomplish this task. These included its review of the studies of health outcomes in theater veterans (presented in Chapter 4), input from several subject-matter experts presented at an October 2019 workshop (listed in Appendix A and summarized in Chapter 3; all presentations are also posted to the web[2]), and the information and recommendations developed by previous National Academies committees that examined similar issues.

The following sections address the Statement of Task issues in the order in which they were posed.

[1] Hereafter referred to as the Southwest Asia theater or theater, in keeping with the other chapters of this report.

[2] See http://nationalacademies.org/hmd/Activities/Veterans/RespiratoryHealthEffectsofAirborneHazardsExposures/2019-OCT-3.aspx (accessed August 24, 2020).

HAZARDS ASSOCIATED WITH BURN PIT EXPOSURES

Literature Regarding the Health Effects of Exposure to Burn Pit Emissions

Concerns have long been raised over the hazards associated with exposure to emissions from the open burn pits used in theater for waste management. These exposures have been the primary topic of four earlier National Academies reports, which are first summarized followed by a discussion of findings from newer research that was summarized in earlier chapters.

Previous National Academies Reports Addressing the Health Effects of Exposure to Burn Pit Emissions

The third volume of the report series *Gulf War and Health* contained a comprehensive review of the literature addressing the association between exposure to fuels, combustion products, and propellants present in the 1990–1991 Gulf War theater and health outcomes (IOM, 2005). Combustion products were defined as "smoke from fires, exhaust from burning fuels, and products of other combustion sources" (IOM, 2005, p. 39), and it was observed that these are also constituents of air pollution in general. As noted in Chapter 4, the committee responsible for that report concluded that there was sufficient evidence of an association between combustion products and lung cancer and limited or suggestive evidence of an association between combustion-product exposure and oral, nasal, and laryngeal cancers and incident asthma. (Volumes 4, 8, and 10 of the series [IOM, 2006, 2010; NASEM, 2016b] addressed burn pit exposures but only as part of a larger examination of the health effects of service during the Gulf War—they did not draw specific conclusions about the association between these exposures in theater and health outcomes.)

Responding to a request from the U.S. Army, the National Academies formed an expert committee to review a report (Engelbrecht et al., 2008) that summarized the results of the Department of Defense's (DoD's) Enhanced Particulate Matter Surveillance Program (EPMSP) (NRC, 2010). EPMSP was an effort to characterize and quantify particulate matter (PM) in the ambient environment at 15 sites[3] in the Persian Gulf Region over 12 months in 2006–2007. That committee was also asked, among other tasks, to consider whether and how such data and other information collected by the U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM) might be put to use in assessing the health outcomes of deployed personnel. It commended the effort but found that the design and conduct of EPMSP limited its usefulness in health studies. The committee concluded that it was plausible that exposure to airborne PM—which it defined as including burn pit emissions but also such sources as windblown dust, dust storms, and diesel exhaust—was associated with adverse health outcomes but that the interpretation of the information collected in theater was encumbered by uncertainties regarding the actual exposures, the small number of study subjects, and the limited amount of exposure data. It recommended that "[a] more complete inventory of all major sources of ambient pollutants and potential emissions in the theater should be constructed before assessment of health effects to ensure that all relevant pollutants are monitored" (NRC, 2010, p. 9).

Of particular relevance to this report, the 2011 report *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan* summarized the results of studies of health effects associated with exposures to 51 pollutants that were detected in air samples taken at Joint Base Balad in Iraq[4] in 2007 and 2009 (IOM, 2011). There were a number of potential sources of these pollutants, and the committee that produced the 2011 report concluded that burn pits were not a major source of many of them. Because there were few studies on exposures of military populations to burn pits available at the time, that committee expanded its literature review to include examinations of surrogate populations whose members had occupational or residential exposures to combustion products, such as firefighters, incinerator workers, and those living near an incinerator. The committee used a

[3] The 15 sites were in the following countries: Djibouti (one), Afghanistan (two, in Bagram and Khowst), Qatar (one), United Arab Emirates (one), Iraq (six, in Balad, Baghdad, Tallil, Tikrit, Taji, and Al Asad), and Kuwait (four, in northern, central, coastal, and southern Kuwait).

[4] Joint Base Balad was one of the largest military bases in Iraq and a central logistics hub for U.S. forces there. Because of its large population, the scale of the Balad burn pit was also large, with estimates of the amount of waste burned ranging from about 2 tons per day early in its operation in 2003 to 200 tons of waste being burned daily in 2007 (APHC, 2010; Taylor et al., 2008). The burn pit ceased operating in late 2009 (IOM, 2011).

weight-of-evidence approach to determine the strength of the association between exposure to combustion products and each health outcome.

The 2011 report concluded that there was inadequate or insufficient evidence of an association between exposure to combustion products and respiratory disease or cancer in general. It did find limited or suggestive evidence of an association between exposure to combustion products and reduced pulmonary function in the study populations, but it was unable to determine whether the long-term health effects were likely to result from service members exposed to emissions from burn pits—specifically the one in operation at Joint Base Balad—because high ambient concentrations of PM from both natural and anthropogenic sources likely modified the effects, but could not be accounted for or adjusted in the analyses. Therefore, that committee concluded that the long-term health risk of airborne toxicants, burn pit, and other related exposures was not clearly defined. The report stated that none of the individual chemical constituents of the combustion products emitted from the burn pit appeared to have been present at concentrations high enough to be responsible for any of the adverse health outcomes. However, it was also noted that "the possibility of exposure to mixtures of those chemicals raises the potential for health outcomes associated with cumulative exposure to combinations of the constituents in burn pit emissions" (IOM, 2011, p. 8). Moreover, given the limitations of the literature, the information "might not provide a comprehensive picture of the risks posed to military personnel from burn pit emissions" (IOM, 2011, p. 103).

More recently, the 2017 National Academies report *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry* included an update (through early 2016) of the scientific literature regarding long-term health outcomes in service members and veterans who served in the Southwest Asia theater (NASEM, 2017). Only four of the papers it identified addressed respiratory outcomes in populations where exposure to burn pit emissions was explicitly factored: Abraham et al. (2014), Liu et al. (2016), Sharkey et al. (2015), and Smith et al. (2012). The committee observed that none of these papers provided a thorough evaluation of the health effects associated with burn pit exposures, nor did they show that service members were at an increased risk of health effects associated with burn pits in particular. It did note, though, that "other hazards may be important contributors to respiratory symptoms and disease" (NASEM, 2017, p. 24). These studies were also summarized in Chapter 4.

Newer Research Addressing the Health Effects of Exposure to Burn Pit Emissions

This report extends the summaries and reviews presented above by considering the literature published through early 2020. One additional epidemiologic study was found that overtly factors in burn pit emissions—Rohrbeck et al. (2016)—but that study addressed only diseases of the respiratory system and signs, symptoms, and ill-defined conditions involving respiratory system and other chest symptoms in general rather than specific outcomes. The study compared diseases identified during post-deployment clinical encounters in 200 service members deployed to either Joint Base Balad (n = 163) or Bagram Airfield, Afghanistan (n = 37)—both of which had burn pits in operation during the time period of their deployments—with 200 who were never deployed. Data were derived from Defense Medical Surveillance System (DMSS) records. The investigators found that when comparing specific deployed cohorts, those at Balad had statistically significant decreased adjusted risk of signs, symptoms, and ill-defined conditions involving respiratory system and other chest symptoms compared with the nondeployed cohort. There were too few counts for an effect estimate to be calculated for Bagram Airfield. Although the estimates were adjusted for age, sex, race/ethnicity, occupation, deployment history, and history of illness prior to deployment, no information on deployment duties or specific individual behaviors, including smoking was included.

Finally, as mentioned elsewhere in the chapter, investigators at the Air Force Research Laboratory (AFRL) have developed a test apparatus for examining the effects of burn pit emissions using a rat model (DelRaso et al., 2018). The apparatus consists of a 6 m high × 6 m wide × 45 m long stainless-steel tunnel with a fan at one end to simulate up to a 5-mph breeze. Materials simulating burn pit waste are burned at the inlet end of the tunnel in a manner that mimics open burn pit conditions. Preliminary results generated by the investigators attributed most of the observed effects in the experimental animals to the stress induced by testing. Additional research is under way (Mauzy, 2019) but had yet to be published when this report was completed.

Literature Regarding the Composition of Burn Pit Emissions

A small literature is also available on the composition of burn pit emissions. Emissions released by burn pits are a complex mixture of various chemicals and particulates that depend on factors such as the composition of the trash burned, the accelerant used, the temperature, the ventilation, and the burn rate (Woodall et al., 2012). Some monitoring of these emissions was conducted during the time that burn pits operated in the theater. The U.S. Army Public Health Command and the Air Force Institute for Operational Health conducted a series of ambient-air sampling and screening health-risk assessments of burn pit exposures at Joint Base Balad in 2007 and again in 2009. The assessments were designed to measure the concentration of airborne pollutants released by burning at several sites on base and to detect potentially harmful inhalation exposures for personnel (APHC, 2010; CHPPM and AFIOH, 2009; Taylor et al., 2008). Even though these efforts were limited by their inability to provide information about individual exposure assessment as well as by their inability to distinguish among the contributions from particular sources (combustion engines, burn pits, dust storms, and the like), they do yield some information about the constituents and ambient levels of airborne toxicants that may have been present on bases with burn pits. A 2011 review of the monitoring efforts at Joint Base Balad conducted by a committee of the Institute of Medicine (IOM, 2011) found that

- PM concentrations in ambient air were on average higher than U.S. pollution standards. PM was most likely a result of local sources (vehicle traffic, aircraft emissions) and regional sources (long-range anthropogenic sources, dust storms), although the burn pit likely made some contribution.
- Polychlorinated dibenzo-*p*-dioxins and dibenzo-*p*-furans (PCDD/Fs) were detected at low concentrations. Although species associated with greater toxicity were higher than generally found in the United States or in urban environments worldwide, they were lower than levels associated with some non-military sources present in the theater.
- Concentrations of volatile organic compounds (VOCs) and polycyclic aromatic hydrocarbons (PAHs) were similar to those reported in major urban areas outside the United States, with major sources being regional background, ground transportation, stationary power generation, and the airport at Joint Base Balad (IOM, 2011).

Subsequent studies also noted the contribution of the Joint Base Balad burn pit to PCDD/Fs on base as well as the important role of other sources of emissions, including the airfield, as the primary source of PAHs. Other important contributors to PAH levels were aircraft, vehicle emissions, space heaters, and diesel generators (Masiol et al., 2016a,b).

These observations were confined to the pollutants that were targeted by DoD and the conditions (meteorological, waste stream composition, operating conditions) present at the time of the measurements. Several criteria pollutants commonly monitored in the United States and likely released by burn pits were omitted by DoD's sampling, including sulfur dioxide, ozone, nitrogen dioxide, and carbon monoxide. Other pollutants not included in the sampling included those known to be associated with the burning of household waste (EPA, 1997, 2001; Lemieux et al., 2003, 2004), geologic material, carbon from combustion sources, metals from regional smelting activities, and other gaseous pollutants produced by combustion engines (Engelbrecht et al., 2009; IOM, 2011). Thus, the available monitoring data provide information on exposures to the major types of constituents from burn pit emissions, but they lack information on other chemicals that were likely present as well as on exposure variability over time (IOM, 2011).

Other data collected as part of a monitoring program for a solid waste disposal facility at the Bagram Airfield in Afghanistan emphasize the variability of exposures associated with burn pits (Blasch et al., 2016). The facility operated a burn pit from 2005 to 2012. The investigators collected breathing zone samples, unlike the case with Joint Base Balad, but only PM and VOCs were studied. The sampling was conducted at four security locations (up to 125 meters from the burn pit) and a control location (4 km from the burn pit) during 30 12-hour shifts. Among VOCs detected, only acrolein exceeded the 1-year military exposure guideline, but benzene was detected in all samples. The range of PM concentrations varied considerably in association with airfield activity (vegetation removal, removing mines and incendiary devices, road construction, vehicle traffic, industrial activity, air traffic). The highest recorded concentrations of environmental $PM_{2.5}$[5] (0.615 mg/m^3) occurred at the solid waste disposal facility where the burn pit and incinerators were located. High $PM_{2.5}$ and PM_{10}[6] concentrations were also noted at the bazaar, a highly populated site with unpaved roads and considerable vehicular traffic. The investigators thus concluded that "[t]he diversity of results support the concept of a complex environment with multiple polluting sources and changing meteorological and operational conditions" (Blasch et al., 2016, p. S38).

This information is supplemented by the content of two presentations made to the committee responsible for the National Academies report (NASEM, 2017) at a May 2015 workshop.

John Kolivosky provided an overview of an in-theater ambient air monitoring program (Kolivosky, 2015). Mr. Kolivosky was the project lead on a burn pit assessment conducted in the Deployment Environmental Surveillance Program at the Army Institute of Public Health, and he provided the committee with details on how the effort was conducted and on the data that were collected. He said that personnel would conduct site surveys to identify potential exposure to airborne hazards and collect 24-hour time-composite samples using Environmental Protection Agency methods or the equivalent. Samples were sent out of theater for analysis and later archived in the Defense Occupational and Environmental Health Readiness System–Industrial Hygiene (DOEHRS-IH). Some 20,000 samples are in the database; most of these were taken within the boundaries of bases. PM—both PM_{10} and $PM_{2.5}$—as well as heavy metals and VOC levels were measured at various times. Mr. Kolivosky indicated that there were a number of challenges associated with operating air sampling equipment in theater that limited the ability to collect good data.

Major Charlie Toth from the U.S. Air Force spoke about environmental sampling at Joint Base Balad (Toth, 2015). Major Toth focused on his knowledge of the design of the burn pit study sampling plan for the site and on personal observations from the actual collection of samples and the subsequent report. The sampling plan was a joint effort with the Army CHPPM and Air Force Institute for Operational Health. The goal was to quantify the worst-case effects of exposures to the open burn pits. The intent of investigators was to gather this information while waste incinerators were still in place and the exposure was still comparable to what the exposed population had experienced. Major Toth described his experience as an environmental engineer tasked with collecting samples near the base and creating the resulting report published from the data gathered (CHPPM and AFIOH, 2009). Between January and May 2007, samples were collected to assess the levels of dioxins, furans, PAHs, VOCs, and PM_{10} particulates. Major Toth said he recalled seeing during his time in theater a number of types of items in burn pits, including plastics, metal/aluminum cans, rubber, chemicals such as paints and solvents, petroleum, oil, lubricant products, munitions, unexploded ordnance, wood waste, and incomplete combustion byproducts, with jet fuel (JP-8) being used as the accelerant. The report summarizing this work noted that the actual number of final samples collected was relatively small and that 15% of the samples were rejected because of damage from shipping or failed pumps. The report's findings did not include input or verification from members of the team involved in the collection of data, which led, in Major Toth's view, to flaws and misinterpretation of information.

Since these reports, there has been scant additional information published on burn pit emissions. The committee identified three studies that addressed the issue. Dominguez et al. (2018) characterized emissions from the burning of meals, ready-to-eat (MRE) packaging typically found at forward operating bases in the theater. It reported that $PM_{2.5}$ constituted the vast majority of these emissions. VOCs and PAHs were also detected, along with relatively small amounts of PCDD/F congeners. Xia et al. (2016) conducted a pilot study that analyzed PAHs and PCDD/Fs in pre- and post-deployment serum samples obtained from 200 service members deployed to Iraq or Afghanistan plus an equivalent number of nondeployed controls. Many of the chemicals were found in the serum of both the deployed and the nondeployed subjects. For PAHs, naphthalene[7] was found in 83% of the samples and was statistically different in post-deployment versus pre-deployment serum, as were several PCDD/Fs. The investigators concluded that the study showed that such measurements had the potential of being used as exposure markers. Subsequently, M. R. Smith et al. (2019c) used high-resolution metabolomics to test for changes

[5] $PM_{2.5}$ refers to particulate matter with a diameter less than 2.5 microns.
[6] PM_{10} refers to particulate matter with a diameter less than 10 microns.
[7] Naphthalene is generated by biomass burning and gasoline and oil combustion. It was also used as a reptilicide in the theater.

in the levels of 271 environmental chemicals in post-deployment serum samples versus pre-deployment levels and in matched controls stationed in the United States. Of that list, 153 chemicals (56%) were detected, with nonsignificant increases in pesticide exposures found in the deployed group relative to the nondeployed. No increases in chemicals related to burn pits were reported.

Observations Regarding the Hazards Associated with Burn Pit Exposures

The committee's literature review identified relatively little evidence addressing how burn pit exposures may result in adverse respiratory health outcomes, and what epidemiologic literature there is has not found an association. This is in contrast to the much larger literature regarding exposure to airborne hazards in general and to PM in particular. Concern over burn pit exposures is understandable, given their prominence as a source of smoke, vapors, gases, and fumes in military facilities where large numbers of service members were present as well as the known toxic effects of the byproducts of combustion of the materials that were burned in them. To date, though—other than the self-reported airborne exposures and health information collected as part of such efforts as the Millennium Cohort Study and the Airborne Hazards and Open Burn Pit Registry—there have been no large-scale systematic data collection or maintenance efforts focused on the effects of exposure to burn pit emissions.[8]

There are means, though, to gain a better understanding of this issue. As part of its Statement of Task, the committee responsible for the 2011 Institute of Medicine report *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan* was asked to assist VA with the design of an epidemiologic study of the potential long-term health effects of exposure to burn pit emissions. The committee developed a detailed research plan that focused on personnel deployed to Joint Base Balad in Iraq but also encompassed veterans exposed to burn pit emissions at any U.S. military base with operating burn pits.

The committee that produced that report recommended that a cohort study of the long-term health effects of exposure to burn pits (evaluated prospectively) be conducted using retrospective estimates of exposure to burn pit emissions in military personnel deployed to the theater. The observation period for health effects would begin retrospectively at first deployment and continue after active-duty service was completed. The committee noted that to determine the incidence of chronic diseases or cancers with long latency, study subjects would need to be followed for many years. That committee recommended that pilot studies be conducted to address issues of statistical power and to develop design features for specific health outcomes, and it stated that once a prospective cohort infrastructure had been established, multiple health outcomes could be studied in the cohort over time. The committee suggested that intermediate outcomes on the pathway to the development of chronic diseases could be studied in a serial manner, offering the example of serial spirometry being used to detect excessive rates of decline in lung function before a diagnosis of chronic obstructive pulmonary disease (COPD).

This committee endorses the approach identified by the committee for *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan* as a template for comprehensively studying respiratory health outcomes in theater veterans exposed to burn pits but notes that nearly 10 years have passed since the development of that report and that refinements in and an expansion of its protocols would be appropriate. The range of exposures examined should not be limited to burn pit emissions but instead be enlarged to include all airborne contaminants for which measurements or exposure surrogates are available.

This committee notes that those deployed are often at the peak of their lung function, which occurs in their early 20s, and that exposures related to deployment, including burn pits, may increase the rate of decline in lung function over time and increase the risk for conditions such as COPD. Longitudinal studies that include baseline and lung function assessment over time as well as imaging and other respiratory assessment could be used to address this question. This chapter also cites advances in retrospective exposure assessment via biomarkers and through the analysis of historic satellite observational data, the latter of which might be particularly useful for veterans who served outside of large-scale bases like Joint Base Balad, where air sampling and other exposure information would have been more limited.

[8] Very limited in-theater air pollution data-gathering efforts have generated information that would aid in studies of those who served in the same place and at the same time as measurements were made.

KNOWLEDGE GAPS

Chapter 4 presents the committee's critique of the epidemiologic literature on respiratory health outcomes associated with in-theater exposures of active and former military personnel. This includes their judgments on the strengths and weaknesses of the current information base, notably, the several outcomes for which there was inadequate or insufficient information from which to draw a conclusion. Here the committee expands on that analysis by taking a broader view: specifically, identifying the common elements that limit our understanding of the possible nexus between in-theater airborne exposures and adverse respiratory health outcomes. Recommendations for addressing these gaps—including research that could be conducted, technologies that could brought to bear, and organizations that VA could partner with to accomplish the work—appear in later sections of the chapter.

This and the following sections of this chapter discuss but do not present comprehensive assessments of the scientific literature regarding the many potential avenues for future research that VA could conduct or foster—an undertaking outside the committee's Statement of Task.

Gaps in Knowledge Concerning Adverse Respiratory Health Outcomes in Theater Veterans

Although there have been a number of studies of respiratory health outcomes in veterans of the Southwest Asia conflicts, the committee found that there was inadequate or insufficient information from which to draw a conclusion about the association between in-theater airborne exposures and several outcomes. The reasons for these findings, as noted in Chapter 4, varied. One underlying reason was that crucial data may not have been available, as would be the case if investigators were using information derived from an administrative data set. The committee notes, for example, that several studies failed to adequately account for cigarette smoking—a known cause of respiratory health problems—in their analyses of outcomes. Another is that some health outcomes, such as pulmonary fibrosis, occur so infrequently that it can be difficult to discern empirically whether the incidence in a study population is different from what would otherwise be expected. This can be the result of a lack of knowledge concerning the background rate or the effort and expense entailed in conducting an adequately powered study. For other outcomes, such as cough, the challenge is that they occur frequently and have many potential underlying causes, making it more difficult to study the influence of any single factor without good exposure information, which the committee lacked. For constrictive bronchiolitis, an outcome that the committee was asked to give special attention to, there is an open question as to whether the diagnostic criteria for the disease are being correctly and consistently applied (Furlow, 2020; Garshick et al., 2019). And, finally, there are circumstances where a disease may not manifest for several years after an adverse exposure takes place, meaning that insufficient time may have passed since an exposure in the theater for that outcome to be observed in an epidemiologic study.

Gaps in Knowledge Concerning In-Theater Airborne Exposures

The committee enumerated a number of airborne exposures that could have influenced respiratory health outcomes in the veterans of the Southwest Asia conflicts. These include environmental and occupational exposures as well as those resulting from personal behavior and the circumstances of being deployed in the Southwest Asia theater.

Exposure characterization is a pervasive challenge in studies of the effects of exposures on military personnel. Basic information is often lacking on who was exposed, what they were exposed to where and when, at what level, over what time period, and with what frequency.

A small number of measurements were taken in various theater locations at specific times. For example, the U.S. Army CHPPM performed ambient air PM monitoring for 5 days in Sykes, Iraq, in August 2008 (CHPPM, 2008) and for 13 days in Kandahar, Afghanistan, in June 2009 (CHPPM, 2009). Longer-term monitoring data for a number of theater locations are available in periodic occupational and environmental monitoring summary (POEMS) files maintained by the Army Public Health Center (APHC, 2018). Results from many of these sampling exercises are located in the DOEHRS-IH database (DHA, 2018). A 2019 review of these POEMS, though, concluded that "inconsistent collection, assessment, and presentation of available data seriously weakens the potential utility of the POEMS files as the primary source of information on toxic exposures" (Williams and Fahey, 2019). Data on air pollutant levels in-theater or personal exposures to specific air contaminants are generally lacking.

Exposure proxies, such as a person's location and proximity to sources at specific times, are sometimes available, but even these data can be difficult to obtain, and self-reports—especially those gathered long after the putative exposure—may be subject to recall bias. Furthermore, the POEMS available are those that have been approved for public release and cleared for open publication.[9]

Past reports in the *Gulf War and Health* series have raised concern over the lack of good exposure information on depleted uranium (IOM, 2000b, 2008); insecticides and solvents (IOM, 2003); and fuels, combustion products, and propellants (IOM, 2005), among other in-theater hazards. As Volume 10 of the series states: "[t]he lack of specific individual exposure information is not unexpected in wartime situations, but it nonetheless limits the ability to draw conclusions about observed health effects" (NASEM, 2016b, p. 240). An additional complication arises with hazards such as burn pit emissions, which were highly variable over time, depending on which materials were burned and at what temperature combustion occurred (IOM, 2011; NASEM, 2017). Burn pits were later supplemented with or replaced by incinerators at some larger installations, which further complicates the evaluation of exposures over time, given the lack of emissions monitoring. These circumstances are illustrative of the gaps in information that represent a major barrier to the analysis of potential health effects.

Gaps in Knowledge Concerning the Biologic and Toxicologic Effects of In-Theater Airborne Exposures

Concomitant with the lack of information on the characteristics and levels of in-theater airborne exposures are the gaps in knowledge concerning the biologic and toxicologic effects of those exposures. The committee's review of the literature identified three major themes that characterize these gaps. All are again pervasive in environmental health studies.

The first gap is the absence of information on mixtures. This is of concern because interactions among exposures may unpredictably result in increased or decreased effects relative to those of individual components, greatly complicating the assessment of risk. Indeed, the committee responsible for the National Academies report *Gulf War and Health: Volume 11: Generational Health Effects of Serving in the Gulf War* (NASEM, 2018b) concluded that the lack of information on exposures and toxicologic information related to the complex chemical mixtures often encountered during environmental and occupational exposures precluded an adequate assessment of the effects of deployment exposures.

A second knowledge gap regarding effects assessment is the lack of good animal models for in-theater exposures. Such models permit a greater understanding of how particular exposures may result in biologic changes, manifestations of signs and symptoms, and specific diseases. Studies have been done with rats and Southwest Asia dust (Porter et al., 2015; Szema et al., 2014; Taylor et al., 2013; Wilfong et al., 2011); cats (Moeller et al., 1994) and hamsters (Brain et al., 1998) and smoke from the Kuwait oil-well fires; and mice and pesticides used during the 1990–1991 conflict (Repine et al., 2016). A few investigators have also directly examined the toxicity of particular hazards experienced by military personnel when deployed to Southwest Asia. Some have focused on PM (Dorman et al., 2012; Porter et al., 2015). In addition, J. P. Smith et al. (2019) examined potentially toxic elements in the fine fraction of soils from Iraq and Kuwait, which the authors indicate could become suspended during wind storms. Others have performed analyses of emissions from the plastics, paper, food, wood, clothing, and Styrofoam materials most commonly found in military operations—singularly (Pan et al., 2013) and in mixtures (Aurell et al., 2012; Dominguez et al., 2018; Woodall et al., 2012)—and characterized their properties.

Investigators at AFRL have developed a model that shows great promise for more completely examining the effects of in-theater inhalation exposure by using simulated burn pit emissions mixed with desert sand to study pulmonary morbidity in rats (DelRaso et al., 2018; Mauzy, 2019). DelRaso et al. (2018) reported on changes in urine metabolites, microRNA (miRNA) expression profiles, and related pathways in rats exposed to sand and burn pit emissions. Paired analysis revealed minor effects due to exposures to sand and burn pit emissions, but the majority of the observed changes were attributed to stress induced by the experimental protocols. Due to

[9] See https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/523009p_1.pdf (accessed July 1, 2020). DoD indicates that release is limited only as necessary to safeguard information requiring protection in the interest of national security or other legitimate governmental interest.

logistic limitations, these exposures were conducted sequentially (sand followed by burn pit emissions), though, and thus do not reflect the real-world exposure scenarios that occurred in-theater. Camilla Mauzy (2019), in an October 2019 presentation before the committee, outlined a number of additional research projects being carried out by AFRL investigators that have not yet been published. These include studies of blood proteomics (including potential biomarkers) and the lung microbiome in exposed animals. The committee encourages AFRL to facilitate the publication of this work in the open literature so that it can reach the broader research community.

The third knowledge gap identified by the committee regards differences in vulnerability and susceptibility[10] to respiratory health problems arising from toxic airborne exposures in military populations. As Falvo et al. (2015) note, while there is a robust literature on the effects of exposure to PM and other air pollutants commonly encountered in the Southwest Asia theater, a knowledge gap exists because "[i]ndividual susceptibility factors in deployed military personnel have not been thoroughly studied in the contexts of airborne hazards exposure" (p. 119). These individual factors include genetic pre-disposition, underlying health issues, social determinants (such as socioeconomic status and access to health care), prior exposures, and the multiple stressors present in a military environment—not just chemical, biologic, radiologic, nuclear, and high-yield explosives exposure, but also combat, noise, altered work/rest patterns, and disruptions to family and other social support systems.

Biologic and toxicologic research published to date has thus made a start on informing questions related to the effects of airborne exposures but has not covered all of the issues of interest—in particular, in the study of clinically relevant endpoints. Analyses of tissue burdens, changes in organ systems, and pathologic and histologic alterations are needed to better relate laboratory results to health effects observed in deployed personnel.

Other Gaps in Knowledge

The lack of good biomarkers of exposure, effect, and susceptibility[11] to in-theater environmental insults is a knowledge gap that has received considerable attention of late, including a long-term DoD study—the Military Biomarkers Research Study (Mallon et al., 2019)—and a 2018 National Academies workshop (NASEM, 2018a). These markers were also addressed by several speakers who presented at the workshop that the committee convened in October 2019. The following are common themes identified by these sources:

- Biomarkers are a new and potentially powerful means of overcoming the lack of specific information on personal exposures in military environments and how they affect deployed personnel.
- Technologic advances allow the identification of candidate biomarkers with far greater speed and at far lower cost than was previously possible.
- Extant collections of biospecimens such as the DoD Serum Repository (DoDSR) and materials collected as part of epidemiologic investigations such as the Millennium Cohort Study are useful in identifying candidate biomarkers.
- Recent advances in research indicate that there are biomarkers associated with service in the Southwest Asia theater and specific exposures found in that theater.

Biomarkers research is addressed in greater detail later in the chapter.

Additional gaps—referenced throughout Chapter 4 and this chapter—relate to issues that limit almost all epidemiologic studies of the effects of occupational and environmental exposures in service members and veterans. These include the reliance on self-reports of exposure and outcomes, the lack of objective tests and measures for

[10] *Vulnerability* in this context refers to an individual at higher risk due to environmental or personal factors, such as from occupational exposures, while *susceptibility* refers to intrinsic biological factors that can increase the health risk of an individual at a given exposure level (Portier et al., 2013).

[11] A biomarker of *exposure* is "an exogenous substance or its metabolite or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism." A biomarker of *effect* is "a measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude can be recognized as an established or potential health impairment or disease." A biomarker of *susceptibility* is "an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance" (NRC, 1989, p. 17).

these exposures and outcomes, the use of deployment as a surrogate for exposure, the number and variety of confounding factors that might influence the outcome under study, and the time that has elapsed between deployment or exposure and evaluation of health outcomes.

RESEARCH THAT COULD FEASIBLY BE CONDUCTED

Given the knowledge gaps identified above, the committee addressed what research could feasibly be conducted to inform these issues and generate answers. In tackling this element of the Statement of Task, it considered not just research that would directly help to answer outstanding questions but also initiatives that would generate data that could be used in the future to move the field forward.

Research Addressing Constrictive Bronchiolitis and Excess Mortality

In the course of its work, the committee identified a number of opportunities to advance knowledge on issues related to respiratory health outcomes related to airborne exposures in Southwest Asia theater veterans. Two outcomes that were highlighted in its Statement of Task—constrictive bronchiolitis and excess mortality from respiratory-related causes—are discussed below.

Constrictive Bronchiolitis

Constrictive bronchiolitis includes several small airway diseases that are defined by the presence of bronchiolar inflammation, fibrosis, or both. The pathological criteria include "a pattern of injury characterized by subepithelial scarring resulting in narrowing or obliteration of the bronchioles, without the presence of luminal plugs" (Garshick et al., 2019).

The interpretation of lung biopsies for the presence of constrictive bronchiolitis has proven to be controversial, leading to uncertainty over the diagnoses of veterans exposed to airborne agents encountered in the Southwest Asia theater. Given the interest surrounding the question of whether in-theater exposures may be responsible for an increase in the prevalence of constrictive bronchiolitis in veterans of the Southwest Asia conflicts, the committee concludes that actions to resolve this issue should be given a high priority by VA.

The central uncertainty at this time (early 2020) is whether case reports of the disease in the population (Garshick et al., 2019; Gutor et al., 2019; King et al., 2011; Madar et al., 2017; Weiler et al., 2018) indicate that it is occurring with greater frequency than would be expected. Among the suggestions offered by the American Thoracic Society workshop participants who addressed this issue in 2018 was the call for

> [m]ore consistent characterization of specific histologic abnormalities, including the prevalence of constrictive bronchiolitis and other small airway abnormalities, established through review of biopsy material using standardized criteria comparable across studies and delineating the relationship of such pathologic abnormalities with PM and other exposures. (Garshick et al., 2019, pp. e-12–e-13)

The committee concurs with this observation. Much of the current debate regarding the prevalence of constrictive bronchiolitis is the result of uncertainty and disagreement over the interpretation of the pathologic findings in symptomatic individuals. In order to better manage these circumstances, **the committee recommends that VA establish an expert panel to advise it on issues related to the diagnosis of constrictive bronchiolitis in veterans and its possible relationship to military service.** This panel should be external to VA and should include a range of expertise in areas such as pulmonary medicine, toxicology, epidemiology, exposure assessment, and radiology but with the primary membership consisting of experienced pulmonary pathologists. The panel should also include veteran representation.

The expert advisory panel would be charged with developing specific guidelines for VA's evaluation of symptomatic Southwest Asia theater–deployed veterans in whom the differential diagnosis includes constrictive bronchiolitis. Its short-term and longer-term tasks would include the following:

- Determination of the adequacy of various lung biopsy approaches for the diagnosis of constrictive bronchiolitis and recommendations for best practices.
- Development of recommendations for consistently processing, handling, and storing lung biopsy materials.
- Creation of consistent histologic/pathologic criteria to be used for confirming a diagnosis of constrictive bronchiolitis in theater veterans with suspected cases who present at a VA facility or who apply for disability compensation for the disease.
- Review—by the pathology working group within the panel—of biopsy slides from cases in which the issue of a diagnosis of constrictive bronchiolitis related to service has been raised. This review should not be limited to controversial cases but instead should be applied to all such cases that fall under VA's areas of responsibility. The working group should be charged with providing a written summary report of each case in a timely manner.
- Establishment of criteria for the evidence base for determining whether an association exists between a veteran's military service and constrictive bronchiolitis, including the types and sources of information that could be considered.
- Recommendations for the research that would help resolve outstanding questions regarding constrictive bronchiolitis in veterans.
- Revision of the guidelines as new evidence becomes available.

The committee notes that it is unclear how many cases of constrictive bronchiolitis might be subject to review under this proposal and that the expert panel may need to adjust the criteria for reviewing cases in order to establish a realistic workload within the confines of achieving these goals. It further recognizes that the creation of this advisory committee and its role in peer review is not without controversy or cost, but it believes that it is critical to ensure that VA has a consistent approach in establishing or denying a diagnosis and evaluating its possible service connection. It should also reassure veterans that they are receiving a fair review that uses the best science. The committee also acknowledges that there are other approaches that could be used to institute a peer-review process for constrictive bronchiolitis that would have their own advantages and disadvantages. No matter which approach VA ultimately chooses, it must have as its foundational principle that all information and actions be documented and—to the extent that protection of privacy and personally identifiable information allows—be made public so that the evidence base used to make decisions on possible links between military service and constrictive bronchiolitis is transparent and the decisions are uniformly reached. The determination of the prevalence of this condition through epidemiologic studies must await the establishment of an agreed-upon selection of clinical criteria for biopsy and agreed-upon pathologic diagnostic criteria.

Excess Respiratory Mortality

The committee's review of the literature found that the last general mortality study of post-9/11 veterans who had been deployed to the theater was generated using data from 2011 (Bollinger et al., 2015). This analysis examined all-cause mortality only and did not present information on specific causes, such as respiratory diseases. The most recently published study of 1990–1991 Gulf War veterans, which did include mortality from COPD or from respiratory system diseases in general, used 2004 as its cutoff date (Barth et al., 2016). An information gap thus exists—one that is important to address in order to identify outcomes that warrant more intense study or surveillance of this population.

Fortunately, data are readily available to fill this gap. The Mortality Data Repository, a joint VA/DoD effort, contains all-cause mortality information for veterans, service members, and Veterans Health Administration users obtained from the National Center for Health Statistics' National Death Index, starting in 1979 (VA, n.d.). Other sources include veteran-specific resources, such as the Beneficiary Identification and Records Locator System death files, VA/Centers for Medicare & Medicaid Services Medicare vital status files, VA facilities patient treatment files, and the VA Corporate Data Warehouse,[12] as well as general mortality information collections, such as the Social Security Administration Death Master File and state death records (VA, 2019).

[12] The Corporate Data Warehouse is a centralized source of digitized Veterans Health Administration information (https://www.hsrd.research.va.gov/for_researchers/vinci/cdw.cfm [accessed July 1, 2020]).

Future mortality studies need to be based on internal analyses that compare veterans exposed to higher and lower levels of airborne agents rather than analyses that compare all veterans to the general population. This in turn requires that a retrospective exposure assessment be a necessary component of any future mortality study if it is to produce useful estimates of exposure-related mortality risk. An informative new study to determine whether there is excess mortality in deployed veterans should also consider a number of parameters. These include not just the cause of death and contributing causes of death but also the following:

- Other underlying health conditions that might not be listed as a cause or contributing cause of death but that might confound an association
- Exposure information from biomarker test results, contemporaneous measurements, retrospective analyses, or self-reports
- The number of deployments
- The timeframes of deployments (not just the dates and number of days or months, but other potentially influential factors such as the season) and of total military service
- As much granularity regarding location in theater as possible, including service at sites with known hazardous airborne exposures
- Demographic and socioeconomic characteristics (age, race/ethnicity, sex, education, family income, and the like)
- Military service information that might influence exposures such as rank and occupational specialty
- Potentially confounding personal characteristics such as alcohol use and smoking history

Changes of effect measurements should be considered in light of baseline physiologic measures of pulmonary function, blood pressure, or existing health conditions (if available) as well as of the other factors mentioned above.

Given this, **the committee recommends that VA conduct or sponsor an updated analysis of total and respiratory disease mortality in Southwest Asia theater veterans.** One means to accomplish this would be to perform an update of the analyses conducted by earlier investigators, using the cohorts they identified and extending the time period to the extent that the data allow. In addition to adding cause-specific mortality for respiratory outcomes, it would be useful to include metrics of airborne exposures, the location and timing of deployments, military occupation, service branch, pre-existing health status, and personal information (including smoking history) to the extent available. The study should perform internal comparisons between more and less exposed veterans in order to permit a better evaluation of the effect of in-theater exposures. Although it is worth replicating the calculations performed in the 2011 study for comparison purposes, the study should also apply survival methods, such as Cox proportional hazards models, to estimate hazard ratios as the measures of association between specific mortality outcomes and exposure to respiratory hazards. The mortality outcomes of interest should include both respiratory cancers and nonmalignant respiratory outcomes, such as asthma and COPD, as well as a calculation of all causes of death combined. Attention, however, should be directed only to outcomes where sufficient time has elapsed since exposure to allow for disease latency and survival. In light of the literature on susceptible populations, effect modification should also be considered to examine whether the exposure–response relationships in these populations vary by education, income, rank, or other socioeconomic factors, as well as by race/ethnicity, sex, age, and smoking history.

Other Outcomes for Which There Is Currently Inadequate or Insufficient Information

As already noted, the committee's review of epidemiologic literature regarding associations between Southwest Asia theater exposures and respiratory health outcomes identified several outcomes for which there is currently inadequate or insufficient information on which to draw any conclusion. For some of these, it is unlikely that further progress will be made from observational studies, such as in circumstances where the outcome is too rare to allow for a meaningful analysis of the effect of in-theater exposures. However, for other outcomes, such as asthma, chronic bronchitis or COPD, and upper airway conditions (sinusitis, for example), future research has the potential to increase our knowledge concerning whether in-theater exposures and outcomes are associated. An important question to answer in this regard is whether research that builds on existing studies would serve this purpose or whether new studies are required. It would likely be more efficient to build onto existing efforts using cohorts such as STAMPEDE or the Millennium Cohort Study. However, in light of the limitations of these cohorts (outlined below), there is a risk that supplementing them with new data will not in fact result in any meaningfully higher level of confidence in the findings.

In order to resolve this question, it is useful to identify some feasible ways to supplement existing studies to help provide a fuller picture of how they might be improved and to provide a better basis for addressing the health outcomes of interest. The following are some possible additions:

- Improved spatio-temporal estimates of ambient air pollution exposures using, for example, the advances in retrospective exposure assessment identified in this chapter.
- More detailed information on the study subjects' personal characteristics (smoking behavior, for example) and their deployments (location, time period, number of deployments) obtained through medical records, administrative data, and other extant sources.
- Biospecimen data.
- Supplementary health status and outcomes data (imaging, physiologic parameters, and the like).

The limitations of the existing studies evaluated by the committee include poor rates of participation, self-selected participant populations, and self-reported health outcomes data. Poor participation rates raise the possibility of selection bias, most likely creating or strengthening associations between exposures and outcomes when such associations do not truly exist.

Other studies of U.S. military and veteran populations have made use of administrative data that for the most part do not rely on self-reports, such as data from the DoD Manpower Data Center (which includes a roster of all military personnel and deployments), the Armed Forces Health Surveillance Branch (which contains deployment information), and DMSS (data on medical encounters). Sources such as the National Death Index, the Armed Forces Medical Examiner System, VA, and the Social Security Administration have also been used to provide supplemental information. Although such administrative data do get around the drawbacks of self-reports, they present a different limitation: they typically do not contain adequate information on important confounding covariates that are desirable to include to reduce uncertainty in these analyses.

As already noted, a characteristic that is common to all of the studies reviewed by the committee is the use of relatively crude estimates of exposure. Typically, deployment status (deployed versus nondeployed) is used, sometimes refined to include features such as the duration and number of deployments. In many circumstances, exposures are self-reported, raising the strong possibility of information bias that may be differential among persons who have the outcome of interest versus those who do not.

The available information suggests that the most feasible and efficient way of supplementing existing cohorts—the way that would have the greatest likelihood of increasing confidence in the study findings—would be to apply spatio-temporal model predictions of ambient air pollution concentrations during periods of deployment, provided that information on deployment location is available. Such an effort would reduce the measurement error and possible information bias inherent in using crude exposure measures that assign the same exposure to all deployed personnel, when there is a wide range of exposure intensity across the deployed population. On the other hand, supplementing existing cohort data with data from biorepositories or additional outcome measurements or records would be less likely to result in any meaningful progress in overcoming the limitations of these cohorts and moving the level of confidence in the evidence from where it is currently. Biorepository specimens that were not collected as part of a systematic research study may be of varying and uncertain quality[13] (IOM, 2012), and outcome measures other than those directly obtained by health professionals from a population that is representative of the individuals who served in theater will suffer from the same problems as the existing information.

[13] An exception to this would be specimens obtained for the DoD Serum Repository (DoD, 2020b), which are subject to uniform and rigorous collection protocols.

Some suggestions for designing a new generation of studies that would deliver more definitive findings are detailed in this chapter, as well as a systematic approach to evaluating suspected cases of constrictive bronchiolitis. In addition, a need was identified for continuing and new experimental studies using appropriate animal models and relevant exposure scenarios. There are currently scant toxicologic data that serve this purpose. Such studies would serve the primary purpose of assessing the plausibility of the associations under study by observational studies and thereby potentially adding to the evidence base as well as providing insights into the pathobiologic mechanisms underlying the effects of the various exposures encountered in the theater. Ongoing and new experimental toxicology studies using appropriate animal models and relevant exposure scenarios should also be encouraged.

Outcomes in Susceptible Subpopulations

As previously noted, almost no information exists on whether particular subpopulations may be at greater risk for respiratory health problems associated with Southwest Asia theater exposures. One paper that did address this topic—Dursa et al. (2019)—examined health outcomes in 1,572 female and 6,532 male veterans of the 1990–1991 Gulf War. The investigators found that deployed female veterans were statistically significantly more likely to report a diagnosis of asthma than deployed male veterans (odds ratio [OR] = 1.82, 95%CI 1.44–2.29), adjusted for age, race, service branch, and unit component. Self-reports of COPD were roughly equal in the cohorts, adjusted for the same factors as asthma (OR = 1.08, 95%CI 0.80–1.36). The committee believes that such work is important to gaining a more complete understanding of the effects of service in the theater. It observes that some analyses of this sort should be possible with already gathered data from the epidemiologic studies reviewed by the committee and that more could be done in the future as validated biomarker and other information becomes available and as the time since exposure increases (which may allow for outcomes with long latency periods to manifest).

Veterans with asthma have also been identified as a potentially susceptible population for respiratory disorders resulting from deployment-related airborne exposures (IOM, 2011). There has been an increase in prevalence of individuals with asthma who are under VA care (Pugh et al., 2016), underscoring the importance of studying this subgroup. Studies investigating the effect of airborne exposures on those with existing asthma require it to be characterized via such parameters as lung function, airways hyperresponsiveness, and clinical asthma status at baseline and post-deployment. A long-term longitudinal follow-up of such a population would provide the ability to study the effect of exposures on the disease course. Changes over time should be analyzed with appropriate statistical methods that quantify within-person effects. Inclusion of biomarkers that provide insight on the immune response to environmental exposures would strengthen future studies.

Generally speaking, future studies of theater veterans need to better evaluate how factors such as race, gender, occupation or operational duties, diet, and the like modify the effects of airborne exposures, which would allow the identification of susceptible subpopulations. In light of the new paradigm for occupational safety and health being promoted by the National Institute for Occupational Safety and Health (Chari et al., 2018), studies of military health should consider work-related environmental, organizational, and psychosocial factors that affect health and well-being as well as modifiers of military exposures to airborne contaminants.

In contrast with previous studies of military as well as other occupational groups, Bollinger et al. (2015) found evidence suggesting that veterans of the Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn conflicts were less healthy than the general U.S. population. Although respiratory outcomes were not the focus of that study, the results provide a context for evaluating such outcomes. Research suggests that low socioeconomic status increases susceptibility to the respiratory and cardiovascular health effects of air pollution (Chi et al., 2016; Hooper and Kaufman, 2018; O'Neil et al., 2003), and it is plausible that respiratory effects associated with effect modification also exist (Keidel et al., 2019). Those who use VA medical services may be particularly vulnerable. Meffert et al. (2019) found that those individuals have a substantially elevated health burden compared with other veterans, perhaps as a result of their lower household incomes and longer service in the military and in combat than those who do not use VA services.

Taken altogether, the literature supports the need to more fully examine effect modification in studies of theater veterans' health. The committee has no specific recommendation in this regard but notes that this is an under-researched area that has the potential to yield a more complete understanding of the determinants of respiratory health outcomes.

Other Research Opportunities for Examining Respiratory Health Outcomes

Several research opportunities exist for expanding on the currently available epidemiologic literature. These include improved consideration of confounders and effect modifiers, such as smoking; using information available from biorepositories to supplement exposure and outcome information; and using integrated health records when possible.

Accounting for Smoking More Comprehensively Given the well-established association between smoking and adverse respiratory health outcomes, it is remarkable that there are studies of these outcomes that do not control for smoking or that control for it in an incomplete manner. Rohrbeck et al. (2016), for example, acknowledge that the lack of individual-level smoking data is a limitation of their study. Others note behavioral choices, such as starting or restarting smoking during deployment, that could complicate analyses (Brown, 2010; Sanders et al., 2005). Smoking can confound the relationship between service and respiratory disease or it may be an effect modifier. In either case, incorrectly accounting for it (e.g., failing to factor that *current* smoking is less common among those with lung cancer who smoked in the past) may lead to a biased estimate. Conceptual models, such as directed acyclic graphs or marginal structural models, can be used in such circumstances to ensure that smoking is accounted for properly in the analysis. It is also important to keep in mind that smoking—or any covariate—will only be a confounder in any particular study if it is associated with the exposure metric as well as with the outcome (if, for example, veterans who were exposed to higher levels of airborne hazards in theater also smoked more).

Furthermore, the committee did not identify any study of theater veterans that measured e-cigarette use, a relatively new and growing exposure that is raising health concerns (Lin et al., 2019). When possible, future studies should account for all forms of smoking—tobacco and otherwise—in order to properly study respiratory health outcomes.

Finally, the committee notes that research on the use of biomarkers for smoking is evolving and will present opportunities for more complete retrospective exposure assessment in the future (Chang et al., 2017).

Using Military Biorepository Information in Epidemiologic Studies Epidemiologic studies of respiratory health effects of airborne hazards exposures in the Southwest Asia theater most often rely on qualitative proxies for exposure, such as deployment status (deployed versus nondeployed) or time spent within the theater. Having multiple, independent sources of exposure information would enhance the ability of investigators to retrospectively assess the effect of airborne contaminants by military personnel. As detailed in the "Organizations That VA Might Partner with to Address Knowledge Gaps" section later in this chapter, one largely untapped source of such information is the material already collected and stored in biorepositories maintained by or affiliated with DoD. One example is the DoDSR, a collection of 62 million sera samples from more than 10 million service members from all branches of the military that were collected at induction and then every 2 years while on active duty, as well as before and after deployment (DoD, 2020b). The serum stored in the DoDSR is used for HIV screening and to conduct epidemiologic studies and inform health policy. It may thus also serve as a supplemental means to identify chemical compounds and molecular changes (e.g., those revealed by genomic, proteomic, or metabolomic analyses) associated with various environmental exposures (Moore et al., 2010; Perdue et al., 2015; Rubertone and Brundage, 2002). To be clear, there are limitations to the utility of some of these specimens, and logistic obstacles and consent considerations to be factored into the use of others,[14] but these are surmountable challenges. Greater use and easier research access to military biorepositories would allow for the evaluation of longitudinal changes in exposure to specific contaminants in targeted analysis as well as to exposures to mixtures using exposomic analysis. Good nested case–control study designs will be crucial in making best use of the materials, though. Linking the results of analyses of biobanked samples to data on service members and their tour of duty, demographics, and lifestyle choices (including smoking histories prior to and during service) data, where available, would facilitate assessments of determinants of exposure, which could in turn be used to evaluate the health effects of that exposure and to develop strategies for exposure mitigation.

[14] A 2012 National Academies report addresses these challenges as they relate to report future uses of the specimens held by DoD's Joint Pathology Center biorepository (IOM, 2012).

Biobank measurements could also support investigations of the impact of military exposure on intermediate endpoints—identified via biologic pathways of disease—through metabolomics, transcriptomics, and proteomics. Importantly, high-throughput pipelines that accommodate multi-omics analyses are already well established in universities and federal agencies, for example, through the National Institute of Environmental Health Sciences (NIEHS) Human Health Exposure Analysis Resource program (NIH, 2020a) and their extramurally funded Environmental Health Sciences Core Centers (NIH, 2020b). Results from such analyses could be combined with those from toxicologic biomarker studies to extend their utility.

The utility of adding information derived from existing biorepository collections to new analyses of health outcomes in veteran populations has been demonstrated in studies of Vietnam veterans. For example, biospecimens from the Air Force Health Study—originally collected in the 1970s through early 2000s—were later used to examine the prevalence of monoclonal gammopathy of undetermined significance (Landgren et al., 2015; Wang et al., 2020) and the association of serum paraoxonase 1 activity and concentration with the development of type 2 diabetes mellitus (Crow et al., 2018).

There would also be merit in expanding these biorepository resources to include routine collection of media such as urine, dried blood spots, or nasal and buccal swabs because these would yield information not available from the more commonly stored specimens: serum, whole blood, and tissue. Given the potential costs of such an expansion, a reasonable first step might be a pilot program that would collect samples of different biologic media and then assesses their suitability for informing specific questions of health outcomes. For example, military personnel who served in theater could be stratified by their exposures, focusing on those with the lowest and highest potential exposure to particular airborne hazards in order to maximize the signal to noise ratio. Biomarkers known to be associated with respiratory disease or biomarkers previously identified in other studies using the biorepository could then be examined.

Another potential use of the biorepository would start with deployed personnel and then identify for analysis subgroups of service members who present with possible deployment-related illnesses. The availability and long-term stability of serum collected in the DoDSR makes it feasible to identify personnel with specific diseases decades after deployment and to compare their immediate post-deployment sera with sera from personnel with similar deployment who did not get ill. Each deployment may leave a distinct biologic signature that would permit exposure and internal dose assessments and biomarker analysis and thereby allow potential linkage with specific health effects.

Taking Advantage of DoD/VA Health Record Integration Efforts DoD and VA have been working toward a modernized and interoperable electronic health record (EHR) since at least 2013 (DoD, 2013). Those efforts are planned to first bear fruit in 2020 when such a system will be rolled out at so-called initial operating capability sites (VA, 2020), with complete interoperability between VA's and DoD's EHRs being phased in thereafter.

An integrated system such as this—in addition to its primary goal of facilitating a secure and seamless transfer of the medical records of active-duty service members as they transition to veteran status—has the potential to enable investigators, with proper human subjects assurances, to far more easily access these data for research purposes. An integrated EHR system would also simplify the monitoring of respiratory health status (including lung function) over time, which is needed for investigations of outcomes that have long latency periods.

In order to accomplish these objectives, **the committee recommends that VA and DoD explicitly integrate research access considerations into their planning as they refine the implementation of their new interoperable electronic health record system.** It further suggests that, as part of this effort, VA and DoD commit resources to developing a database of research study data derived from the integrated records. Data integration is still at a relatively early stage, and it is important for VA to be planning now for how it might use the information derived from EHRs so that it can properly configure the system for access.

There is also a plan to link EHRs with the individual longitudinal exposure records (ILERs) currently being developed jointly by DoD and VA. ILER combines (declassified) location, exposure, and health care–related databases (including DOEHRS-IH and the Defense Manpower Data Center) to create a complete record of a service member's occupational and environmental health exposures over the course of his or her career by linking individuals to known exposure events and incidents and compiling the exposure history to distill and report the relevant data and information. This application is in the final stages of development, and when it achieves full operational capacity in 2023 it will, among other capabilities, "[allow] near real-time creation of retrospective exposure registries sorted by location, exposure agent, or other demographic variables [and provide] a framework for identifying previously unknown health effects associated with environmental exposures" (DoD, 2019a). It thus has the potential to fill knowledge gaps by improving exposure assessment.

The committee anticipates that the next few years will see the first studies using ILER data to characterize exposures of theater-deployed veterans. These initial efforts are likely to uncover strengths and weaknesses in the application of it as a tool in epidemiologic studies that should be identified and disseminated throughout the research community.

Research Addressing the Mechanisms of Effects of Airborne Exposures

Knowledge is lacking on how measured levels of environmental contaminants in serum, tissue, and the like translate to biologic effects and, separately, health outcomes. Among the areas of research of greatest relevance to studies of the health of theater veterans are basic science studies addressing biologic mechanisms and also those examining the biomarkers of effect and susceptibility.

The potential for such research is illustrated, for example, by a study by Thakar et al. (2019), who developed an integrative network analysis linking clinical outcomes with environmental exposures and molecular variations in service personnel deployed to the Balad and Bagram bases in Iraq and Afghanistan, respectively, using samples from the DoDSR. Comparisons between personnel exhibiting new cardiopulmonary diagnoses after deployment start date and personnel exhibiting no symptoms identified biomarkers associated with cardiopulmonary conditions. It provided a proof of principle establishing a computational framework for an integrative analysis of deployment-related exposures, molecular responses, and health outcomes.

Biologic Mechanisms Research

Much of the research to date regarding the biologic mechanisms that may underlie health effects related to airborne exposures has focused on $PM_{2.5}$. Some recent publications illuminate the state of the literature. A 2018 review article by Cho et al. identifies the potential mechanisms, stating that the components of $PM_{2.5}$ responsible for cellular toxicity—including free radicals, organic chemicals, and transition metals[15] on particle surfaces—may induce or produce reactive oxygen species that impair cellular-level physiologic and biochemical processes by inducing oxidative stress, inflammation, genotoxicity, and other effects that alter the normal physiological functions or fates of target cells, thereby resulting in tissue and organ damage. Several investigators have used in vitro experimental studies to examine $PM_{2.5}$-induced cell damage and have discovered a variety of ways in which exposure affects methylation, signaling, and cell viability. Wei and Tang (2018) examined how airborne $PM_{2.5}$ exposure affects the pulmonary immune system. They focused on the regulation of immune responses, observing that while a number of studies indicate that $PM_{2.5}$ exposure may modulate the Th1/Th2 balance[16] by altering the expression of transcription factors, the details of this mechanism had yet to be elucidated. Platel et al. (2020) looked at genotoxic effects. The researchers—who used in vitro comet, micronucleus, and gene mutation assays of immortalized lung cell lines and primary normal human bronchial epithelial cells—found that $PM_{2.5}$ and quasi ultra-fine ($PM_{0.18}$) particles induced primary DNA damage but no chromosome aberrations in the immortalized cells. Furthermore, they did not observe in vitro genotoxic effects in primary normal human bronchial epithelial cells. Given these results and what is known about the relationship between PM exposure and lung cancer, the authors suggested that mechanisms other than genotoxicity, such as epigenetic alteration, deserved more research attention.

[15] Transition metals are metals including vanadium, chromium, iron, nickel, copper, and platinum that are characterized in part by the tendency to easily form oxides. Sørensen et al. (2005) note that "soluble transition metals are abundant in the water-soluble PM fraction" (p. 1340).

[16] T-helper (Th) lymphocytes play a role in immune function. Cells expressing the Th1 and Th2 profiles release different cytokines upon activation that influence host defenses against infection, modulate airway function, and orchestrate various cellular immune responses. The balance between the two profiles affects how the body responds to environmental insults (IOM, 2000a).

Separately, other investigators are exploring the use of animal models to better capture the complexity entailed in biological responses to airborne exposures. Curbani et al. (2019) conducted a review of this literature through the end of 2017. They found that the majority of PM studies had used mice or rat models. While inhalation better mimics the circumstances in which exposure occurs, it is technically difficult to standardize exposure levels, and intra-tracheal or nasal instillation was typically used in its place. The authors found that existing studies were characterized by a diversity of experimental protocols, which made it difficult to compare them. Importantly, the authors noted that the median PM inhalation rate from the experiments was three orders of magnitude higher than the rate found under ambient environmental conditions. These observations led them to conclude that the applicability of the results to human exposures and outcomes was open to question. Curbani et al. (2019) concluded that future animal studies need to address how to more accurately represent the conditions under which airborne exposure take place and to standardize how such exposures are managed in experiments to allow better comparability.

These publications, along with those summarized earlier in the report, illustrate that airborne exposures and biologic mechanisms research has produced some provocative results but that it is still very much in its infancy, and there are a number of knowledge gaps that remain to be filled before the work can contribute materially to the understanding of human health effects. Research in areas outside of PM is lacking, as are studies that explore how to relate the results of cellular and animal models to humans.

The committee thus believes that it would be desirable and feasible to expand the knowledge base by conducting further toxicologic studies using exposure parameters that realistically reflect the experience of those who have served in the Southwest Asia theater. Such studies should focus on inhalation studies of the primary airborne exposures of concern—burn pit emissions and PM from indigenous sources such as ambient dust and sand—and should mirror the composition, size, and concentration of these identified by exposure characterization research. The research should evaluate both short-term (days) and long-term (months) effects and include single, repeated, and intermittent exposures and appropriate negative and positive controls. Such studies are already being carried out by investigators and can and should be expanded. The committee observes that access is extremely limited to representative and well-characterized PM and dust from the Southwest Asia theater and comparison samples from non-theater military sites. The creation of standardized, representative samples of these materials for animal experiments would be a boon to researchers.

The animal models used in these studies also need to reflect the realities of service in theater. This means moving from models that use only healthy young adults to models that allow for a better understanding of the effects of airborne exposures on those who are, for example, asthmatic or allergic, have other respiratory diseases or cardiovascular disease, or are obese. Studies that additionally factor in the effects of smoking or stressors like heat, blast, and noise would be particularly valuable.

The committee also believes that studies of some other exposures that are not unique to the Southwest Asia theater but that are particular to the circumstances of military service are appropriate. These would include investigations of the effects of diesel exhaust, where there may be extended exposure to emissions from multiple vehicles in convoys; JP-8, a fuel used extensively by U.S. military aircraft and as an accelerant in burn pits; and CARC (chemical agent resistant coating), a paint that is applied to military vehicles to resist corrosion and chemical warfare agents. In vitro toxicologic studies, while useful in the understanding of the basic biologic effects of particular chemicals and in elucidating mechanisms, are less likely to generate information relevant to veterans.

Biomarkers of Effect and Susceptibility Research

Human biomonitoring, in combination with environmental sample analysis, permits a greater understanding of the external sources of exposure and its relationship to internal dose, and it yields valuable information on the exposure sources and pathways. Advancing research on the biomarkers of effect and susceptibility, especially as it relates to the early identification of adverse outcomes—including those with known long-latency periods—is especially important in this regard. Such research could include studies of inflammatory, histologic, genomic, and metabolomic changes.

Because unknown and transient exposures can cause long-term harm and often cannot be measured in real time, one way to assess exposure response is to use biomonitoring for chemical exposures and complement this with measurement of biomarkers for biological responses (e.g., metabolic response patterns, cytokines, miRNA, and DNA methylation). High-resolution metabolomics for exposome research provides the capability to link exposures to internal dose to molecular responses to biomarkers of risk and health outcomes (Walker et al., 2016) using chromatography, high-resolution mass spectrometry, and chemometrics working together to provide a framework for high-resolution metabolomics. Gas or high-performance liquid chromatography separates the chemicals; high-resolution mass spectrometry measures the mass; and chemometrics allow for computation, data extraction, alignment, and characterization.

Research Addressing Retrospective Exposure Characterization

It is difficult to relate exposures to health outcomes without measurements of individual exposure, whether these come from biomarkers or a better understanding of the levels of contaminants in the environment. Research on these fronts is described below.

Biomarkers of Exposure Research

The complex composition of Southwest Asia theater airborne contaminants means that there are few data in the medical literature to help understand the half-lives of those contaminants in humans. However, trace elements absorbed and retained in the biopsied lung tissues or other biospecimens (serum and urine, for example) of veterans may yield biomarkers of cumulative exposure to contaminants even after more than a decade of deployment, depending on how these contaminants have been metabolized and eliminated. More accurate estimates of exposure to Southwest Asia theater airborne contaminants, as might be gained from trace element biomarkers, would almost certainly improve the accuracy of etiologic studies of disease suspected of being due to exposures. Examples of these analyses include 8-hydroxy-2'-deoxyguanosine and other oxidative stress biomarkers in human urine; melatonin in serum; thyroid hormones (including thyroxine [T]1, T2, T3, and T4) in the thyroid gland, brain, and serum; and iodine in serum. The feasibility of this approach was demonstrated in an animal inhalation study (Cohen et al., 2015) that showed that trace element profiles bearing the World Trade Center dust signature were retained in rat lungs 1 year post-exposure, mirroring findings in humans (Marmor et al., 2009).

Research on biomarkers to assess environmental exposures and health outcomes in military personnel deployed to the theater is being pursued under the umbrella of the Military Biomarkers Research Study. This is a multiphase study sponsored by DoD that is intended to “assess whether biomarkers can be used to retrospectively assess deployment exposures and health impacts related to deployment environmental exposures” (Mallon et al., 2019). Phase I of the study examined the feasibility of using service members’ stored sera to assess biomarkers of internal dose and of effect, Phase II used available field measurements to evaluate whether there were correlations between these exposure surrogates and identified biomarkers, Phase III examined the relationships between these biomarkers and health outcomes, and Phase IV will investigate in vitro biomarker changes associated with exposures to chemicals of interest (Mallon et al., 2016, 2019). In brief, studies that were a part of the Military Biomarkers Research Study efforts have identified several novel miRNA biomarkers and metabolomic biomarkers, and significant associations were noted between deployment exposures, these biomarkers, and deployment health outcomes (Go et al., 2019; M. R. Smith et al., 2019a,b,c; Thakar et al., 2019; Thatcher et al., 2019; Woeller et al., 2019). Some of these are summarized elsewhere in this report, and all point to the potential for such research to better characterize in-theater exposures. To be successful, though, this research will need high-quality biospecimens that are acquired, handled, and processed in a standardized fashion that preserves their molecular integrity.

Other Potential Exposure Characterization Research

Research published in late 2019 found that “MOS (military occupational specialty) codes that were scored using a respiratory hazard exposure matrix may be helpful in characterizing some but not all inhalation hazards confronting land-based post-9/11 military deployers to Southwest Asia” (Zell-Baran et al., 2019, p. 1039). While such an approach has limitations—immediate needs in a deployed environment often lead service members to perform tasks outside of their defined responsibilities—it has the potential to allow a more informed analysis of health outcomes in high-exposure-potential versus low-exposure-potential persons. This could be especially true for service members with multiple deployments or extended deployment to remote forward operating bases (which may entail additional or higher exposures to airborne contaminants due to the lack of an infrastructure for managing waste). The committee suggests that a feasibility study for constructing a specific job-exposure matrix for airborne hazards be considered as an exposure assessment tool. Zell-Baran et al. (2019) proposed that such work include "direct measurement of airborne particulate concentrations for higher hazard MOS codes and combat-related job duties" (p. 1039), which would serve to enrich and validate the model. Such a job-exposure matrix may also prove informative in interpreting the results of biomarker and other biomonitoring testing because certain occupational series or specialties may have differing -omic characteristics related to training- and occupation-specific exposures in addition to deployments.

Remote Measurement and Estimation of Airborne Pollutant Levels

Recent advances in technology present the opportunity to use satellite-based remote sensing observations to improve retrospective air quality assessments (EPA, 2019). There are several instruments aboard polar-orbiting National Aeronautics and Space Administration (NASA) and European Space Agency (ESA) satellites that retrieve atmospheric properties that can be related to air quality. Two such instruments that observe aerosol properties are the Moderate Resolution Imaging Spectroradiometer (MODIS) and the Multi-angle Imaging SpectroRadiometer (MISR). The Earth Observing System satellite Terra—which has both MODIS and MISR on board—was launched in late 1999 while Aqua—which has MODIS only—was launched in mid-2002 (ESA, 2020a,c). Both were still operating in early 2020. Recent algorithmic implementations of data from these instruments have resulted in aerosol optical depth[17] retrievals at fine spatial (1 × 1 km for MODIS and 4.4 × 4.4 km for MISR) and temporal (daily for MODIS and weekly for MISR) levels that can be used in exposure assessments of PM for health effects studies (Garay et al., 2017; Lyapustin et al., 2018). Because the satellite sensors do not provide a direct measure of PM, it is necessary to calibrate the data against ground-level measurements in order to generate retrospective exposures, but some of the data needed to perform this exist. Ground measurements made through the DoD Enhance Surveillance Project at 15 sites in 2006–2007 (Engelbrecht et al., 2009) and at Joint Base Balad (CHPPM, 2008), for example, could be used for this calibration. The MISR instrument has the additional capability of distinguishing aerosol optical depth types (size, shape, absorption), which can be used to assess chemically speciated PM concentrations and thus source-specific profiles (Chau et al., 2020; Franklin et al., 2017, 2018; Meng et al., 2018).

The Ozone Mapping Instrument aboard NASA's Aura satellite also observes aerosols but since its launch in late 2004 has been primarily used for assessing the gaseous criteria pollutants ozone, nitrogen dioxide (NO_2), and sulfur dioxide (Krotkov et al., 2016). At 13 km × 25 km, the Ozone Mapping Instrument has a relatively coarse spatial resolution for exposure assessment but is globally observing on a daily overpass schedule. It has been used to assess ground-level NO_2 for the United States (Di et al., 2020) and over the Middle East (Daneshvar et al., 2017). TROPOMI (TROPOspheric Monitoring Instrument), a newer satellite (launched in 2017 by a consortium of European aerospace organizations), measures NO_2 at better resolution than the U.S. instruments, and its data are also available to researchers through the ESA Copernicus Open Access Hub (ESA, 2020b; KNMI, 2020).

For future exposure assessments, the most promising data source may be the upcoming NASA Multi-Angle Imager for Aerosols (MAIA) (Diner et al., 2018; Liu and Diner, 2017). The primary objective of MAIA, which is to be launched in 2022, is to assess the impacts of different $PM_{2.5}$ (fine) and $PM_{10-2.5}$ (coarse) species (sulfates, nitrates, carbons, dust) on human health. It builds on the MISR legacy to provide an integrated satellite-surface data collection and modeling strategy at fine (1 km × 1 km) spatial resolution that is tailored for assessing health effects. The challenge is that MAIA is a targeted mission, meaning that while it is polar orbiting it does not see the entire globe but rather targets particular areas for more detailed assessment. A target area covering an approxi-

[17] Aerosol optical depth is a measure of light extinction through the column of the atmosphere and is a quantitative estimate of the abundance of aerosols in the atmosphere.

mately 300 km × 300 km region around Kuwait has been planned, though, and it is possible to implement others (M. Franklin, University of Southern California, personal communication, 2020).

Remote Detection of Burn Pits

Another emerging technology entails the repurposing of remote sensing observations of fires from the NASA Fire Information for Resource Management System database[18] to identify historical burn pit activity. Through this system, global historical fire detections are available from the MODIS active fire product (Giglio et al., 2016). Fires are detected as thermal anomalies and represent the center of a 1 km pixel that is flagged by the Fire and Thermal Anomalies algorithm as containing one or more active fires from sources including biomass burning (Freeborn et al., 2014). Coupled with the locations of military bases and camps, MODIS active fire detections could assist in pinpointing the locations and assessing the durations of historical burn pits on or near in-theater operations.

New Epidemiologic Studies of Respiratory Health Outcomes

The committee is concerned that without changing the paradigm for how epidemiologic studies of respiratory health outcomes are conducted, many questions regarding their possible association with Southwest Asia theater exposures will remain unanswered. To address this it has developed some alternative study designs that it believes would lead to more definitive results. For the reasons presented below, the committee does not offer these as research recommendations but rather as illustrations of the kind of prospective information gathering that is needed to perform informative respiratory health assessments of military populations that are subject to environmental exposure hazards. Two designs for studies of COPD are presented as examples; these could be adapted for other respiratory health outcomes.

The study designs highlight the need for improved characterization of pre- and post-deployment lung function in combination with better measures of actual exposures in theater. Because—in the specific case of COPD—both the level of and the change in pulmonary function are required to assess the degree of presence and severity of obstructive (as well as restrictive) pulmonary disease, the study designs require pulmonary function testing to be done in a standardized manner so as to allow a comparison of the outcomes over time. In addition, repeated measures in well-characterized populations are called for to measure short-term reversibility.

Illustrative Study Design 1

The first illustrative study design developed by the committee uses what might be termed a "prospective wave" approach. It would best be accomplished via a joint effort between DoD and VA to establish a cohort of personnel selected with the characteristics indicated below. The cohort would be followed for a minimum of 15 years with examinations every 3 years. It would be made up of three age groups—18–24, 25–34, and 35–44 years of age—of approximately 5,000 subjects each that constitute a representative racial/ethnic sample. To the degree possible, the persons would be active-duty personnel at the beginning of the study. A prospective wave design offers the opportunity, if the sample is appropriately selected, to provide an assessment of risk over an extended period of time, extending from age 18 to age 60, and to allow varying degrees of latency to be assessed.

Because it will be important to be able to track and assess these subjects repeatedly over time, appropriate incentives and a commitment at the time of enrollment would need to be considered. To the degree possible, detailed exposure data gathered from the time of enrollment onward would be part of the study. These data might combine historical records with the best available current and developing technology. Upon enrollment, subjects would complete standardized questionnaires, pulmonary function assessments carried out by uniformly trained technicians, and a thorough health examination performed by a medical professional. The assessments would be repeated every 3 years, and an effort would be made to capture all major medical events that occurred between examinations. Because there is significant effort that must be committed to establishing such a cohort and the cohort would obviously be well characterized, it clearly could be used in a "nested case–control" fashion to answer a

[18] See https://firms.modaps.eosdis.nasa.gov (accessed July 1, 2020).

number of questions outside the domain of chronic respiratory disease. In addition, as the field of "omics" becomes more sophisticated, it would be important to obtain biologic specimens on these subjects.

Illustrative Study Design 2

The second illustrative study design developed by the committee is less ambitious than the first alternative but could be accomplished more quickly and easily and with fewer resources.

This study would more generally examine pre-deployment versus post-deployment health status. It would test the premise that in-theater exposures could cause new-onset COPD over a relatively short period of time, similar to what was observed in post-9/11 New York City rescue workers (firefighters and EMS personnel) (Aldrich et al., 2010)—a scenario that is arguably more relevant to the 1990–1991 Gulf War exposure setting. It is in contrast to the approach taken by many of the COPD studies examined by the committee that were based, at least implicitly, on what is known about the relationship between cigarette smoking and COPD, where the disease develops over a long time period and is associated with an extended history of exposure.

In the study design presented here, pre-deployment spirometry would be used to identify a cohort of previously nondeployed participants without pre-existing COPD, using the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2018) or other appropriate criteria. Both pre- and post-bronchodilator spirometry data would be desirable in order to exclude participants with pre-existing asthma. Pre-deployment participant data would ideally include demographic information, respiratory illness history, smoking history, and family history of respiratory disease. In light of the anticipated low likelihood of developing new-onset COPD, a relatively large cohort would be needed. Table 5-1 shows the required sample size for different detectable exposure effect sizes, assuming that a multiple logistic regression model and a dichotomized exposure were used in the analyses. The five scenarios demonstrate the effect of different assumptions on sample size.

Rigorous exposure estimation would be essential to such an analysis. This might be accomplished using a combination of point predictions of concurrent spatio-temporal ambient air pollution concentrations, the documentation of participants' locations in theater, and contemporaneous ground measurements to validate modeled estimates if available. Covariate data would ideally include cigarette smoking, combat experience, and blast exposure. Variable timeframes for post-deployment pre- and post-bronchodilator spirometry could be factored in, ranging from immediately after deployment to later times after return from deployment, although testing immediately after deployment and 1 year later would likely be adequate in light of the presumed natural history of COPD in this setting. It would be desirable if post-deployment spirometry was performed using the same protocol as the pre-deployment exam, with spirometry technicians blinded to exposure.

The primary analysis would use multiple logistic regression models to evaluate the risk of developing COPD (assessed using post-deployment spirometry data), related to the degree of exposure, while controlling for effects of smoking and other covariates. Aldrich et al. (2010) found that forced vital capacity (FVC) declined to a lesser extent in concert with the fall in forced expiratory volume in 1 second (FEV_1) in the 9/11 firefighters, suggesting that FEV_1/FVC may not be able to reliably detect COPD onset. Therefore, in a secondary analysis, a 5% decline in percent predicted FEV_1 (to account for potential lung growth between the pre- and post-deployment exams), or approximately 200 mL from the pre-deployment level without a significant improvement after bronchodilator, could be used to define new-onset COPD. This secondary criterion is presumed to be more sensitive than FEV_1/FVC in detecting new-onset COPD with consequent smaller sample size requirements (see Table 5-1 Scenario 5).

This proposed study design would include the following advantages:

- a comparison group composed of concurrently deployed personnel;
- an objective measure of outcome;
- a relatively short study duration;
- individual-level estimates of airborne exposures, ensuring a wide range of exposures;
- adequate power to detect an association with exposure;
- control for cigarette smoking;
- a means of accounting for potential lung growth in this relatively young cohort; and
- exclusion of participants with asthma either before or after deployment.

TABLE 5-1 Required Sample Sizes to Detect COPD in a Hypothetical Pre- Versus Post-Deployment Study of Theater Veterans, as a Function of Various Assumptions[a]

Scenario	Covariate: COPD OR	Prevalence of COPD	Exposure OR	Required Sample Size
1	1.2	0.05	1.10	77,525
2	**1.1**	0.05	1.10	79,532
3	1.2	0.05	**1.05**	304,318
4	1.2	**0.02**	1.10	191,564
5	1.2	**0.10**	1.10	42,405

NOTES: Changes from the Scenario 1 assumptions are **bolded**. Common assumptions: covariate-exposure OR = 1.1; 2-sided p-value = 0.05; power = 0.80. COPD, chronic obstructive pulmonary disorder; OR, odds ratio.

[a] Sample sizes calculated using "Power/Sample Size Calculation for Logistic Regression with Binary Covariate(s)." See https://www.dartmouth.edu/~eugened/power-samplesize.php (accessed June 15, 2020).

Its disadvantages include the large number of participants needed, the fact that it would not pick up delayed development of COPD over the longer term, and the potential that some participants developing deployment-related asthma could still potentially be mistakenly included.

Observations Regarding the Illustrative Study Designs

The two designs developed by the committee would address many of the flaws identified in the epidemiologic studies reviewed in this report. However, there are reasons why such approaches have not been implemented by the research teams who have been and are trying to understand whether in-theater airborne exposures are resulting in adverse respiratory health outcomes in the Southwest Asia theater veterans. Primary among these is that pre-deployment lung function data were generally not collected, and there are far too few service members being deployed now to mount an informative study. The committee, as discussed in Chapter 4, does not believe that the issue of the utility of gathering pre-deployment lung function data for the purpose of surveillance has been resolved. Such data collection would be costly and time consuming but would greatly aid the evaluation of respiratory health outcomes in the future. This program could begin with a cohort of military occupational specialties that are more likely associated with deployment exposures, prior to expanding to other service members. The U.S. Congress and federal government will need to evaluate whether the upfront costs of performing this and other health status benchmarking yield sufficient benefits in the long term when service members become veterans and questions arise regarding whether a particular health problem may be associated with military service.

Other Research Opportunities

Studies of Non-Military Personnel Providing In-Theater Support Services

DoD civilian employees and contractors play a large role in delivering in-theater services to the U.S. military, including activities such as waste management, base security, and transportation, that may have entailed significant exposure to airborne hazards (DoD, 2019b; Schwartz and Church, 2013). Specific concerns have been raised about the health of DoD contractors who were exposed to burn pit emissions (Chiaramonte, 2016). However, data on the health of these personnel are not systematically collected, and the committee identified only one analysis of respiratory health outcomes in the population (Krefft et al., 2017).

Non-military personnel serving in theater thus represent an untapped source of information on airborne exposures and the respiratory health outcomes resulting from them. DoD delivered health care to private-sector personnel while they were deployed and billed the cost to their employers (DoD OIG, 2012) so documentation must exist. The committee acknowledges that there would be considerable barriers to accessing such information—not just those involved with the protection of personally identifiable information but, more fundamentally, the potential reluctance of contractors to allowing access to data on their employees. Nonetheless, contractors have been an important component of U.S. deployments to the theater. Studying health outcomes in this population would provide information that would benefit service members, veterans, and the civilian employees themselves.

NEWLY EMERGING TECHNOLOGIES TO ADDRESS KNOWLEDGE GAPS

Previous sections of this chapter have already identified many of the major technologies that will help to better characterize airborne exposures in Southwest Asia theater veterans. These include satellite measurements of PM, other pollutants, and burn pits—combined with advances in data processing—to estimate past ambient levels, biomarker discovery (including the algorithms that allow for the rapid screening of candidates), and the rapidly evolving field of -omics (epigenomics, genomics, metabolomics, proteomics, etc.) that help to bring about a comprehensive understanding of how airborne exposure affects humans.

While VA's responsibility lies with persons who have completed their military service, the committee thought it appropriate in this section to briefly touch on some of the new technologies that might be brought to bear to gather information during active duty that would aid in the future evaluation of airborne exposures and health outcomes. Four examples are offered below.

The challenge is that any technology, no matter how effective or well intentioned it is, will take a back seat to the exigencies of operating in the field. It will not gain acceptance unless it can be seamlessly incorporated into operations, can be used in a way that does not encumber or otherwise limit personnel, and does not compromise their security. That said, there appear to be multiple technologies that hold the promise of developing information on active duty personnel that would later aid VA in its evaluation of the health effects of military exposure to airborne agents. While it will be the responsibility of DoD to develop and deploy such technologies and to gather and maintain the information they generate, VA has a role to play in defining the type and form of that information that would be most useful, in fostering studies that take advantage of the information to better understand health outcomes in veterans, and in keeping abreast of advancements in health and benefits domains that they do have responsibility for that might feed into the development of exposure assessment technologies.

Silicone Wristbands for Exposure Detection

Silicone wristbands have been developed for use as personal passive samplers capable of sequestering organic compounds as measures of an individual's external exposure. Research indicates that they are capable of capturing and detecting more than 1,500 chemicals (Dixon et al., 2019). Silicone wristbands have been identified as a possible means of exposure assessment in military settings (Horne et al., 2020), and some small-scale testing has been performed with them (Hardos et al., 2019). An October 2019 presentation to the committee by Jennifer Therkorn of the Johns Hopkins University Applied Physics Laboratory reported the results of a proof-of-concept field test of silicone wristbands' potential to detect fuel vapors which was conducted for the Army Public Health Center. The test concluded that the wristbands provided reliable, simple, cost-effective, yes/no profiling for organic compound detection. The investigators noted, though, that they could not provide information on concentrations and that the correlation between detection of and actual exposure to airborne agents was unknown (Therkorn, 2019). The committee understands that further research is being conducted by DoD on the utility of wristbands as an exposure assessment tool.

Advances in Exposure Monitoring Applications for Deployed Environments

A 2019 request for information (RFI) issued by DoD's Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense in collaboration with the Defense Health Agency (DHA) identified several potential near-term (2019–2024 timeframe) innovations in exposure monitoring applications for deployed environments (JPEO-CBRND, 2019). The intent was to solicit ideas for low-cost technologies that could be used to support real-time health risk assessment and mitigation decision making and generate data that could be made a part of individual longitudinal exposure records.

The RFI classified these prospective technologies into a number of categories:

- "outward looking" wearable environmental hazard detectors or samplers;
- "inward looking" wearable physiologic status, health effects, and biomarker monitoring applications (non-invasive and invasive in vitro and in vivo devices and validated model of health effects) with sensing applications integrated with existing DoD on-body communications devices;
- point or handheld sensors for toxic industrial chemicals and toxic industrial materials;
- miniaturized, unattended ground sensors for area hazard monitoring or meteorological data collection;
- lightweight power solutions for sensor applications;
- geotagging and timing devices (for individuals and also those able to be added to existing point and areas sensors);
- portable field analytical platforms for rapid, on-site analysis of collected environmental samples for toxic industrial chemicals and materials; and
- self-sampling devices for the collection and preservation of clinical sample matrices while deployed, related to post-deployment lab analysis of transient biomarkers of exposure or effect (JPEO-CBRND, 2019).

The RFI also sought information on validated biomarkers for pre-disposition and pre- and post-deployment screening for exposure or for the health effects of ambient environment and manmade environmental hazards. The committee understands that, as of early 2020, elements of this RFI have been initiated.

If such technologies were to be developed and implemented in the future, they would not only inform retrospective exposure assessments but would also generate information that field commanders and medical support personnel could use to lower exposure potential by, for example, limiting outdoor missions or elective activities or providing personal protective equipment on "high exposure" days. Low-cost sensor technology to measure levels of airborne agents at fixed locations such as bases—which could in turn be coupled with remote sensing data—could be used in the same manner. Such devices would need to be hardened to function reliably in the extreme environments in which military operations often occur, small and light enough to not further encumber personnel, and able to transmit their information in a manner that did not compromise the security of forces.

Wearable and Portable Devices to Assess Intermediate Health Outcomes

Wearable devices are increasingly common in real-world settings and are being applied in research studies. Smart watches monitor rest/activity cycles, heart rate, and sleep patterns. Handheld spirometry includes electronic data capture for serial use as a personal device. Systems that are larger than personal samplers but more amenable to field-based research are increasingly available to assess respiratory physiology beyond spirometry. Measurements of gas transfer (diffusing capacity of carbon monoxide) and airway mechanics (impulse oscillometry) can be made with lower-cost, portable equipment and may provide additional insight concerning the effects of environmental exposures on respiratory health. Exhaled gases, such as nitric oxide, can be measured with portable devices as a non-invasive assessment of airway inflammation. Technology to assess sleep-disordered breathing has moved from lab-based to home-based testing in clinical practice. In research, sleep studies are performed remotely with equipment that can be shipped and self-applied. These innovations have increased the scale of research that can be conducted to address gaps in understanding of the prevalence and risk factors for sleep-disordered breathing among military personnel and veterans at home and, eventually, in deployed settings.

Advances in Epigenetic Monitoring

The Defense Advanced Research Projects Agency (DARPA) is fostering research aimed at developing a field-deployable epigenome "reader" for the real-time evaluation of exposure threats. The goal of the Epigenetic

Characterization and Observation program is to "identify and discriminate epigenetic signatures created by exposure to threat agents and to create technology that performs highly specific forensic and diagnostic analyses to reveal the exact type and time of exposure" (DARPA, 2018). While focused on the detection of weapons, the technology could have application in identifying exposures to airborne agents.

ORGANIZATIONS THAT VA MIGHT PARTNER WITH TO ADDRESS KNOWLEDGE GAPS

A number of federal agencies, investigators in the United States and abroad, and other governmental and private-sector organizations are currently conducting research relevant to theater veterans' health or else have information that could improve the conduct of such work. These entities are listed in the sections below. While the committee offers one specific recommendation regarding partnering, it identifies a broad range of organizations that have potentially useful exposure or health information that VA should consider collaborating with in order to address specific needs and pursue new research opportunities.

Department of Defense

VA already partners extensively with DoD on issues related to the effect of occupational and environmental exposures on military and veteran health. The organizations related most closely to the evaluation of respiratory health issues are noted below.

Defense Health Agency

DHA is a joint, integrated combat support agency tasked with providing "a medically ready force and ready medical force to Combatant Commands in both peacetime and wartime" (DoD, 2020a). As part of this task, DHA (within the Occupational and Environmental Health Branch of its Public Health Division) is responsible for DOEHRS-IH, which captures military occupational and environmental health risk data and actively tracks biologic, chemical, physical, and other health hazards (DHA, 2018).[19] These are consolidated into a web-based application that can be used for risk management and epidemiologic studies. DHA also leads the DoD component of a joint effort with VA, the ILER web-based application, discussed earlier in the chapter. The challenge will be to integrate such information with other sources, such as DoD site sampling (DOEHRS-IH) data and NASA satellite observations (discussed below), to paint a more complete picture of individual exposures and refine the periodic occupational and environmental monitoring summary.

The Armed Forces Health Surveillance Branch also resides within DHA's Public Health Division. It is responsible for the DoDSR (mentioned earlier in this chapter) and DMSS, a relational database containing personnel (including military occupational specialty codes), medical (in-patient, ambulatory, reportable event, immunization, and prescription information), laboratory (serologic specimens, chemistry and microbiology results), and deployment (including pre- and post-deployment health assessments) data throughout service members' careers (DHA, n.d.). DMSS data have proven utility in studies of respiratory health outcomes in theater veterans, having been used in studies of respiratory diseases (Rohrbeck et al., 2016), respiratory pathogens (Eick et al., 2011), sarcoidosis (Forbes et al., 2020), and biomarkers of exposure (Mallon et al., 2019; Thakar et al., 2019; Thatcher et al., 2019). Mallon et al. (2016) assert that the linking of DMSS data with other information resources "provides a powerful epidemiological resource that allowed us to investigate the relationship between deployment burn pit exposures, serum biomarkers, and potential health outcomes."

However, there is a major obstacle to fully exploiting DMSS information: the lack of an interoperable DoD–VA EHR and the subsequent difficulties in combining active-duty and post-service medical data held by the departments. This is a long-standing and complex issue that DoD and VA have been working on for several years. The

[19] DOEHRS-IH and ILER are also described in Chapter 3 in the section "Exposure Tracking by DoD."

VA–DoD joint strategic plan for fiscal years 2019–2021 lists interoperability as a strategic goal, and the following is one of its objectives:

> Objective 4.1—Electronic Health Record Modernization Interoperability—Enhance health data interoperability between VA, DoD, and their private partners as VA and DoD continue their electronic health record (EHR) modernization efforts. (VA–DoD Joint Executive Committee, 2019, p. 5)

VA indicates that its EHR modernization effort, which has interoperability with DoD as a primary component, will go live in spring 2020 and is scheduled for completion in 2026 (P. Hastings, Veterans Health Administration, personal communication, February 20, 2020; VA, 2020). The committee notes that while this effort does not have the facilitation of epidemiologic research as a primary objective, more seamless integration will greatly enhance such work.

DoD and DoD-Affiliated Biorepositories

DoD maintains or supports a number of biorepositories that store materials of potential utility to studies of respiratory health outcomes in theater veterans, Prominent among these, as already noted, is the DoDSR. Mancuso et al. (2015) noted that as of 2015 more than 80% of the repository's specimens were linked to individual health outcomes data, the result of an effort that began in 1990. DoDSR-supplied specimens have been used in studies of biomarkers, including the Military Biomarkers Research Study (Go et al., 2019; Mallon et al., 2019; M. R. Smith et al., 2019a,b,c; Thatcher et al., 2019), and have great potential in future investigations in this area.

Another major DoD biorepository is maintained by the Joint Pathology Center (JPC), which serves as the central repository for collected biologic materials submitted for consultation by military, other government, and civilian medical providers (IOM, 2012). JPC's holdings include three relevant war-related registries—Kuwait/Persian Gulf War, Operation Iraqi Freedom/Iraq Service, and Operation Enduring Freedom/Afghanistan Service—plus one registry focused on specimens of service members with embedded depleted uranium. There are many challenges associated with the research use of these specimens, but they are nonetheless a resource for pathology-related research. Ladich et al. (2002), for example, conducted a histopathologic study of head and neck specimens in the Kuwait/Persian Gulf War registry that found a number of cases of chronic sinusitis and allergic rhinitis but few neoplasms (which the authors speculated was a consequence of the relatively young age of the cohort). JPC pathologists additionally could serve as a source of expertise on difficult-to-interpret pathologic specimens and have done so in the past on cases of suspected constrictive bronchiolitis (Lewin-Smith et al., 2015; Madar et al., 2017).

The 2018 National Academies publication *Feasibility of Addressing Environmental Exposure Questions Using Department of Defense Biorepositories: Proceedings of a Workshop—in Brief* highlighted additional biorepositories that hold materials that may be of use in studies of Southwest Asia theater veterans (NASEM, 2018a). One of these is at the John P. Murtha Cancer Center. The biorepository there is a joint effort of DoD, the Uniformed Services University of the Health Sciences, and the Walter Reed National Military Medical Center that collects and maintains biospecimens (including tissue, blood, urine, and saliva) from patients in military hospitals who have been diagnosed with, or are suspected to have, a malignancy. It has other information, including self-reported environmental exposures, related to some specimens. The other biorepository was assembled in support of the Army Study to Assess Risk and Resilience in Servicemembers and the Study to Assess Risk and Resilience in Servicemembers–Longitudinal Study. One component of this effort was a study of soldiers assigned to service in Afghanistan that obtained blood samples and survey data before the soldiers' deployments and reassessed the subsets of the cohort 1, 3, and 9 months after they returned from deployment (Ursano et al., 2014). The complete collection includes whole blood and plasma, buffy coat, and DNA aliquots. The specimens and associated data in these biorepositories were not collected with the intent of studying the effects of in-theater environmental exposures on respiratory health outcomes, but it is possible that they contain information that might be useful in such studies, especially if they were combined with data from other sources. The committee did not identify any such studies to date, but representatives of the repository have indicated that they would make their materials available to other investigators upon application (NASEM, 2018a).

While it is not under DoD's aegis, the biorepository assembled as part of the Detection of Early Lung Cancer Among Military Personnel (DECAMP) series of studies receives support from DoD under its lung cancer research program, which is in turn a part of the Congressionally Directed Medical Research Programs (CDMRP).[20] The DECAMP consortium includes military treatment facilities and VA hospitals. Biospecimens collected in the research effort include nasal brushings, serum, plasma, and intrathoracic airway samples (bronchial brushings and bronchial biopsies) from normal-appearing airway epithelium; computed tomography (CT) scans obtained during routine clinical care are also part of the database (Billatos et al., 2019; Spira and Moses, 2017). These are currently being used for studies of biomarkers and gene expression. It is not clear from published information whether and to what extent the subjects may include theater veterans. A 2019 paper on the cohort indicated that data sets were still being generated and that data sharing would not be available until after the completion of study enrollment (Billatos et al., 2019).

The Boston Biorepository, Recruitment, and Integrative Network for Gulf War Illness is a CDMRP-funded biorepository network that also has potential to inform studies of theater veterans' health outside those that are its focus. Kimberly Sullivan, the principal investigator, and Nancy Klimas gave a presentation to the committee on this network during its October 2019 workshop (Sullivan and Klimas, 2019). Their inventory includes whole blood, serum, plasma, buffy coat, urine, and DNA samples.

DoD and Armed Forces Research Organizations

DoD and the service branches maintain a number of other organizations that generate knowledge in support of DoD's mission. Two of these that conduct or support research relevant to the evaluation of the effects of airborne exposures have already been cited in this chapter. AFRL is performing innovative biologic and toxicologic research on the effects of burn pit exposures using animal models (DelRaso et al., 2018; Mauzy, 2019), while DARPA is sponsoring cutting-edge work on a device that could identify the epigenetic "fingerprint" of adverse exposures in the field (DARPA, 2018). Both organizations are generating information that may inform future studies of theater veterans' health, and VA could choose to help shape that work via collaboration to better address its needs.

Concluding Remarks Concerning Partnerships with DoD

VA thus already partners extensively with DoD and is well aware of the usefulness of this relationship. These collaborations are yielding benefits for both service members and veterans in the form of information that may be used to identify, manage, and cope with potentially harmful exposures. **The committee recommends that VA continue and expand its partnership with DoD on environmental health issues, focusing on the free flow of information on exposures encountered during military service and the health of personnel before, during, and after deployment and after transition to veteran status. This should include cooperation on identifying which respiratory health status information should be gathered during active duty for later use as baseline data in evaluating veterans' health for treatment, benefits, and research purposes.**

Researchers Conducting Studies of Theater Veterans' Health

There are a number of epidemiologic studies and research centers that address respiratory health issues in Southwest Asia theater veterans. Some of these are under the guidance of VA investigators—the Airborne Hazards and Burn Pits Center of Excellence; the Comparative Health Assessment Interview, Million Veteran Program, National Health Study for a New Generation of U.S. Veterans, and Service and Health Among Deployed Veterans studies; and the Gulf War Era Cohort and Biorespository project—while others, such as the Millennium Cohort Study, Military Biomarkers Research Study, and Study of Active Duty Military for Pulmonary Disease Related to Environmental

[20] See https://cdmrp.army.mil/lcrp/default (accessed August 11, 2020). The operation of the Congressional Directed Medical Research Programs is addressed in the 2016 National Academies report *Evaluation of the Congressionally Directed Medical Research Programs Review Process* (NASEM, 2016a).

Deployment Exposures, are being conducted under DoD sponsorship and the aegis of DoD principal investigators. In addition to the guidance that VA provides to its own investigators on future research directions coming out of this report, the committee believes that there are partnering opportunities with these initiatives related to both new analyses of existing data and the collection of data to address knowledge gaps. The National Academies 2018 report *Gulf War and Health: Volume 11* noted this potential. While it was referring to research on the generational health effects of theater exposures, its observations are also applicable to respiratory health effects:

> [T]he committee proposes … to leverage ongoing veterans' health research programs, such as the Million Veteran Program and the Millennium Cohort Study. Such an approach would greatly benefit from past investments and take advantage of existing infrastructure.… These programs … have already enrolled large cohorts and are linked to a variety of rich big data sources, and some of them already have in place protocols for the collection of biological specimens.

This committee has made clear its concerns about the often selective nature of the study participants involved in these efforts and other weaknesses that limit the extent to which informative studies can be performed with these populations. Nevertheless, there are areas where fruitful additional research can be performed.

Other U.S. Federal Agencies

National Aeronautics and Space Administration

As detailed earlier in this chapter, NASA and ESA administer satellites and airborne and ground-based observation projects that collect environmental data that can be used to model ground-level exposure to airborne agents. Their instrumentation is capable of providing information on parameters associated with PM (aerosol index, aerosol optical depth), carbon monoxide, nitric acid, nitrous oxide, ozone, and sulfur dioxide as well as information on dust storms and fires (NASA, 2020). Data sets for some of these go back several years, allowing for retrospective estimation of levels. Much of the research related to health issues is focused on PM and, in particular, $PM_{2.5}$. This includes work sponsored by VA under its Cooperative Studies Program that has demonstrated how satellite data can be used to estimate historical $PM_{2.5}$ levels in the theater (Chudnovsky et al., 2017; Masri et al., 2017a,b).

Diao et al. (2019, p. 1391) highlight the challenges associated with such modeling:

> We find inconsistencies among several publicly available $PM_{2.5}$ estimates, highlighting uncertainties in the exposure datasets that are often overlooked in health effects analyses. Major differences among $PM_{2.5}$ estimates emerge from the choice of data (ground-based, satellite, and/or model), the spatiotemporal resolutions, and the algorithms used to fuse data sources.

This suggests that further and more in-depth research in the area would be appropriate.

A VA partnership with NASA could help to address these challenges in a way that generated information that would aid in characterizing theater veterans' exposures. The discussions of new technologies and feasible research above highlight the potential of such of a partnership.

National Oceanic and Atmospheric Administration

The National Oceanic and Atmospheric Administration (NOAA), like NASA, has a robust research effort centered around the collection and analysis of atmospheric data—information that can be applied to models of exposure to airborne agents. NOAA's Air Resources Laboratory is the home of a tool that has been used to help characterize airborne hazards levels and exposures: the Hybrid Single Particle Lagrangian Integrated Trajectory (HYSPLIT) is a transport and dispersion modeling system that can be used to retrospectively construct site exposure profiles (Stein et al., 2015; Wardall and Grabinski, 2018). It has been used by investigators in studies of veterans (Rinker, 2011; Smith et al., 2002) and, more generally, of Southwest Asia locations (Alolayan et al., 2013; Li et al., 2020; Querol et al., 2019; Yassin et al., 2018). HYSPLIT is freely available and is implemented online as part of NOAA's Real-Time Environmental Applications and Display System suite of applications (NOAA, 2020).

National Institute of Environmental Health Sciences

The committee responsible for the 2018 National Academies report *Gulf War and Health: Volume 11* (NASEM, 2018b) cited work being conducted by NIEHS's Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription program as an existing federal effort that might facilitate VA's health research efforts. The program is focused on the development of epigenetic biomarkers in animal models for eventual application in humans (NIEHS, 2020). It is ongoing as of early 2020. The current phase has funded a consortium of universities to pursue work characterizing epigenetic changes in tissues and cells induced by environmental exposures and to investigate the role of such factors as the timing of exposure. Wang et al. (2018) note that this includes investigating how blood, skin, and nasal epithelial cells might be used to investigate the effects of $PM_{2.5}$ exposure on cardiopulmonary outcomes, a topic of direct relevance to studies of theater veterans.

National Institute for Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) developed and maintains the Spirometry Longitudinal Data Analysis (SPIROLA) software tool, which helps researchers and medical professionals monitor and analyze variability in spirometry test results over time (Hnizdo and Halldin, 2015). The committee earlier concluded that there was insufficient evidence to draw a conclusion about the efficacy of pre- versus post-deployment spirometry in informing questions regarding the respiratory health of theater veterans or to offer advice about the circumstances under which such data gathering might be appropriate.

Morris (2015, pp. 98–99) observed the following:

> An essential component for obtaining spirometry in a large group, such as a military population, would be a central database to collect, store, and track information aside from the current electronic medical record. Although many tracking systems exist for other military health issues, it would be burdensome to establish such a system for spirometry. Current electronic medical records in both DoD and VA do not allow the direct uploading of spirometry or other pulmonary test results into a predesignated section. Results are generally scanned in with PDF (Portable Document Format) files and located in different places in the medical record, severely limiting searching for results.

SPIROLA provides electronic transfer of standardized data output from spirometers to health records in an occupational setting. Thus, if a decision was made to pursue the systematic collection of pre- and post-deployment spirometry information, then it would be important to establish such a capability, and it would benefit VA to partner with NIOSH to determine how best to use, adapt, or extend SPIROLA in a manner that would allow for easier transfer of its data to VA medical records for both screening and research purposes.

Department of State

The Department of State stations personnel around the globe in support of the nation's foreign policy goals, including U.S. service members who are detailed to provide military liaison with foreign governments and security at some locations. The adverse effects of airborne exposures on staff and their families is of great concern to the department,[21] which has partnered with the Environmental Protection Agency to establish and manage the AirNow Department of State program.[22] AirNow has real-time and historic ozone and $PM_{2.5}$ measurements for a number of locations, including Kabul, Afghanistan; Manama, Bahrain; Bagdad, Iraq; Kuwait City, Kuwait; and Abu Dhabi and Dubai, United Arab Emirates. While they are single-site observations, they provide a means for validating other measurements and proxies used in exposure characterization and epidemiologic studies. It may also be possible to

[21] For example, the Department of State requested the National Academies to establish the Standing Committee on Medical and Epidemiological Aspects of Air Pollution on U.S. Government Employees and Their Families in 2016 to "provide a forum for discussion of scientific, technical, and social issues relevant to effective health management and protection of family members assigned to overseas locations with severe air pollution" (https://www.nationalacademies.org/our-work/standing-committee-on-medical-and-epidemiological-aspects-of-air-pollution-on-us-government-employees-and-their-families [accessed August 11, 2020]).

[22] See https://www.airnow.gov/international/us-embassies-and-consulates (accessed August 11, 2020).

gain insights from marrying AirNow data with health information on the military personnel serving at these sites since their dates of deployment and locations would be better known than is the case for many others (although the relatively small numbers of persons involved might limit the usefulness of the analyses).

Other Nations Involved in the Southwest Asia Theater of Military Operations

A coalition of nations have taken part in military operations in the Southwest Asia theater since 1990. Studies of respiratory health issues have been performed on the personnel involved in these operations. Chapter 4 cites some of these, including investigations of veterans of the militaries of Australia (Davy et al., 2012; Ighani et al., 2019; Sim et al., 2003, 2015), Canada (Statistics Canada, 2005), France (Salamon et al., 2006), Poland (Korzeniewski and Brzozowski, 2011; Korzeniewski et al., 2013), Sweden (Saers et al., 2017), and the United Kingdom (Cherry et al., 2001; Unwin et al., 1999). In addition, Canada (Robinson, 1995) and the United Kingdom (Coker et al., 1999) have established health registries of veterans involved in the 1990–1991 conflict (Gray and Kang, 2006). The Australian Department of Veterans' Affairs maintains the Preliminary Gulf War Nominal Roll, which lists Australian Defence Force personnel involved in that conflict (Australian Government DVA, 2019).

Although studies of coalition partners have much smaller numbers of potential subjects than those of U.S. veterans, research is aided by the more detailed information on health status and outcomes available through these nations' national health programs. It is also the case that these forces were deployed in more limited areas, which allows for easier estimation of potential exposures.

As mentioned earlier—in contrast to many of the studies of theater veterans from the United States—several studies of European veterans have been able to achieve relatively good participation rates, which may provide insight into how future U.S. studies could be improved. For example, Cherry et al. (2001) realized a response rate of 85.7% of the 4,755 eligible UK service personnel deployed to the 1990–1991 Gulf War. Participation rates were higher in active-duty service personnel (93%) than in those who had left the service (80%). In the Danish Gulf War Study (Ishoy et al., 1999), of those deployed in the 1990–1997 period as part of the United Nations peacekeeping mission, 686 (84%) participated while 231 (58%) of the eligible randomly selected nondeployed service members took part. For the Australian Gulf War Veterans' Health Study's baseline cohort, 1,456 Gulf War veterans (81% of those eligible) and 1,588 comparison group members (57% of those eligible) participated (Ikin et al., 2017). These rates of participation are all better than is typical of U.S. studies. For example, in the Millennium Cohort study (Smith et al., 2009), the initial response rate was 37%, of which 60% remained for follow-up (22% participation overall), and 85% of those were eventually included in the data analysis, yielding a 19% participation rate overall.

There is an open question, though, regarding whether something would be gained in attempting to partner with researchers who study forces from other nations to carry out future work. While it might be possible to obtain good response rates and to collect rich health outcome data by exploiting national health system resources, there are also some issues. The most obvious of these is the relatively small number of service members from other nations deployed to the Southwest Asia theater, which limits future studies to essentially all but studies of the more common health outcomes unless a spike is observed in a relatively rare disease. When coupled with questions about generalizability of findings from studies involving other nations to the U.S. military and veteran population, there would seem to be limited potential for realizing advantage from pursuing such partnerships.

Health Care Providers

More than 50% of military personnel do not enter the VA health care system after they leave the military (NASEM, 2018b). They may be eligible for TRICARE or TRICARE for Life through DoD,[23] obtain services from private-sector health maintenance organizations or clinicians through their employer, pay out of pocket for care, or

[23] TRICARE is DoD's integrated, single-payer health services provider that combines the health care resources of military treatment facilities with networks of civilian health care professionals, medical facilities, and suppliers, TRICARE for Life provides supplementary coverage for TRICARE beneficiaries who have Medicare Parts A and B.

use federal (Medicare/Medicaid), state (Medi-Cal in California, for example), or local options. VA thus only has direct access to the medical records of a subset of veterans, a subset whose demographics are not representative of the veterans cohort as a whole (Meffert et al., 2019). This means that outside of the information developed in the epidemiologic studies cited in this report and those like them, relatively little is known about the health of many in-theater veterans after they have completed their service.

This is a knowledge gap. There are currently unexploited opportunities to learn more about respiratory (and other) health outcomes in theater veterans through the use of data from such sources to significantly expand the number and diversity of study subjects. Such data could be used in case studies, epidemiologic investigations, and so-called big data analyses that take advantage of high-speed, large-capacity empirical methodologies to uncover possibly unexpected relationships between variables. A 2018 National Academies workshop titled Informing Environmental Health Decisions Through Data Integration addressed the utility of this final approach. Chris Gennings, the director of the Division of Biostatistics and a research professor in the Department of Environmental Medicine and Public Health at the Icahn School of Medicine at Mount Sinai, noted that big data analysis can be productively applied to both integrate data from disparate study types (such as those linking environmental exposures and health outcomes) and to integrate data across epidemiology studies (NASEM, 2018c). The challenge, she observed, is compatibility: whether different data sets should be combined and how to determine if the data integration is done correctly.

Potential partnering organizations in addition to TRICARE include private-sector health providers and the Centers for Medicare & Medicaid Services system. It should be noted, though, that significant challenges exist in gaining permission to access medical information and in harmonizing or integrating disparate databases. Partnering will thus require the expenditure of resources, an extended commitment to making health information compatible across systems and providers, and—importantly—compromises from all parties to further the greater good.

REFERENCES

Abraham, J. H., A. Eick-Cost, L. L. Clark, Z. Hu, C. P. Baird, R. DeFraites, S. K. Tobler, E. E. Richards, J. M. Sharkey, R. J. Lipnick, and S. L. Ludwig. 2014. A retrospective cohort study of military deployment and postdeployment medical encounters for respiratory condition. *Military Medicine* 176(5):540–546.

Aldrich, T. K., J. Gustave, C. B. Hall, H. W. Cohen, M. P. Webber, R. Zeig-Owens, K. Cosenza, V. Christodoulou, L. Glass, F. Al-Othman, and M. D. Weiden. 2010. Lung function in rescue workers at the World Trade Center after 7 years. *New England Journal of Medicine* 362(14):1263–1272.

Alolayan, M. A., K. W. Brown, J. S. Evans, W. S. Bouhamra, and P. Koutrakis. 2013. Source apportionment of fine particles in Kuwait City. *Science of the Total Environment* 448:14–25.

APHC (Army Public Health Command). 2010. *Screening health risk assessments: Joint Base Balad, Iraq, 11 May–19 June 2009*. Aberdeen Proving Ground, MD: U.S. Army Center for Health Promotion and Preventive Medicine.

APHC. 2018. *Periodic occupational and environmental monitoring summary (POEMS)*. https://phc.amedd.army.mil/topics/envirohealth/hrasm/Pages/POEMS.aspx (accessed April 27, 2020).

Aurell, J., B. K. Gullett, and D. Yamamoto. 2012. Emissions from open burning of simulated military waste from forward operating bases. *Environmental Science & Technology* 46(20):11004–11012.

Australian Government DVA (Department of Veterans' Affairs). 2019. *Preliminary Gulf War nominal roll*. https://www.dva.gov.au/recognition/events-and-reminders-all-who-served/records-and-military-history/preliminary-gulf-war (accessed May 5, 2020).

Barth, S. K., H. K. Kang, and T. Bullman. 2016. All-cause mortality among US veterans of the Persian Gulf War: 13-year follow-up. *Public Health Reports* 131(6):822–830.

Billatos, E., F. Duan, E. Moses, H. Marques, I. Mahon, L. Dymond, C. Apgar, D. Aberle, G. Washko, and A. Spira. 2019. Detection of Early Lung Cancer among Military Personnel (DECAMP) consortium: Study protocols. *BMC Pulmonary Medicine* 19(1):59.

Blasch, K. W., J. E. Kolivosky, and J. M. Heller. 2016. Environmental air sampling near burn pit and incinerator operations at Bagram Airfield, Afghanistan. *Journal of Occupational and Environmental Medicine* 58(8 Suppl 1):S38–S43.

Bollinger, M. J., S. Schmidt, J. A. Pugh, H. M. Parsons, L. A. Copeland, and M. J. Pugh. 2015. Erosion of the healthy soldier effect in veterans of U.S. military service in Iraq and Afghanistan. *Population Health Metrics* 13(1):8.

Brain, J. D., N. C. Long, S. F. Wolfthal, T. Dumyahn, and D. W. Dockery. 1998. Pulmonary toxicity in hamsters of smoke particles from Kuwaiti oil fires. *Environmental Health Perspectives* 106(3):141–146.

Brown, D. W. 2010. Smoking prevalence among U.S. veterans. *Journal of General Internal Medicine* 25(2):147–149.

Chang, C. M., S. H. Edwards, A. Arab, A. Y. Del Valle-Pinero, L. Yang, and D. K. Hatsukami. 2017. Biomarkers of tobacco exposure: Summary of an FDA-sponsored public workshop. *Cancer Epidemiology, Biomarkers & Prevention* 26(3):291–302.

Chari, R., C. C. Chang, S. L. Sauter, E. L. P. Sayers, J. L. Cerully, P. Schulte, A. L. Schill, and L. Uscher-Pines. 2018. Expanding the paradigm of occupational safety and health. A new framework for worker well-being. *Journal of Occupational and Environmental Medicine* 60(7):589–593.

Chau, K., M. Franklin, and W. J. Gauderman. 2020. Satellite-derived $PM_{2.5}$ composition and its differential effect on children's lung function. *Remote Sensing* 12(6):1028.

Cherry, N., F. Creed, A. Silman, G. Dunn, D. Baxter, J. Smedley, S. Taylor, and G. J. Macfarlane. 2001. Health and exposure of United Kingdom Gulf War veterans. Part I: The pattern and extent of ill health. *Journal of Occupational and Environment Medicine* 58:291–298.

Chi, G. C., A. Hajat, C. E. Bird, M. R. Cullen, B. A. Griffin, K. A. Miller, R. A. Shih, M. L. Stefanick, S. Vedal, E. A. Whitsel, and J. D. Kaufman. 2016. Individual and neighborhood socioeconomic status and the association between air pollution and cardiovascular disease. *Environmental Health Perspectives* 124(12):1840–1847.

Chiaramonte, P. 2016. *Contractors sickened by military burn pits left to fend for themselves*. https://www.foxnews.com/us/contractors-sickened-by-military-burn-pits-left-to-fend-for-themselves (accessed August 24, 2020).

Cho, C. C., W. Y. Hsieh, C. H. Tsai, C. Y. Chen, H. F. Chang, and C. S. Lin. 2018. In vitro and in vivo experimental studies of $PM_{2.5}$ on disease progression. *International Journal of Environmental Research and Public Health* 15(7):1380.

CHPPM (U.S. Army Center for Health Promotion and Preventive Medicine), 2008. *Deployment OEH risk characterization: Ambient air PM samples, Sykes, Iraq, 10–14 Aug 08, 2008*. U.S. Army Center for Health Promotion and Preventive Medicine. https://phc.amedd.army.mil/PHC%20Resource%20Library/U_IRQ_SYKES_CM_A10_25_20080814_Redacted.pdf (accessed March 6, 2020).

CHPPM. 2009. *Deployment occupational and environmental health risk characterization: Ambient air particulate matter samples, Kandahar, Afghanistan, 16–28 June 2009*. U.S. Army Center for Health Promotion and Preventive Medicine. https://phc.amedd.army.mil/PHC%20Resource%20Library/U_AFG_KANDAHAR_CM_A10_20090628_Redacted.pdf (accessed March 6, 2020).

CHPPM and AFIOH (U.S. Air Force Institute for Operational Health). 2009. *Addendum 2. Screening health risk assessment burn pit exposures, Balad Air Base, Iraq*, May 2008. USACHPPM Report No. 47-MA-08PV-08/AFIOH Report No. IOH-RS-BR-TR-2008-0001. Aberdeen Proving Ground, MD: U.S. Army Center for Health Promotion and Preventive Medicine.

Chudnovsky, A. A., P. Koutrakis, A. Kostinski, S. P. Proctor, and E. Garshick. 2017. Spatial and temporal variability in desert dust and anthropogenic pollution in Iraq, 1997–2010. *Journal of the Air & Waste Management Association* 67(1):17–26.

Cohen, M. D., J. M. Vaughan, B. Garrett, C. Prophete, L. Horton, M. Sisco, A. Ghio, J. Zelikoff, and L. C. Chen. 2015. Impact of acute exposure to WTC dust on ciliated and goblet cells in lungs of rats. *Inhalation Toxicology* 27(7):354–361.

Coker, W. J., B. M. Bhatt, N. F. Blatchley, and J. T. Graham. 1999. Clinical findings for the first 1000 Gulf war veterans in the Ministry of Defence's medical assessment programme. *British Medical Journal* 318(7179):290–294.

Crow, J. A., E. C. Meek, R. W. Wills, and J. E. Chambers. 2018. A case–control study: The association of serum paraoxonase 1 activity and concentration with the development of type 2 diabetes mellitus. *Diabetes/Metabolism Research and Reviews* 34(3):e2967.

Curbani, F., D. N. Olivieri, and C. E. Tadokoro. 2019. Inhale, exhale: Why particulate matter exposure in animal models are so acute? *Environmental Pollution* 251:230–237.

Daneshvar, M. R. M., and N. H. Abadi. 2017. Spatial and temporal variation of nitrogen dioxide measurement in the Middle East within 2005–2014. *Modeling Earth Systems and Environment* 3(1):20.

DARPA (Defense Advanced Research Projects Agency). 2018. *Reading the body's history of threat exposure: Epigenetic technology would provide new tool in fight against WMD proliferation*. February 1. https://www.darpa.mil/news-events/2018-02-01 (accessed March 19, 2020).

Davy, C., A. Dobson, E. Lawrence-Wood, M. Lorimer, K. Moores, A. Lawrence, K. Horsley, A. Crockett, and A. McFarlane. 2012. The Middle East Area of Operations (MEAO) health study: Prospective study. University of Adelaide, Centre for Military and Veterans Health, Adelaide, Australia. https://www.defence.gov.au/Health/Home/Docs/130318-MEAOProspectiveStudyReportVol1.pdf (accessed April 2, 2020).

DelRaso, N. J., C. A. Mauzy, B. A. Wong, and N. V. Reo. 2018. *Burn pit emission and respirable sand exposures in rats: NMR-based urinary metabolomic assessment*. No. AFRL-RH-WP-TR-2018-0061. Wright-Patterson Air Force Base United States: Henry M. Jackson Foundation for the Advancement of Military Medicine.

DHA (Defense Health Agency). 2018. *Fact sheet. Defense Occupational and Environmental Health Readiness System–Industrial Hygiene (DOEHRS-IH)*. https://health.mil/Reference-Center/Fact-Sheets/2019/04/05/DOEHRS-IH (accessed April 21, 2020).

DHA. n.d. *Defense Medical Surveillance System*. https://www.health.mil/Military-Health-Topics/Combat-Support/Armed-Forces-Health-Surveillance-Branch/Data-Management-and-Technical-Support/Defense-Medical-Surveillance-System (accessed February 21, 2020).

Di, Q., H. Amini, L. Shi, I. Kloog, R. Silvern, J. Kelly, M. B. Sabath, C. Choirat, P. Koutrakis, A. Lyapustin, Y. Wang, L. Mickley, and J. Schwartz. 2020. Assessing NO2 concentration and model uncertainty with high spatiotemporal resolution across the contiguous United States using ensemble model averaging. *Environmental Science and Technology* 54:1372–1384.

Diao, M., T. Holloway, S. Choi, S. M. O'Neill, M. Z. Al-Hamdan, A. Van Donkelaar, R. V. Martin, X. Jin, A. M. Fiore, D. K. Henze, and F. Lacey. 2019. Methods, availability, and applications of $PM_{2.5}$ exposure estimates derived from ground measurements, satellite, and atmospheric models. *Journal of the Air & Waste Management Association* 69(12):1391–1414.

Diner, D. J., S. W. Boland, M. Brauer, C. Bruegge, K. A. Burke, R. Chipman, L. Di Girolamo, M. J. Garay, S. Hasheminassab, and E. Hyer. 2018. Advances in multiangle satellite remote sensing of speciated airborne particulate matter and association with adverse health effects: From MISR to MAIA. *Journal of Applied Remote Sensing* 12(4):042603.

Dixon, H. M., G. Armstrong, M. Barton, A. J. Bergmann, M. Bondy, M. L. Halbleib, W. Hamilton, E. Haynes, J. Herbstman, P. Hoffman, and P. Jepson. 2019. Discovery of common chemical exposures across three continents using silicone wristbands. *Royal Society Open Science* 6(2):181836.

DoD (Department of Defense). 2013. Memorandum for Under Secretary of Defense for Acquisition, Technology, and Logistics; Acting Under Secretary of Defense for Personnel and Readiness. Subject: Integrated electronic health records. May 21, 2013. https://www.health.mil/Reference-Center/Policies/2013/05/21/Memorandum-on-the-Integrated-Electronic-Health-Record (accessed March 8, 2020).

DoD. 2019a. *Fact sheet. ILER. Individual longitudinal exposure record*. https://health.mil/Reference-Center/Fact-Sheets/2019/03/15/ILER (accessed June 12, 2020).

DoD. 2019b. *Open burn pit report to Congress*. https://www.acq.osd.mil/eie/Downloads/Congress/Open%20Burn%20Pit%20Report-2019.pdf (accessed June 12, 2020).

DoD. 2020a. *Defense Health Agency*. https://www.health.mil/About-MHS/OASDHA/Defense-Health-Agency (accessed February 2, 2020).

DoD. 2020b. *Department of Defense serum repository*. https://www.health.mil/Military-Health-Topics/Combat-Support/Armed-Forces-Health-Surveillance-Branch/Data-Management-and-Technical-Support/Department-of-Defense-Serum-Repository (accessed March 22, 2020).

DoD OIG (Office of Inspector General). 2012. *DoD needs to improve the billing system for health care provided to contractors at medical treatment facilities in Southwest Asia*. Report No. DODIG-2012-106. June 27. https://media.defense.gov/2012/Jun/27/2001712409/-1/-1/1/DODIG-2012-106.pdf (accessed June 12, 2020).

Dominguez, T., J. Aurell, B. Gullett, R. Eninger, and D. Yamamoto. 2018. Characterizing emissions from open burning of military food waste and ration packaging compositions. *Journal of Material Cycles and Waste Management* 20(2):902–913.

Dorman, D. C., V. Mokashi, D. J. Wagner, A. O. Olabisi, B. A. Wong, O. R. Moss, J. A. Centeno, G. Guandalini, D. A. Jackson, W. E. Dennis, and J. A. Lewis. 2012. Biological responses in rats exposed to cigarette smoke and Middle East sand (dust). *Inhalation Toxicology* 24(2):109–124.

Dursa, E. K., S. K. Barth, B. W. Porter, and A. I. Schneiderman. 2019. Health status of female and male Gulf War and Gulf Era veterans: A population-based study. *Women's Health Issues* 29:S39–S46.

Eick, A. A., D. J. Faix, S. K. Tobler, R. L. Nevin, L. E. Lindler, Z. Hu, J. L. Sanchez, V. H. MacIntosh, K. L. Russell, and J. C. Gaydos. 2011. Serosurvey of bacterial and viral respiratory pathogens among deployed U.S. service members. *American Journal of Preventive Medicine* 41(6):573–580.

Engelbrecht, J. P., E. V. McDonald, J. A. Gillies, and A. W. Gertler. 2008. *Department of Defense Enhanced Particulate Matter Surveillance Program (EPMSP). Final report*. Reno, NV: Desert Research Institute. https://phc.amedd.army.mil/PHC%20Resource%20Library/Final%20EPMSP%20Report%20without%20appx%20Feb08.pdf (accessed September 4, 2016).

Engelbrecht, J. P., E. V. McDonald, J. A. Gillies, R. K. M. Jayanty, G. Casuccio, and A. W. Gertler. 2009. Characterizing mineral dusts and other aerosols from the Middle East—Part 1: Ambient sampling. *Inhalation Toxicology* 21(4):297–326.

EPA (Environmental Protection Agency). 1997. *Evaluation of emissions from the open burning of household waste in barrels, Vol 1*. Technical Report EPA/600/R-97-134a. Research Triangle Park, NC: Environmental Protection Agency.

EPA. 2001. *Database of sources of environmental releases of dioxin-like compounds in the United States*. EPA/600/C-01/012. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20797 (accessed June 12, 2020).

EPA. 2019. *Integrated science assessment (ISA) for particulate matter*. EPA/600/R-19/188. http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=539935 (accessed March 22, 2020).

ESA (European Space Agency). 2020a. *Aqua mission (EOS/PM-1)*. https://directory.eoportal.org/web/eoportal/satellite-missions/a/aqua (accessed April 26, 2020).

ESA. 2020b. *Copernicus open access hub*. https://scihub.copernicus.eu (accessed April 21, 2020).

ESA. 2020c. *Terra mission (EOS/AM-1)*. https://directory.eoportal.org/web/eoportal/satellite-missions/t/terra (accessed April 26, 2020).

Falvo, M. J., O. Y. Osinubi, A. M. Sotolongo, and D. A. Helmer. 2015. Airborne hazards exposure and respiratory health of Iraq and Afghanistan veterans. *Epidemiologic Reviews* 37(1):116–130.

Forbes, D. A., J. T. Anderson, J. A. Hamilton, F. A. Rawlins, C. Tinkelpaugh, J. H. Abraham, and M. J. Morris. 2020. Relationship to deployment on sarcoidosis staging and severity in military personnel. *Military Medicine* 185(5–6):e804–e810.

Franklin, M., O. V. Kalashnikova, and M. J. Garay. 2017. Size-resolved particulate matter concentrations derived from 4.4 km-resolution size-fractionated Multi-angle Imaging SpectroRadiometer (MISR) aerosol optical depth over Southern California. *Remote Sensing of Environment* 196:312–323.

Franklin, M., K. Chau, O. V. Kalashnikova, M. J. Garay, T. Enebish, and M. Sorek-Hamer. 2018. Using Multi-angle Imaging SpectroRadiometer aerosol mixture properties for air quality assessment in Mongolia. *Remote Sensing* 10(8):1317.

Freeborn, P. H., M. J. Wooster, D. P. Roy, and M. A. Cochrane. 2014. Quantification of MODIS fire radiative power (FRP) measurement uncertainty for use in satellite-based active fire characterization and biomass burning estimation. *Geophysical Research Letters* 41:1988–1994.

Furlow, B. 2020. American Thoracic Society calls for more research into military deployment respiratory exposures. *The Lancet Respiratory Medicine* 8(1):17.

Garay, M. J., O. V. Kalashnikova, and M. A. Bull. 2017. Development and assessment of a higher-spatial-resolution (4.4 km) MISR aerosol optical depth product using AERONET-DRAGON data. *Atmospheric Chemistry and Physics* 17:5095–5106.

Garshick, E., J. H. Abraham, C. P. Baird, P. Ciminera, G. P. Downey, M. J. Falvo, J. E. Hart, D. A. Jackson, M. Jerrett, W. Kuschner, and D. A. Helmer. 2019. Respiratory health after military service in Southwest Asia and Afghanistan. An official American Thoracic Society workshop report. *Annals of the American Thoracic Society* 16(8):e1–e16.

Giglio, L., W. Schroeder, and C. O. Justice. 2016. The collection 6 MODIS active fire detection algorithm and fire products. *Remote Sensing of Environment* 178:31–41.

Go, Y. M., M. R. Smith, D. I. Walker, K. Uppal, P. Rohrbeck, P. L. Krahl, P. K. Hopke, M. J. Utell, T. M. Mallon, and D. P. Jones. 2019. Metabolome-wide association study of deployment to Balad, Iraq, or Bagram, Afghanistan. *Journal of Occupational and Environmental Medicine* 61:S25–S34.

GOLD (Global Initiative for Chronic Obstructive Lung Disease). 2018. *Global strategy for prevention, diagnosis and management of* COPD (2018 Report). www.goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf (accessed March 28, 2020).

Gray, G. C., and H. K. Kang. 2006. Healthcare utilization and mortality among veterans of the Gulf War. *Philosophical Transactions of the Royal Society B: Biological Sciences* 361(1468):553–569.

Gutor, S., R. H. Du, R. F. Miller, B. W. Richmond, P. P. Massion, T. S. Blackwell, and V. V. Polosukhin. 2019. The histopathological basis of airflow limitation in small airways disease. Meeting abstracts. American Thoracic Society 2019 International Conference. https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A5784 (accessed June 12, 2020).

Hardos, J. E., M. Rubenstein, and S. Pfahler. 2019. *Organophosphate skin exposure and biological burden of aircraft maintainers*. No. AFRL-SA-WP-TR-2019-0013. Wright-Patterson Air Force Base United States. https://apps.dtic.mil/dtic/tr/fulltext/u2/1071660.pdf (accessed March 19, 2020).

Hnizdo, E., and C. Halldin. 2015. Spirometry monitoring and prevention using SPIROLA software. In C. P. Baird and D. K. Harkins, eds., *Airborne hazards related to deployment*. Fort Sam Houston, TX: Borden Institute, U.S. Army Medical Department and School. Pp. 103–117.

Hooper, L. G., and J. D. Kaufman. 2018. Ambient air pollution and clinical implications for susceptible populations. *Annals of the American Thoracic Society* 15(Suppl 2):S64–S68.

Horne, K. M., J. E. Nichols, D. Logsdon, H. Phipps, S. Sanders, M. Wojtyniak, L. J. McKnight, R. Vigneulle, D. Jackson, and J. Elliott. 2020. Survey of occupational and environmental exposure monitoring solutions. *Military Medicine* 185(Suppl 1):396–403.

Ighani, H., E. Lawrence-Wood, S. J. Neuhaus, and A. McFarlane. 2019. Systematic review of the impact of deployment on respiratory function of contemporary international and Australian veterans'. *Journal of Military and Veterans' Health* 27(1):74–100.

Ikin, J. F., H. L. Kelsall, D. P. McKenzie, S. M. Gwini, A. B. Forbes, D. C. Glass, A. C. McFarlane, D. Clarke, B. Wright, A. Del Monaco, and M. R. Sim. 2017. Cohort profile: The Australian Gulf War Veterans' Health Study cohort. *International Journal of Epidemiology* 46(1):31.

IOM (Institute of Medicine). 2000a. *Clearing the air: Asthma and indoor air exposures*. Washington, DC: National Academy Press.

IOM. 2000b. *Gulf War and health: Volume 1: Depleted uranium, pyridostigmine bromide, sarin, and vaccines*. Washington, DC: National Academy Press.

IOM. 2003. *Gulf War and health: Volume 2: Insecticides and solvents*. Washington, DC: The National Academies Press.

IOM. 2005. *Gulf War and health: Volume 3: Fuels, combustion products, and propellants*. Washington, DC: The National Academies Press.

IOM. 2006. *Gulf War and health: Volume 4: Health effects of serving in the Gulf War*. Washington, DC: The National Academies Press.

IOM. 2008. *Gulf War and health: Updated literature review of depleted uranium*. Washington, DC: The National Academies Press.

IOM. 2010. *Gulf War and health: Volume 8: Update of health effects of serving in the Gulf War*. Washington, DC: The National Academies Press.

IOM. 2011. *Long-term health consequences of exposure to burn pits in Iraq and Afghanistan*. Washington, DC: The National Academies Press.

IOM. 2012. *Future uses of the Department of Defense Joint Pathology Center Biorepository*. Washington, DC: The National Academies Press.

Ishoy, T., P. Suadicani, B. Guldager, M. Appleyard, H. O. Hein, and F. Gyntelberg. 1999. State of health after deployment in the Persian Gulf: The Danish Gulf War Study. *Danish Medical Bulletin* 46(5):416–419.

JPEO-CBRND (Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense). 2019. *Request for Information. Joint Health Risk Management—Environmental Hazard and Health Effects Monitoring Technologies*. Issued by U.S. Army Contracting Command-Aberdeen Proving Ground, Natick Contracting Division, Fort Detrick Branch. http://www.rfpdb.com/view/document/name/Joint-Health-Risk-Management-_-Environmental-Hazard-and-Health-Effects-Monitoring-Technologies_W911QY_19_S_0004 (accessed July 21, 2020).

Keidel, D., J. M. Anto, X. Basagaña, R. Bono, E. Burte, A. E. Carsin, B. Forsberg, E. Fuertes, B. Galobardes, J. Heinrich, and K. de Hoogh. 2019. The role of socioeconomic status in the association of lung function and air pollution—a pooled analysis of three adult ESCAPE cohorts. *International Journal of Environmental Research and Public Health* 16(11):1901.

King, M. S., R. Eisenberg, J. H. Newman, J. J. Tolle, F. E. Harrell Jr, H. Nian, M. Ninan, E. S. Lambright, J. R. Sheller, J. E. Johnson, and R. F. Miller. 2011. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. *New England Journal of Medicine* 365(3):222–230.

KNMI (Koninklijk Nederlands Meteorologisch Instituut). 2020. TROPOMI: Data access. http://www.tropomi.eu/data-products/data-access (accessed April 21, 2020).

Kolivosky, J. E. 2015. *Ambient air monitoring at deployment locations in the Middle East*. Presentation before the Committee on the Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry. May 1, 2015.

Korzeniewski, K., and R. Brzozowski. 2011. Sickness profile among Polish troops deployed to Afghanistan in the years 2003–2005. *International Maritime Health* 62(1):63–70.

Korzeniewski, K., A. Nitsch-Osuch, M. Konarski, A. Guzek, E. Prokop, and K. Bieniuk. 2013. Prevalence of acute respiratory tract diseases among soldiers deployed for military operations in Iraq and Afghanistan. *Advances in Experimental Medicine and Biology* 788:117–124.

Krefft, S. D., M. Strand, J. Smith, C. Stroup, R. Meehan, and C. Rose. 2017. Utility of lung clearance index testing as a noninvasive marker of deployment-related lung disease. *Journal of Occupational and Environmental Medicine* 59(8):707–711.

Krotkov, N. A., C. A. McLinden, C. Li, L. N. Lamsal, E. A. Celarier, S. V. Marchenko, W. H. Swartz, E. J. Bucsela, J. Joiner, B. N. Duncan, and K. F. Boersma. 2016. Aura OMI observations of regional SO_2 and NO_2 pollution changes from 2005 to 2015. *Atmospheric Chemistry and Physics* 16(7):4605–4629.

Ladich, E. R., M. R. Lewin-Smith, C. S. Specht, A. L. Moroz, V. F. Kalasinsky, and F. G. Mullick. 2002. Histopathological study of head and neck specimens from a cohort of Persian Gulf War military veterans. *Military Medicine* 167(10):864–867.

Landgren, O., Y. K. Shim, J. Michalek, R. Costello, D. Burton, N. Ketchum, K. R. Calvo, N. Caporaso, E. Raveche, D. Middleton, and G. Marti. 2015. Agent orange exposure and monoclonal gammopathy of undetermined significance: An Operation Ranch Hand veteran cohort study. *JAMA Onology* 1(8):1061–1068.

Lemieux, P. M., B. K. Gullett, C. C. Lutes, C. K. Winterrowd, and D. L. Winters. 2003. Variables affecting emissions of PCDD/Fs from uncontrolled combustion of household waste in barrels. *Journal of the Air & Waste Management Association* 53(5):523–531.

Lemieux, P. M., C. C. Lutes, and D. A. Santoianni. 2004. Emissions of organic air toxics from open burning: A comprehensive review. *Progress in Energy and Combustion Science* 30(1):1–32.

Lewin-Smith, M. R., M. J. Morris, J. R. Galvin, R. A. Harley, and T. J. Franks. 2015. The problems with constrictive bronchiolitis: Histopathological and radiological perspectives. In C. P. Baird and D. K. Harkins, eds., *Airborne hazards related to deployment*. Fort Sam Houston, TX: Borden Institute, U.S. Army Medical Department and School. Pp. 153–161.

Li, J., E. Garshick, A. Al-Hemoud, S. Huang, and P. Koutrakis. 2020. Impacts of meteorology and vegetation on surface dust concentrations in Middle Eastern countries. *Sciences of the Total Environment* 712(136597):1–9.

Lin, J., K. Zhu, P. K. Hoang, A. M. Soliván-Ortiz, S. L. Larsen, S. P. Irwin, T. R. Schneid, C. D. Shriver, and S. Lee. 2019. Electronic cigarette use and related factors among active duty service members in the U.S. military. *Military Medicine* 185(3–4):418–427.

Liu, J., N. Lezama, J. Gasper, J. Kawata, S. Morley, D. Helmer, and P. Ciminera. 2016. Burn pit emissions exposure and respiratory and cardiovascular conditions among Airborne Hazards and Open Burn Pit Registry participants. *Journal of Occupational and Environmental Medicine* 58(7):e249–e255.

Liu, Y., and D. J. Diner. 2017. Multi-angle imager for aerosols: A satellite investigation to benefit public health. *Public Health Reports* 132(1):14–17.

Lyapustin, A., Y. Wang, S. Korkin, and D. Huang. 2018. MODIS collection 6 MAIAC algorithm. *Atmospheric Measurement Techniques* 11:5741–5765.

Madar, C. S., M. R. Lewin-Smith, T. J. Franks, R. A. Harley, J. S. Klaric, and M. J. Morris. 2017. Histological diagnoses of military personnel undergoing lung biopsy after deployment to Southwest Asia. *Lung* 195(4):507–515.

Mallon, T. M., M. P. Rohrbeck, M. K. M. Haines, D. P. Jones, M. Utell, P. K. Hopke, R. P. Phipps, D. I. Walker, T. Thatcher, C. F. Woeller, and C. P. Baird. 2016. Introduction to Department of Defense research on burn pits, biomarkers, and health outcomes related to deployment in Iraq and Afghanistan. *Journal of Occupational and Environmental Medicine* 58(8):S3–S11.

Mallon, T. M., P. K. Krahl, K. M. Haines Jr, D. I. Walker, T. Thatcher, C. F. Woeller, J. Thakar, P. K. Hopke, J. C. Gaydos, M. R. Smith, and K. Uppal. 2019. Use of biomarkers to assess environmental exposures and health outcomes in deployed troops. *Journal of Occupational and Environmental Medicine* 61:S1–S4.

Mancuso, J. D., T. M. Mallon, and J. C. Gaydos. 2015. Maximizing the capabilities of the DoD serum repository to meet current and future needs: Report of the needs panel. *Military Medicine* 180(Suppl 10):13–24.

Marmor, M., D. J. Stein, and A. C. Todd. 2009. Pilot study of X-ray fluorescence for estimation of exposure to World Trade Center (WTC) dust and smoke. Meeting abstract. Annual Meeting of the American Thoracic Society. San Diego, CA. https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2009.179.1_MeetingAbstracts.A3667 (accessed June 12, 2020).

Masiol, M., C. T. M. Mallon, K. M. Haines, Jr., M. J. Utell, and P. K. Hopke. 2016a. Airborne dioxins, furans, and polycyclic aromatic hydrocarbons exposure to military personnel in Iraq. *Journal of Occupational and Environmental Medicine* 58(8S):S22–S30.

Masiol, M., C. T. M. Mallon, K. M. Haines, Jr., M. J. Utell, and P. K. Hopke. 2016b. Source apportionment of airborne dioxins, furans, and polycyclic aromatic hydrocarbons at a United States forward operating air base during the Iraq war. *Journal of Occupational and Environmental Medicine* 58(8S):S31–S37.

Masri, S., E. Garshick, B. A. Coull, and P. Koutrakis. 2017a. A novel calibration approach using satellite and visibility observations to estimate fine particulate matter exposures in Southwest Asia and Afghanistan. *Journal of the Air and Waste Management Association* 67(1):86–95.

Masri, S., E. Garshick, J. Hart, W. Bouhamra, and P. Koutrakis. 2017b. Use of visual range measurements to predict fine particulate matter exposures in Southwest Asia and Afghanistan. *Journal of the Air and Waste Management Association* 67(1):75–85.

Mauzy, C. 2019. *Toxicity evaluation and biomarker identification in rats exposed to burn pit emissions and respirable sand from Afghanistan*. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019.

Meffert, B. N., D. M. Morabito, D. A. Sawicki, C. Hausman, S. M. Southwick, R. H. Pietrzak, and A. J. Heinz. 2019. U.S. veterans who do and do not utilize VA health care services: Demographic, military, medical, and psychosocial characteristics. *Primary Care Companion for CNS Disorders* 21(1):18m02350.

Meng, X., M. J. Garay, D. J. Diner, O. V. Kalashnikova, J. Xu, and Y. Liu. 2018. Estimating $PM_{2.5}$ speciation concentrations using prototype 4.4 km-resolution MISR aerosol properties over Southern California. *Atmospheric Environment* 181:70–81.

Moeller, J. R., V. F. Kalasinsky, M. Razzaque, J. A. Centeno, E. J. Dick, M. Abdal, I. I. Petrov, T. W. DeWitt, M. Al-Attar, and J. M. Pletcher. 1994. Assessment of the histopathological lesions and chemical analysis of feral cats to the smoke from the Kuwait oil fires. *Journal of Environmental Pathology, Toxicology and Oncology* 13(2):137–149.

Moore, M., E. Eiseman, G. Fisher, S. S. Olmsted, P. R. Sama, and J. A. Zambrano. 2010. *Harnessing full value from the DoD Serum Repository and the Defense Medical Surveillance System*. Santa Monica, CA: RAND Corporation. https://www.rand.org/pubs/monographs/MG875.html (accessed March 22, 2020).

Morris, M. J. 2015. Discussion summary: Recommendation for surveillance spirometry in military personnel (Chapter 9). In C. P. Baird and D. K. Harkins (eds.), *Airborne hazards related to deployment*. Fort Sam Houston, TX: The Borden Institute, U.S. Army Medical Department. Pp. 95–102.

NASA (National Aeronautics and Space Administration). 2020. *Air quality*. https://earthdata.nasa.gov/earth-observation-data/near-real-time/hazards-and-disasters/air-quality (accessed June 12, 2020).

NASEM (National Academies of Sciences, Engineering, and Medicine). 2016a. *Evaluation of the Congressionally Directed Medical Research Programs review process*. Washington, DC: The National Academies Press.

NASEM. 2016b. *Gulf War and health: Volume 10: Update of health effects of serving in the Gulf War, 2016*. Washington, DC: The National Academies Press.

NASEM. 2017. *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry*. Washington, DC: The National Academies Press.

NASEM. 2018a. *Feasibility of addressing environmental exposure questions using the Department of Defense biorepositories: Proceedings of a workshop—in brief*. Washington, DC: The National Academies Press.

NASEM. 2018b. *Gulf War and health: Volume 11: Generational health effects of serving in the Gulf War*. Washington, DC: The National Academies Press.

NASEM. 2018c. *Informing environmental health decisions through data integration: Proceedings of a workshop—in brief*. Washington, DC: The National Academies Press.

NIEHS (National Institute of Environmental Health Sciences). 2020. *Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription (TaRGET) program*. https://www.niehs.nih.gov/research/supported/health/envepi/target/index.cfm (accessed April 27, 2020).

NIH (National Institutes of Health). 2020a. *Exposure analysis resources*. https://www.niehs.nih.gov/research/supported/exposure/hhear/index.cfm (accessed March 8, 2020).

NIH. 2020b. *Environmental health sciences core centers*. https://www.niehs.nih.gov/research/supported/centers/core/index.cfm (accessed March 8, 2020).

NOAA (National Oceanic and Atmospheric Administration). 2020. *READY: Real-Time Environmental Applications and Display sYstem*. https://www.ready.noaa.gov (accessed March 8, 2020).

NRC (National Research Council). 1989. *Biologic markers in pulmonary toxicology*. Washington, DC: National Academy Press.

NRC. 2010. *Review of the Department of Defense Enhanced Particulate Matter Surveillance Program report*. Washington, DC: The National Academies Press.

O'Neill, M. S., M. Jerrett, I. Kawachi, J. I. Levy, A. J. Cohen, N. Gouveia, P. Wilkinson, T. Fletcher, L. Cifuentes, J. Schwartz, and Workshop on Air Pollution and Socioeconomic Conditions. 2003. Health, wealth, and air pollution: Advancing theory and methods. *Environmental Health Perspectives* 111(16):1861–1870.

Pan, Y. L., J. D. Houck, P. A. Clark, and R. G. Pinnick. 2013. Single particle size and fluorescence spectra from emissions of burning materials in a tube furnace to simulate burn pits. *Applied Physics B* 112(1):89–98.

Perdue, C. L., A. A. Cost, M. V. Rubertone, L. E. Lindler, and S. L. Ludwig. 2015. Description and utilization of the United States Department of Defense Serum Repository: A review of published studies, 1985–2012. *PLOS ONE* 10:e0114857

Platel, A., K. Privat, S. Talahari, A. Delobel, G. Dourdin, E. Gateau, S. Simar, Y. Saleh, J. Sotty, S. Antherieu, and L. Canivet. 2020. Study of in vitro and in vivo genotoxic effects of air pollution fine ($PM_{2.5–0.18}$) and quasi-ultrafine ($PM_{0.18}$) particles on lung models. *Science of the Total Environment* 711:134666.

Porter, K. L., F. H. Y. Green, R. A. Harley, V. Vallyathan, V. Castranova, N. R. Waldron, S. S. Leonard, D. E. Nelson, J. A. Lewis, and D. A. Jackson. 2015. Evaluation of the pulmonary toxicity of ambient particulate matter from Camp Victory, Iraq. *Journal of Toxicology and Environmental Health, Part A* 78(23–24):1385–1408.

Portier, C. J., K. T. Tart, S. R. Carter, C. H. Dilworth, A. E. Grambsch, J. Gohlke, J. Hess, S. N. Howard, G. Luber, J. T. Lutz, and T. Maslak. 2013. A human health perspective on climate change: A report outlining the research needs on the human health effects of climate change. *Journal of Current Issues in Globalization* 6(4):621.

Pugh, M. J., C. A. Jaramillo, K. Leung, P. Faverio, N. Fleming, E. Mortensen, M. E. Amuan, C. Wang, B. Eapen, M. Restrepo, and M. J. Morris. 2016. Increasing prevalence of chronic lung disease in veterans of the Wars in Iraq and Afghanistan. *Military Medicine* 181(5):476-481.

Querol, X., A. Tobaís, N. Perez, A. Karanasiou, F. Amato, M. Stafoggia, C. Pérez García-Pando, P. Ginoux, F. Forastiere, S. Gumy, P. Mudu, and A. Alastuey. 2019. Monitoring the impact of desert dust outbreaks for air quality for healthy studies. *Environment International* 130(104867):1–16.

Repine, J. E., P. Wilson, N. Elkins, J. Klawitter, U. Christians, B. Peters, and D. M. Smith. 2016. Inhalation of two putative Gulf War toxins by mice. *Journal of Environmental Science and Health, Part B* 51(6):366–373.

Rinker, J. P. 2011. *Retrospective geospatial modeling of* PM_{10} *exposures from open burning at Joint Base Balad, Iraq*. Thesis presented to the faculty, Department of Systems and Engineering Management, Graduate School of Engineering and Management, Air Force Institute of Technology, Air University, Air Education and Training Command, in partial fulfillment of the requirements for the Degree of Master of Science in Industrial Hygiene. http://www.dtic.mil/dtic/tr/fulltext/u2/a539684.pdf (accessed February 20, 2020).

Robinson, A. 1995. Veterans worry that unexplained medical problems a legacy of service during Gulf War. *Canadian Medical Association Journal* 152:944–947.

Rohrbeck, P., Z. Hu, and T. M. Mallon. 2016. Assessing health outcomes after environmental exposures associated with open pit burning in deployed U.S. service members. *Journal of Occupational and Environmental Medicine* 58(8 Suppl 1):S104–S110.

Rubertone, M. V., and J. F. Brundage. 2002. The Defense Medical Surveillance System and the Department of Defense Serum Repository: Glimpses of the future of public health surveillance. *American Journal of Public Health* 92(12):1900–1904.

Saers, J., L. Ekerljung, B. Forsberg, and C. Janson. 2017. Respiratory symptoms among Swedish soldiers after military service abroad: Association with time spent in a desert environment. *European Clinical Respiratory Journal* 4:1–6.

Salamon, R. C. Verret, M. A. Jutand, M. Bégassat, F. Laoudj, F. Conso, and P. Brochard. 2006. Health consequences of the first Persian Gulf War on French troops. *International Journal of Epidemiology* 35:479–487.

Sanders, J. W., S. D. Putnam, C. Frankart, R. W. Frenck, M. R. Monteville, M. S. Riddle, D. M. Rockabrand, T. W. Sharp, and D. R. Tribble. 2005. Impact of illness and non-combat injury during Operations Iraqi Freedom and Enduring Freedom (Afghanistan). *American Journal of Tropical Medicine and Hygiene* 73(4):713–719.

Schwartz, M., and J. Church. 2013. *Department of Defense's use of contractors to support military operations: Background, analysis, and issues for Congress*. Washington DC: Congressional Research Service. https://fas.org/sgp/crs/natsec/R43074.pdf (accessed June 12, 2020).

Sharkey, J. M., C. Baird, A. Eick-Cost, L. Clark, Z. Hu, S. Ludwig, and J. Abraham. 2015. Review of epidemiological analyses of respiratory health outcomes after military deployment to burn pit locations with respect to feasibility and design issues highlighted by the Institute of Medicine. In *Airborne hazards related to deployment*, edited by C. P. Baird and D. K. Harkins. Fort Sam, TX: Borden Institute, U.S. Army Medical Department Center and School. Pp. 291–304.

Sim, M., M. Abramson, A. Forbes, D. Glass, J. Ikin, P. Itak, H. Kelsall, K. Leder, D. McKenzie, and J. McNeil. 2003. *Australian Gulf War Veterans' Health Study 2003*. Canberra, Australia: Department of Veterans' Affairs. https://www.dva.gov.au/sites/default/files/files/consultation%20and%20grants/healthstudies/gulfwar/gulfwarvolone.pdf (accessed July 21, 2020).

Sim, M., D. Clarke, B. Forbes, D. Glass, S. Gwini, J. Ikin, H. Kelsall, D. McKenzie, B. Wright, A. McFarlane, M. Creamer, and K. Horsley. 2015. *Australian Gulf War Veterans' Follow Up Health Study technical report 2015*. Canberra, Australia: Department of Veterans' Affairs. https://www.dva.gov.au/sites/default/files/files/consultation%20and%20grants/healthstudies/gulfwar/follow_up2015/aus_gulf_war_follow_up_tech_report2015.pdf (accessed June 12, 2020).

Smith, B., C. A. Wong, T. C. Smith, E. J. Boyko, G. D. Gackstetter, and A. K. Margaret Ryan for the Millennium Cohort Study Team. 2009. Newly reported respiratory symptoms and conditions among military personnel deployed to Iraq and Afghanistan: A prospective population-based study. *American Journal of Epidemiology* 170(11):1433–1442.

Smith, B., C. A. Wong, E. J. Boyko, C. J. Phillips, G. D. Gackstetter, M. A. Ryan, T. C. Smith, and Millennium Cohort Study Team. 2012. The effects of exposure to documented open-air burn pits on respiratory health among deployers of the Millennium Cohort Study. *Journal of Occupational and Environmental Medicine* 54(6):708–716.

Smith, J. P., D. J. Brabander, L. A. Panek, and J. R. Besancon. 2019. Enrichment of potentially toxic elements in the fine fraction of soils from Iraq and Kuwait. *Journal of Soils and Sediments* 19:3545–3563.

Smith, M. R., D. I. Walker, K. Uppal, M. J. Utell, P. K. Hopke, T. M. Mallon, P. L. Krahl, P. Rohrbeck, Y.-M. Go, and D. P. Jones. 2019a. Benzo[a]pyrene perturbs mitochondrial and amino acid metabolism in lung epithelial cells and has similar correlations with metabolic changes in human serum. *Journal of Occupational and Environmental Medicine* 61:S73–S81.

Smith, M. R., C. F. Woeller, K. Uppal, T. H. Thatcher, D. I. Walker, P. K. Hopke, P. Rohrbeck, T. M. Mallon, P. L. Krahl, M. J. Utell, Y.-M. Go, and D. P. Jones. 2019b. Associations of benzo(ghi)perylene and heptachlorodibenzo-*p*-dioxin in serum of service personnel deployed to Balad, Iraq, and Bagram, Afghanistan, correlates with perturbed amino acid metabolism in human lung fibroblasts. *Journal of Occupational and Environmental Medicine* 61:S35–S44.

Smith, M. R., K. Uppal, D. I. Walker, M. J. Utell, P. K. Hopke, T. M. Mallon, P. L. Krahl, P. Rohrbeck, Y. M. Go, and D. P. Jones. 2019c. Environmental chemicals altered in association with deployment for high risk areas. *Journal of Occupational and Environmental Medicine* 61:S15–S24.

Smith, T. C., J. M. Heller, T. I. Hooper, G. D. Gackstetter, and G. C. Gray. 2002. Are Gulf War veterans experiencing illness due to exposure to smoke from Kuwaiti oil well fires? Examination of Department of Defense hospitalization data. *American Journal of Epidemiology* 155(10):908–917.

Sørensen, M., R. P. Schins, O. Hertel, and S. Loft. 2005. Transition metals in personal samples of $PM_{2.5}$ and oxidative stress in human volunteers. *Cancer Epidemiology and Prevention Biomarkers* 14(5):1340–1343.

Spira, A. E., and E. Moses. 2017. *Detection of Early Lung Cancer Among Military Personnel (DECAMP)*. Report to the U.S. Army Medical Research and Materiel Command. Contract W81XWH-11-2-0161. https://apps.dtic.mil/dtic/tr/fulltext/u2/1047603.pdf (accessed March 6, 2020).

Statistics Canada. 2005. *The Canadian Persian Gulf Cohort Study: Detailed report*. https://www.veterans.gc.ca/pdf/about-us/research-directorate/gulf-war-linkage-project.pdf (accessed June 12, 2020).

Stein, A. F., R. R. Draxler, G. D. Rolph, B. J. B. Stunder, M. D. Cohen, and F. Ngan. 2015. NOAA's HYSPLIT atmospheric transport and dispersion modeling system. *Bulletins of the American Meteorological Society* 96:2059–2077.

Sullivan, K., and N. Klimas. 2019. *Military veteran biorepositories*. Presented to the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019. https://www.nationalacademies.org/event/10-03-2019/committee-on-the-respiratory-health-effects-of-airborne-hazards-exposures-in-the-southwest-asia-theater-of-military-operations-workshop-and-meeting-3 (accessed February 21, 2020).

Szema, A. M., R. J. Reeder, A. D. Harrington, M. Schmidt, J. Liu, M. Golightly, T. Rueb, and S. A. Hamidi. 2014. Iraq dust is respirable, sharp, metal-laden, and induces lung inflammation with fibrosis in mice via IL-2 upregulation and depletion of regulatory T cells. *Journal of Occupational and Environmental Medicine* 56(3):243–251.

Taylor, G., V. Rush, A. Deck, and J. A. Vietas. 2008. *Screening health risk assessment: Burn pit exposures, Balad Air Base, Iraq, and addendum report*. IOH-RS-BR-TR-2008-0001/USACHPPM 47-MA-08PV-08. Brooks City-Base, TX: Air Force Institute for Operational Health and U.S. Army Center for Health Promotion and Preventative Medicine. May.

Taylor, K., M. L. Foster, J. M. Law, J. A. Centeno, E. Fornero, M. S. Henderson, S. A. Trager, M. G. Stockelman, and D. C. Dorman. 2013. Assessment of geographical variation in the respiratory toxicity of desert dust particles. *Inhalation Toxicology* 25(7):405–416.

Thakar, J., T. H. Thatcher, M. R. Smith, C. F. Woeller, D. I. Walker, M. J. Utell, P. K. Hopke, T. M. Mallon, P. L. Krahl, P. Rohrbeck, Y.-M. Go, D. P. Jones, and K. Uppal. 2019. Integrative network analysis linking clinical outcomes with environmental exposures and molecular variations in service personnel deployed to Balad and Bagram. *Journal of Occupational and Environmental Medicine* 61(12S):S65–S74.

Thatcher, T. H., C. F. Woeller, J. Thakar, A. Khan, P. K. Hopke, M. R. Smith, K. Uppal, D. I. Walker, Y.-M. Go, D. P. Jones, P. L. Krahl, T. M. Mallon, P. J. Sime, R. P. Phipps, and M. J. Utell. 2019. Analysis of postdeployment serum samples identifies potential biomarkers of exposure to burn pits and other environmental hazards. *Journal of Occupational and Environmental Medicine* 61:S45–S54.

Therkorn, J. 2019. *Exposure assessment in a military environment: Tools and methods*. Presentation before the Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations. October 3, 2019.

Toth, C. 2015. *Balad Air Base burn pit study observations (Boots on the ground)*. Presentation before the Committee on the Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry. May 1, 2015.

Unwin, C., N. Blatchley, W. Coker, S. Ferry, M. Hotopf, L. Hull, K. Ismail, I. Palmer, A. David, and S. Wessely. 1999. Health of UK servicemen who served in Persian Gulf War. *Lancet* 353:169–178.

Ursano, R. J., L. J. Colpe, S. G. Heeringa, R. C. Kessler, M. Schoenbaum, M. B. Stein, and Army STARRS collaborators. 2014. The Army Study To Assess Risk and Resilience in Servicemembers (Army STARRS). *Psychiatry: Interpersonal and Biological Processes* 77(2):107–119.

VA (Department of Veterans Affairs). 2019. *Database and methods cyberseminar series session #4: Ascertaining veterans' vital status: VA data sources for mortality ascertainment and cause of death*. Presentation, VA Health Services Research and Development. https://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/3544-notes.pdf (accessed February 23, 2020).

VA. 2020. *Electronic health record modernization fact sheet*. (Revised January 2020). Office of Electronic Health Record Modernization. https://www.ehrm.va.gov/resources/factsheet (accessed February 21, 2020).

VA. n.d. *Using data to prevent veteran mortality. A guide to accessing and understanding mortality data in the VA Mortality Data Repository*. https://www.mirecc.va.gov/suicideprevention/documents/VA_DoD-MDR_Flyer.pdf (accessed February 23, 2020).

VA–DoD Joint Executive Committee. 2019. *Joint Strategic Plan Fiscal Years 2019–2021*. https://prhome.defense.gov/Portals/52/Documents/VA-DoD%20FY%202019-2021%20JSP%20(signed%20March%2018%202019).pdf (accessed July 21, 2020).

Walker, D. I., T. Mallon, P. K. Hopke, K. Uppal, YM. Go, P. Rohrbeck, K. D. Pennell, and D. P. Jones. 2016. Deployment-associated exposure surveillance with high-resolution metabolomics. *Journal of Occupational and Environmental Medicine* 58(8):S12–S21.

Wang, T., E. C. Pehrsson, D. Purushotham, D. Li, X. Zhuo, B. Zhang, H. A. Lawson, M. A. Province, C. Krapp, Y. Lan, C. Coarfa, T. A. Katz, W. Y. Tang, Z. Wang, S. Biswal, S. Rajagopalan, J. A. Colacino, Z. T.-Y. Tsai, M. A. Sartor, K. Neier, D. C. Dolinoy, J. Pinto, R. B. Hamanaka, G. M. Mutlu, H. B. Patisaul, D. L. Aylor, G. E. Crawford, T. Wiltshire, L. H. Chadwick, C. G. Duncan, A. E. Garton, K. A. McAllister, TaRGET II Consortium, M. S. Bartolomei, C. L. Walker, and F. L. Tyson. 2018. The NIEHS TaRGET II consortium and environmental epigenomics. *Nature Biotechnology* 36(3):225–227.

Wang, W., Y. K. Shim, J. E. Michalek, E. Barber, L. M. Saleh, B. Y. Choi, C. P. Wang, N. Ketchum, R. Costello, G. E. Marti, and R. F. Vogt, 2020. Serum microRNA profiles among dioxin exposed veterans with monoclonal gammopathy of undetermined significance. *Journal of Toxicology and Environmental Health, Part A* 83(7):269–278.

Wardall, A., and C. Grabinski. 2018. *Use of air quality dispersion models to reconstruct site exposure profiles*. No. AFRL-SA-WP-TR-2018-0011. USAFSAM/FHOF Wright-Patterson Air Force Base United States. https://apps.dtic.mil/sti/citations/AD1056010 (accessed June 12, 2020).

Wei, T., and M. Tang. 2018. Biological effects of airborne fine particulate matter ($PM_{2.5}$) exposure on pulmonary immune system. *Environmental Toxicology and Pharmacology* 60:195–201.

Weiler, B. A., T. V. Colby, T. J. Floreth, and S. E. Hines. 2018. Small airways disease in an Operation Desert Storm deployer: Case report and review of the literature on respiratory health and inhalational exposures from Gulf War I. *American Journal of Industrial Medicine* 61(10):793–801.

Wilfong, E. R., M. Lyles, R. L. Rietcheck, D. P. Arfsten, H. J. Boeckman, E. W. Johnson, T. L. Doyle, and G. D. Chapman. 2011. The acute and long-term effects of Middle East sand particles on the rat airway following a single intratracheal instillation. *Journal of Toxicology and Environmental Health, Part A* 74(20):1351–1365.

Williams, K. M., and J. Fahey. 2019. *Periodic occupational and environmental monitoring summary (POEMS) visualization pilot project*. Washington, DC: Center for a New American Security. https://www.cnas.org/publications/reports/periodic-occupational-and-environmental-monitoring-summary (accessed March 7, 2020).

Woeller, C. F., T. H. Thatcher, J. Thakar, A. Cornwell, M. R. Smith, D. P. Jones, P. K. Hopke, P. J. Sime, P. Krahl, T. M. Mallon, R. P. Phipps, and M. J. Utell. 2019. Exposure to heptachlorodibenzo-p-dioxin (HpCDD) regulates microRNA expression in human lung fibroblasts. *Journal of Occupational and Environmental Medicine* 61:S82–S89.

Woodall, B. D., D. P. Yamamoto, B. K. Gullett, and A. Touati. 2012. Emissions from small-scale burns of simulated deployed U.S. military waste. *Environmental Science and Technology* 46:10997–11003.

Xia, X., A. Carroll-Haddad, N. Brown, M. J. Utell, T. Mallon, and P. K. Hopke. 2016. Polycyclic aromatic hydrocarbons and polychlorinated dibenzo-p-dioxins/dibenzofurans in microliter samples of human serum as exposure indicators. *Journal of Occupational and Environmental Medicine* 58(8):S72–S79.

Yassin, M. F., S. K. Almutairi, and A. Al-Hemoud. 2018. Dust storms backward trajectories and source identification over Kuwait. *Atmospheric Research* 212:158–171.

Zell-Baran, L. M., R. Meehan, J. Wolff, M. Strand, S. D. Krefft, E. B. Gottschall, T. V. Macedonia, J. E. Gross, O. L. Sanders, G. C. Pepper, and C. S. Rose. 2019. Military occupational specialty codes: Utility in predicting inhalation exposures in post-9/11 deployers. *Journal of Occupational and Environmental Medicine* 61(12):1036–1040.

Appendix A

Public Meeting Agendas

March 27, 2019
OPEN SESSION
Keck Center of the National Academies
500 Fifth Street, NW, Washington, DC
Keck Room 106

1:00 p.m. **Welcome, notes on the conduct of the open session, and introduction of participants**
Mark Utell, M.D.
Chair, Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations

1:10 p.m. **Charge to the committee and background on the study—presentation and Q&A**
R. Loren Erickson, M.D., Dr.P.H.
Chief Consultant, Post Deployment Health, Patient Care Services, Veterans Health Administration (VHA), Department of Veterans Affairs (VA)

Eric Shuping, M.D., M.P.H., FAAFP
Director, Environmental Health Program—Post 911, Post Deployment Health Services, VHA, VA

2:15 p.m. **Open session adjourns**

October 3–4, 2019
OPEN SESSION
Keck Center of the National Academies
500 Fifth Street, NW, Washington, DC
E Street Conference Room

Thursday, October 3

9:15 a.m. **Meeting room opens to speakers and observers**

9:30 a.m. **Welcome, notes on the conduct of the open session, and introduction of participants**
Mark Utell, M.D.
Chair, Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations

9:45 a.m. **Roundtable on Epidemiologic Studies of Military and Veterans Health**
Michael J. Morris, M.D.
representing the Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE)

Eric Garshick, M.D., M.O.H.
representing the Service and Health Among Deployed Veterans (SHADE) study

Rudolph P. Rull, Ph.D., M.P.H.
representing the Millennium Cohort Study

Aaron Schneiderman, Ph.D., M.P.H., RN
representing the National Health Study for a New Generation of U.S. Veterans (NewGen) and Comparative Health Assessment Interview (CHAI) study

Michael J. Falvo, Ph.D.
representing the Effects of Deployment Exposures on Cardiopulmonary and Autonomic Function (AirHzds) study

Drew A. Helmer, M.D., M.S.
representing the VA Airborne Hazards and Burn Pits Center of Excellence (AHBPCE) at the War Related Illness and Injury Study Center (WRIISC) in New Jersey

R. Ryanne Wu, M.D., M.H.S.
representing the Gulf War Era Cohort and Biorepository

Colloquy on how these studies inform questions regarding the association between in-theater exposures and respiratory health outcomes

12:00 p.m. **Lunch break**

1:00 p.m. **Health research issues related to in-theater exposures**
Presenters
Timothy S. Blackwell, M.D.
Vanderbilt University Medical Center

Michael J. Morris, M.D.
Brooke Army Medical Center

Kimberly Sullivan, Ph.D.
Boston University School of Public Health

Joan Reibman, M.D.
New York University Langone Health

Karan Uppal, Ph.D.
Emory University School of Medicine

4:15 p.m. **Break**

4:30 p.m. **Public comments**
Interested persons may sign up to present their views to the committee (5 minutes per person or organization). Presentations may be made in person or remotely. The opportunity to make a presentation is offered on a first-come/first-served basis.

5:30 p.m. **Workshop suspends for the day**

Friday, October 4

8:45 a.m. **Meeting room opens to speakers and observers**

9:00 a.m. **Welcome, notes on the conduct of the open session, and introduction of participants**
Mark Utell, M.D.
Chair, Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations

9:15 a.m. **Exposure characterization and science and technology issues related to in-theater exposures**
Presenters
Steven L. Patterson, M.S.P.H., REHS/RS, CPH
Johns Hopkins University Applied Physics Laboratory

Jennifer Therkorn, Ph.D., M.P.H.
Johns Hopkins University Applied Physics Laboratory

William E. Funk, Ph.D.
Northwestern University Feinberg School of Medicine

Eric A. Hoffman, Ph.D.
University of Iowa Health Care, Carver College of Medicine

Camilla A. Mauzy, Ph.D.
Air Force Research Laboratory

Katrina M. Waters, Ph.D.
Pacific Northwest National Laboratory

12:15 p.m. **Workshop wrap-up and thank yous**
Mark Utell, M.D.
Chair, Committee on the Respiratory Health Effects of Airborne Hazards Exposures in the Southwest Asia Theater of Military Operations

12:30 p.m. **Workshop ends**

Appendix B

National Academies Reports Related to Gulf Theater Veterans' Health

Title	Year
Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Immediate Action	1995
Health Consequences of Service During the Persian Gulf War: Recommendations for Research and Information Systems	1996
Adequacy of the Comprehensive Clinical Evaluation Program: A Focused Assessment	1997
Measuring the Health of Persian Gulf Veterans: Workshop Summary	1998
Gulf War Veterans: Measuring Health	1999
Gulf War and Health: Volume 1: Depleted Uranium, Sarin, Pyridostigmine Bromide, and Vaccines	2000
Strategies to Protect the Health of Deployed U.S. Forces: Detecting, Characterizing, and Documenting Exposures	2000
Gulf War Veterans: Treating Symptoms and Syndromes	2001
Gulf War and Health: Volume 2: Insecticides and Solvents	2003
Gulf War and Health: Updated Literature Review of Sarin	2004
Gulf War and Health: Volume 3: Fuels, Combustion Products, and Propellants	2005
Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature	2006
Gulf War and Health: Volume 4: Health Effects of Serving in the Gulf War	2006

Title	Year
Posttraumatic Stress Disorder: Diagnosis and Assessment	2006
Gulf War and Health: Volume 5: Infectious Diseases	2007
Epidemiologic Studies of Veterans Exposed to Depleted Uranium: Feasibility and Design Issues	2008
Gulf War and Health: Updated Literature Review of Depleted Uranium	2008
Gulf War and Health: Volume 6: Physiologic, Psychologic, and Psychosocial Effects of Deployment-Related Stress	2008
Gulf War and Health: Volume 7: Long-Term Consequences of Traumatic Brain Injury	2009
Gulf War and Health: Volume 8: Update of Health Effects of Serving in the Gulf War	2010
Returning Home from Iraq and Afghanistan: Preliminary Assessment of Readjustment Needs of Veterans, Service Members, and Their Families	2010
Review of the Department of Defense Enhanced Particulate Matter Surveillance Program Report	2010
Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan	2011
Gulf War and Health: Treatment for Chronic Multisymptom Illness	2013
Returning Home from Iraq and Afghanistan: Assessment of Readjustment Needs of Veterans, Service Members, and Their Families	2013
Chronic Multisymptom Illness in Gulf War Veterans: Case Definitions Reexamined	2014
Gulf War and Health: Volume 9: Long-Term Effects of Blast Exposures	2014
Considerations for Designing an Epidemiologic Study for Multiple Sclerosis and Other Neurologic Disorders in Pre and Post 9/11 Gulf War Veterans	2015
Gulf War and Health: Volume 10: Update of Health Effects of Serving in the Gulf War, 2016	2016
Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry	2017
Gulf War and Health: Volume 11: Generational Health Effects of Serving in the Gulf War	2018

List current as of May 1, 2020.

REFERENCES*

IOM (Institute of Medicine). 1995. *Health consequences of service during the Persian Gulf War: Initial findings and recommendations for immediate action*. Washington, DC: National Academy Press. https://www.nap.edu/catalog/4904.

IOM. 1996. *Health consequences of service during the Persian Gulf War: Recommendation for research and information systems*. Washington, DC: National Academy Press. https://www.nap.edu/catalog/5272.

*All URLs in the references were accessed and verified on March 27, 2020.

IOM. 1997. *Adequacy of the comprehensive clinical evaluation program: A focused assessment*. Washington, DC: National Academy Press. https://www.nap.edu/catalog/6004.

IOM. 1998. *Measuring the health of Persian Gulf veterans: Workshop summary*. Washington, DC: National Academy Press. https://www.nap.edu/catalog/6260.

IOM. 1999. *Gulf War veterans: Measuring health*. Washington, DC: National Academy Press. https://www.nap.edu/catalog/9636.

IOM. 2000. *Gulf War and health: Volume 1: Depleted uranium, sarin, pyridostigmine bromide, and vaccines*. Washington, DC: National Academy Press. https://www.nap.edu/catalog/9953.

IOM. 2001. *Gulf War veterans: Treating symptoms and syndromes*. Washington, DC: National Academy Press. https://www.nap.edu/catalog/10185.

IOM. 2003. *Gulf War and health: Volume 2: Insecticides and solvents*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/10628.

IOM. 2004. *Gulf War and health: Updated literature review of sarin*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/11064.

IOM. 2005. *Gulf War and health: Volume 3: Fuels, combustion products, and propellants*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/11180.

IOM. 2006. *Amyotrophic lateral sclerosis in veterans: Review of the scientific literature*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/11757.

IOM. 2006. *Gulf War and health: Volume 4: Health effects of serving in the Gulf War*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/11729.

IOM. 2006. *Posttraumatic stress disorder: Diagnosis and assessment*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/11674.

IOM. 2007. *Gulf War and health: Volume 5: Infectious diseases*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/11765.

IOM. 2008. *Epidemiologic studies of veterans exposed to depleted uranium: Feasibility and design issues*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/12200.

IOM. 2008. *Gulf War and health: Updated literature review of depleted uranium*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/12183.

IOM. 2008. *Gulf War and health: Volume 6: Physiologic, psychologic, and psychosocial effects of deployment-related stress*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/11922.

IOM. 2009. *Gulf War and health: Volume 7: Long-term consequences of traumatic brain injury*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/12436.

IOM. 2010. *Gulf War and health: Volume 8: Update of health effects of serving in the Gulf War*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/12835.

IOM. 2010. *Returning home from Iraq and Afghanistan: Preliminary assessment of readjustment needs of veterans, service members, and their families*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/12812.

IOM. 2011. *Long-term health consequences of exposure to burn pits in Iraq and Afghanistan*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/13209.

IOM. 2013. *Gulf War and health: Treatment for chronic multisymptom illness*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/13539.

IOM. 2013. *Returning home from Iraq and Afghanistan: Assessment of readjustment needs of veterans, service members, and their families*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/13499.

IOM. 2014. *Chronic multisymptom illness in Gulf War veterans: Case definitions reexamined*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/18623.

IOM. 2014. *Gulf War and health: Volume 9: Long-term effects of blast exposures*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/18253.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2015. *Considerations for designing an epidemiologic study for multiple sclerosis and other neurologic disorders in pre and post 9/11 Gulf War veterans*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/21870.

NASEM. 2016. *Gulf War and health: Volume 10: Update of health effects of serving in the Gulf War, 2016*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/21840.

NASEM. 2017. *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/23677.

NASEM. 2018. *Gulf War and health: Volume 11: Generational health effects of serving in the Gulf War*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/25162.

NRC (National Research Council). 2000. *Strategies to protect the health of deployed U.S. forces: Detecting, characterizing, and documenting exposures*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/9767.

NRC. 2010. *Review of the Department of Defense Enhanced Particulate Matter Surveillance Program report*. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/12911.

Appendix C

Epidemiologic Studies of Respiratory Health Outcomes in Southwest Asia Theater Veterans Newly Reviewed* by the Committee

Reference[a]	Population	1990–1991 Gulf War	Post-9/11	Study Population[b]	Outcomes Assessed[c]	Smoking Status Collected[d]
Abraham and Baird, 2012	U.S. active-duty service members		X		Asthma; COPD; Pneumonia	
Abraham et al., 2012	U.S. service members		X		Respiratory Symptoms (ICD-9-CM 786); Asthma; COPD; Chronic Bronchitis	
Abraham et al., 2014	U.S. service members		X	AFHSC	Respiratory Symptoms (ICD-9-CM 786); Asthma; COPD	
Baird et al., 2012	U.S./active-duty Army personnel		X		Respiratory Symptoms (ICD-9-CM 786); Sinusitis and Rhinitis; Asthma; COPD; Acute Bronchitis (ICD-9-CM 460–466)	
Banoei et al., 2019	U.S. veterans	X	X		Interstitial Lung Disease (sarcoidosis)	
Barth et al., 2014	U.S. veterans		X	NewGen	Sinusitis and Rhinitis; Asthma; Chronic Bronchitis	X

continued

Reference[a]	Population	1990–1991 Gulf War	Post-9/11	Study Population[b]	Outcomes Assessed[c]	Smoking Status Collected[d]
Barth et al., 2016a	U.S. veterans		X	NewGen	Sinusitis and Rhinitis; Asthma; Chronic Bronchitis	X
Barth et al., 2016b	U.S. veterans	X			Mortality	
Bollinger et al., 2015	U.S. veterans		X		Mortality	
Butzko et al., 2019	U.S. veterans		X	WRIISC	Pulmonary Function Testing	X
Davy et al., 2012	Australian Defence Force active-duty personnel		X		Pulmonary Function Testing; COPD	X
DelVecchio et al., 2015	U.S. active-duty Army personnel		X		Asthma	
Díaz Santana et al., 2017	U.S. veterans		X	NewGen	Sleep Apnea	
Dion et al., 2013	U.S. Army soldiers		X		Vocal Cord Dysfunction	X
Eick et al., 2011	U.S. active-duty service members		X		Pneumonia	
Falvo et al., 2016a	U.S. veterans		X	WRIISC	Pulmonary Function Testing	X
Falvo et al., 2016b	U.S. veterans		X	WRIISC	Pulmonary Function Testing	
Forbes et al., 2019	U.S. active-duty service members		X		Interstitial Lung Disease (sarcoidosis)	
Gwini et al., 2016	Australian veterans	X			Sleep Apnea; Asthma	X
Hines et al., 2013	U.S. veterans	X		VA Depleted Uranium Surveillance Program	Respiratory Symptoms (frequent cough, coughing up phlegm, shortness of breath, wheezing); Sinusitis and Rhinitis; Pulmonary Function Testing; Asthma; Emphysema	X
Holley et al., 2016	U.S. service members, National Guard/reserves		X		Pulmonary Function Testing	X

Reference[a]	Population	1990–1991 Gulf War	Post-9/11	Study Population[b]	Outcomes Assessed[c]	Smoking Status Collected[d]
Hooper et al., 2008	U.S. active-duty veterans of Gulf War	X			Sinusitis and Rhinitis; Interstitial Lung Disease (sarcoidosis); Pneumonia	
Jani et al., 2017a	U.S. service members		X	AH&OBP Registry/ WRIISC	Respiratory Symptoms (dyspnea, decreased exercise tolerance)	X
Jani et al., 2017b	U.S. service members		X	AH&OBP Registry	Constrictive Bronchiolitis	X
Khalil et al., 2018	U.S. veterans	X		Gulf War Era Cohort and Biorepository	Respiratory Symptoms (difficulty breathing, shortness of breath, frequent coughing without a cold, wheezing in chest); Sleep Apnea; COPD; Emphysema; Constrictive Bronchiolitis; TB; Cancers	
King et al., 2011	U.S. active-duty Army soldiers		X		Constrictive Bronchiolitis	X
Krefft et al., 2017	U.S. veterans		X		Respiratory Symptoms (cough, chest tightness, wheezing, shortness of breath, decreased exercise tolerance); Pulmonary Function Testing; Emphysema; Constrictive Bronchiolitis; Interstitial Lung Disease (hypersensitivity pneumonitis)	X
Krefft et al., 2020	U.S. service members		X		Pulmonary Function Testing; Emphysema; Constrictive Bronchiolitis; Interstitial Lung Disease (hypersensitivity pneumonitis)	X
Lindheimer et al., 2019	U.S. veterans	X		WRIISC	Pulmonary Function Testing	X

continued

Reference[a]	Population	1990–1991 Gulf War	Post-9/11	Study Population[b]	Outcomes Assessed[c]	Smoking Status Collected[d]
Liu et al., 2016	U.S. service members		X	AH&OBP Registry	Asthma; COPD; Emphysema; Chronic Bronchitis	X
Madar et al., 2017	U.S. military personnel	X	X		Pulmonary Function Testing; Constrictive Bronchiolitis; Interstitial Lung Disease (sarcoidosis, acute eosinophilic pneumonia, pulmonary alveolar proteinosis, idiopathic interstitial pneumonia)	X
Matthews et al., 2014	U.S. active-duty service members		X		Pulmonary Function Testing; COPD; Emphysema	X
Maule et al., 2018	Veterans (Australia, Denmark, United Kingdom, United States)	X			Respiratory Symptoms (coughing, wheezing, shortness of breath); Sinusitis and Rhinitis; Asthma	
Morris et al., 2014	U.S. active-duty service members		X	STAMPEDE	Respiratory Symptoms (dyspnea, cough, wheeze, sputum production); Pulmonary Function Testing	
Morris et al., 2019	U.S. active-duty Army personnel		X	STAMPEDE	Respiratory Symptoms (dyspnea, cough, wheezing, sputum production, exercise intolerance); Pulmonary Function Testing	X
Morris et al., 2020	U.S. service members		X	STAMPEDE	Respiratory Symptoms (exertional dyspnea, cough, wheeze, sputum production, decreased exercise tolerance); Pulmonary Function Testing; Constrictive Bronchiolitis	X
OIF SAPEG, 2003	U.S. active duty military personnel, Reserve/National Guard		X		Interstitial Lung Disease (acute eosinophilic pneumonia)	X

Reference[a]	Population	1990–1991 Gulf War	Post-9/11	Study Population[b]	Outcomes Assessed[c]	Smoking Status Collected[d]
Peacock et al., 1997	U.S. veterans	X		Comprehensive Clinical Evaluation Program	Sleep Apnea	
Pugh et al., 2016	U.S. veterans		X		Asthma; COPD; Interstitial Lung Disease	X
Rivera et al., 2018	U.S. service members, Reserve/ National Guard		X	Millennium Cohort Study	Asthma	X
Rohrbeck et al., 2016	U.S. active-duty service members		X		Respiratory Symptoms (ICD-9-CM 786); Sleep Apnea; Cancers	
Roop et al., 2007	U.S. active-duty Army soldiers		X		Asthma	X
Saers et al., 2017	Swedish military personnel		X		Respiratory Symptoms (wheeze, wheeze with breathlessness, wheeze without a cold, nocturnal chest tightness, nocturnal breathlessness, nocturnal cough); Chronic Bronchitis	X
Sharkey et al., 2015	U.S. service members		X	AFHSC	Respiratory Symptoms (ICD-9-CM 786); Asthma; COPD; Acute Bronchitis	X
Sharkey et al., 2016	U.S. service members		X	AFHSC	Respiratory Symptoms (ICD-9-CM 786); Asthma; COPD	X
Shorr et al., 2004	U.S. active-duty service members		X		Interstitial Lung Disease (acute eosinophilic pneumonia)	X
Sine et al., 2018	U.S. active-duty service members		X		Interstitial Lung Disease (acute eosinophilic pneumonia)	X
Smith et al., 2008	U.S. active-duty service members		X	Millennium Cohort Study	Sinusitis and Rhinitis; Sleep Apnea; Asthma; Emphysema; Chronic Bronchitis	

continued

Reference[a]	Population	1990–1991 Gulf War	Post-9/11	Study Population[b]	Outcomes Assessed[c]	Smoking Status Collected[d]
Smith et al., 2009	U.S. service members, Reserve/National Guard		X	Millennium Cohort Study	Respiratory Symptoms (persistent or recurring cough or shortness of breath); Asthma; Emphysema; Chronic Bronchitis	X
Smith et al., 2012	U.S. service members		X	Millennium Cohort Study	Respiratory Symptoms (persistent or recurring cough or shortness of breath); Asthma; Emphysema; Chronic Bronchitis	X
Soltis et al., 2009	U.S. active-duty service members		X		Acute Bronchitis	
Szema et al., 2010	U.S. veterans		X		Asthma	
Szema et al., 2011	U.S. veterans		X		Pulmonary Function Testing	X
Taylor and Ross, 2019	British active-duty service personnel		X		Respiratory Symptoms (shortness of breath, wheeze, cough); Sinusitis and Rhinitis	
Weinstein et al., 2016	U.S. active-duty service members		X		Pulmonary Function Testing	
Woods et al., 2018	U.S. active-duty Army personnel				Asthma	X
Zundel et al., 2019	U.S. veterans	X			Asthma; Chronic Bronchitis	X

* "Newly Reviewed" studies are those that have not been addressed in previous National Academies reports.
[a] Full citations may be found in the References section of Chapter 4.
[b] Study populations of cohorts that were specified in the Statement of Task are noted.
[c] Only those outcomes that are addressed in the report are listed. A study may have also addressed other outcomes.
[d] An "X" indicates that information on smoking was collected, but this does not necessarily mean that it was collected consistently or used in analyses.
NOTE: AFHSC, Armed Forces Health Surveillance Center; AH&OBP, Airborne Hazards and Open Burn Pit; COPD, chronic obstructive pulmonary disease; ICD-9-CM, *International Classification of Diseases, 9th edition, Clinical Modification*; NewGen, National Health Study for a New Generation of U.S. Veterans; STAMPEDE, Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures; TB, tuberculosis; WRIISC, VA War Related Illness and Injury Study Center.

Appendix D

Committee Member and Staff Biographical Sketches

COMMITTEE MEMBERS

Mark J. Utell, M.D. (*Chair*), is a professor of medicine and environmental medicine, the director of occupational and environmental medicine, and the former director of pulmonary and critical care medicine at the University of Rochester Medical Center. His research interests center on the effects of environmental toxicants on the human respiratory tract. Dr. Utell has published extensively on the health effects of inhaled gases, particles, and fibers in the workplace and other indoor and outdoor environments. He was the co-principal investigator of an Environmental Protection Agency (EPA)-funded particulate matter research center and is a former chair of the Health Effects Institute's research committee. Dr. Utell has served as the chair of EPA's Environmental Health Committee and on the executive committee of the EPA science advisory board. He is a recipient of the National Institute of Environmental Health Sciences Academic Award in Environmental and Occupational Medicine and the Mercer Award from the International Society for Aerosols in Medicine. Dr. Utell has served on several National Academies committees, including the Committee on Research Priorities for Airborne Particulate Matter; the Committee on Research Strategy for Environmental, Health, and Safety Aspects of Engineered Nanomaterials; the Committee on Gulf War and Health: Literature Review of Selected Environmental Agents, Pollutants, and Synthetic Chemical Compounds; and the Committee on the Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry. He previously chaired the Committee on the Review of Environmental Protection Agency's Science to Achieve Results Research Program, the Committee to Review the NIOSH Respiratory Disease Research Program, the Committee for Review of the DOD's Enhanced Particulate Matter Surveillance Program Report, and the Committee on the Review of the Department of Labor's Site Exposure Matrix (SEM) Database. He also served on the Board on Environmental Studies and Toxicology. Dr. Utell received his B.A. from Dartmouth College and his M.D. from the Tufts University School of Medicine.

Lung-Chi Chen, Ph.D., is a professor in the Department of Environmental Medicine at the New York University School of Medicine. Dr. Chen's field of study is inhalation toxicology, and he has extensive experience in the measurement of the cardiopulmonary effects of inhaled pollutants. He is also an expert in the generation and characterization of exposure atmospheres and in the performance of toxicology studies using multiple routes of exposure, primarily those involving pulmonary exposure. He has served on a number of national and international committees and study sections in these areas. Dr. Chen has previously served on two National Academies committees: the Committee on Acute Exposure Guideline Levels and the Committee on Beryllium Alloy Exposures.

He is the author of more than 200 research papers and book chapters dealing with the mechanisms underlying the adverse cardiopulmonary effects resulting from exposure to occupational and environmental air pollutants. Dr. Chen earned a B.S. in public health from the National Taiwan University and an M.S. and a Ph.D. in environmental health science from New York University.

Ellen A. Eisen, Sc.D., is a professor in the School of Public Health at the University of California, Berkeley. Dr. Eisen is an occupational epidemiologist, bridging the fields of environmental health science, biostatistics, and epidemiology. Her research focuses on exposure–response modeling in occupational cohort studies, with a particular interest in methods to reduce selection bias and address time-varying confounding. She has published studies on mortality and the incidence of ischemic heart and lung disease and cancer in worker populations, with a focus on the quantitative assessment of long-term exposure to chemicals and fine particulate matter. Her professional activities include service on the editorial board of the *American Journal of Epidemiology* and on the scientific committee of the International Congress on Occupational Health—Epidemiology section. Dr. Eisen has served on numerous committees for the National Academies, including the Committee on Gulf War and Health, Volume 10: Update of Health Effects of Serving in the Gulf War and the Committee on the Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan. She earned an M.S. in operations research and statistics from the Massachusetts Institute of Technology, an M.S. in biostatistics and a Sc.D. in biostatistics and occupational health from the Harvard T.H. Chan School of Public Health.

Meredith Franklin, Ph.D., is an associate professor in the Division of Biostatistics at the Keck School of Medicine of the University of Southern California (USC). She is also the director of M.S. programs in biostatistics, health data science, and epidemiology at the Keck School of Medicine and holds an appointment at the USC Dornsife College of Letters, Arts and Sciences' Spatial Sciences Institute. Dr. Franklin's interests are in the areas of environmental statistics and epidemiology. Her research includes the development of functional regression models for dealing with spatially misaligned environmental data, spatio-temporal methods for remote sensing data, and assessment of the human health impact associated with exposure to particulate matter air pollution. She holds a B.Sc. in mathematics from McGill University, an M.Sc. in statistics from the Ottawa-Carleton Institute for Mathematics and Statistics, and a Ph.D. in statistics and environmental health from Harvard University.

Kirk D. Jones, M.D., is a clinical professor at the University of California, San Francisco (UCSF). Dr. Jones's specialty areas are pulmonary pathology and cytopathology. His research and clinical interests are primarily in pulmonary pathology and cytopathology. He is currently working on elucidating the role of airway rejection in chronic obliterative bronchiolitis, the leading cause of the failure of lung transplant graft survival. In addition, he is participating in a project to investigate the pathophysiology of acute lung injury. Dr. Jones has many publications on topics relating to these interests. He is a member of the United States & Canadian Academy of Pathology, Pulmonary Pathology Society, International Association for the Study of Lung Cancer, College of American Pathologists, and South Bay Pathology Society. Dr. Jones earned his M.D. and completed his residency in anatomic pathology and laboratory medicine at UCSF. He also completed a fellowship in cytopathology at UCSF and was subsequently a visiting scholar at the Mayo Clinic in Scottsdale, Arizona, where he studied pulmonary pathology.

Meredith C. McCormack, M.D., M.H.S., is an associate professor of medicine at the Johns Hopkins University School of Medicine with a joint appointment in environmental health and engineering at the Johns Hopkins Bloomberg School of Public Health. Dr. McCormack has clinical expertise in asthma, chronic obstructive pulmonary disease (COPD), general pulmonary and critical care medicine, as well as pulmonary physiology and pulmonary function testing. She serves as the medical director of the Johns Hopkins University Pulmonary Function Laboratory and the vice chair of the American Thoracic Society Committee on Proficiency Standards for Pulmonary Function Laboratories. Dr. McCormack is a physician–scientist with a research focus on the effect of environmental influences on underlying obstructive lung disease—specifically air pollution, diet, and obesity influences on COPD and asthma. She has been funded by the National Institute of Environmental Health Sciences and the Environmental Protection Agency to conduct environmental cohort studies to understand the effects of indoor and outdoor air pollution on children and adults with underlying respiratory disease. Her work is largely focused in Baltimore City but has included rural areas of Washington State, Appalachia, and the Caribbean. Dr. McCormack serves as the associate program director of the Johns Hopkins Pulmonary and Critical Care Fellowship program and plays an active role in mentoring fellows and junior faculty. She earned her M.D. from Jefferson Medical College of Thomas Jefferson University and her M.H.S. from the Johns Hopkins Bloomberg School of Public Health. Dr. McCormack completed an internal medicine residency at Thomas Jefferson University Hospital and a fellowship in pulmonary and critical care medicine at Johns Hopkins.

Cecile S. Rose, M.D., is a professor of medicine at National Jewish Health in the Division of Environmental and Occupational Health Sciences, with an academic appointment at the University of Colorado School of Medicine in the Division of Pulmonary Sciences and Critical Care Medicine. Her research interests focus on environmental and occupational lung diseases, specifically respiratory diseases affecting active-duty military personnel and veterans. Dr. Rose has been involved in multidisciplinary collaborative research in non-infectious granulomatous lung diseases, including sarcoidosis and hypersensitivity pneumonitis, and in mining-related lung diseases, including silicosis and rapidly progressive pneumoconiosis in coal miners. Dr. Rose has served on several National Academies committees, including the Standing Committee on Personal Protective Equipment in the Workplace, the Committee on the Study of Control of Respirable Coal Mine Dust Exposure in Underground Mines, the Committee on the Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry, the Planning Committee for the Workshop on the Integration of FDA and NIOSH Processes Used to Evaluate Respiratory Protective Devices for Health Care Workers, and the Planning Committee for a Workshop on the Use and Effectiveness of Powered Air Purifying Respirators in Health Care. Dr. Rose received her M.D. and M.P.H. from the University of Illinois. She completed her residency in internal medicine and a fellowship in pulmonary medicine at the Medical College of Virginia. She is board-certified in internal medicine, pulmonary medicine, and occupational/environmental medicine.

Frank E. Speizer, M.D., is a professor of environmental science at the Harvard T.H. Chan School of Public Health and the Edward H. Kass Distinguished Professor of Medicine at the Harvard Medical School. Dr. Speizer's research efforts are divided between his role as a senior investigator in the Environmental Epidemiology Program in the Department of Environmental Health and his responsibilities in the Channing Division of Network Medicine in the Department of Medicine. The two programs are integrated in the area of study of the natural history of respiratory diseases and in studies of environmental risks for chronic diseases, including risks for cancer and cardiorespiratory diseases. The projects in respiratory diseases involve population-based studies of large groups of subjects who are identified by acute and chronic exposure to indoor and outdoor air pollutants and monitored for symptoms and pulmonary function. He has more than 500 papers and reports published on these and on several other topics. Dr. Speizer is a member of the National Academy of Medicine. His other honors include the 2010 John Goldsmith Award in Environmental Epidemiology from the International Environmental Epidemiology Society. He has previously served on the National Academies Committee on Acute Exposure Guideline Levels, the IG14 Planning Committee, the Committee on Research Priorities for Airborne Particulate Matter, the Committee on an Assessment of a Study of Possible Occupational Health Effects on Ionizing Radiation Among Nuclear Utility Workers, and the Subcommittee on Pulmonary Toxicology. Dr. Speizer earned his M.D. from the Stanford University School of Medicine.

Elaine Symanski, Ph.D., is a professor in the Center for Precision Environmental Health and the Department of Medicine at the Baylor College of Medicine. She serves as the director of the Program in Environmental and Population Health Disparities. Dr. Symanski's primary research interests include the investigation of health effects associated with environmental and occupational exposures in vulnerable populations using community-engaged approaches; the development and application of quantitatively based approaches for evaluating occupational and environmental exposures; and retrospective exposure assessment. Her professional activities include serving as the president of the American Association of Programs in Occupational Safety and Health (in 2018), a member of the advisory committee to the Texas Cancer Registry, and an advisory board member of the Texas Occupational Health and Safety Surveillance Program. Dr. Symanski has previously served on two National Academies committees: the

Committee to Review the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens and the Committee on Contaminated Drinking Water at Camp Lejeune. She also served on the Working Group for the IARC Monograph on the Evaluation of Carcinogenic Risks to Humans–Volume 120 (Benzene). She received her Ph.D. in environmental sciences and engineering and her M.S.P.H. in environmental sciences and engineering from the University of North Carolina at Chapel Hill Gillings School of Global Public Health.

Sverre Vedal, M.D., M.Sc., is a professor emeritus in the Department of Environmental and Occupational Health Sciences at the University of Washington (UW) School of Public Health. He holds the AXA Research Fund Chair in Air Pollution and Health at the Chinese Research Academy of Environmental Sciences in Beijing, China, and works with collaborators on air pollution exposure and health studies in China. Dr. Vedal is an epidemiologist with research interests in occupational lung disease and in the adverse health effects of community air pollution. He was the director of the Environmental Protection Agency's (EPA's) Center for Clean Air Research at UW, which employed the disciplines of exposure science, toxicology, epidemiology, and biostatistics to investigate the cardiovascular health effects of exposure to multi-pollutant atmospheres. Dr. Vedal has published widely on air pollution exposure and health effects and served on advisory committees of EPA and the National Institutes of Health. He has been on two previous National Academies committees: the Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans and the Committee on Air Quality Management in the United States. Dr. Vedal received his M.D. from the University of Colorado and M.Sc. in epidemiology from Harvard University. He is board-certified in internal medicine and pulmonary medicine.

Jody Wireman, Ph.D., M.S.P.H., M.P.A., CIH, DABT, is an environmental health advisor for the Defense Health Agency, counseling senior Department of Defense officials on public health, toxicology, environmental exposure, and occupational health and safety for industrial and operational chemical, biological, and radiological hazards. In that capacity, he leads efforts to evaluate historical, ongoing, and future exposures, refining Joint Health Risk Management–related capabilities and supporting personal sample collection advancements. Dr. Wireman has more than 25 years of experience as a public health professional, manager, and educator. He previously served as the director of Force Health Protection at the North American Aerospace Defense Command and U.S. Northern Command. Earlier, he was a toxicologist and a human and ecological health scientist at the U.S. Air Force School of Aerospace Medicine. His previous efforts focused on worker health protection and environmental restoration of radiologically and chemically contaminated hazardous waste sites. Dr. Wireman earned a B.S. in safety sciences from Indiana University of Pennsylvania, an M.S.P.H. from the University of Alabama at Birmingham, a mid-career M.P.A. from Harvard University, and a Ph.D. in environmental toxicology from Texas Tech University.

STAFF

David A. Butler, Ph.D., is a scholar in and the director of the Office of Military and Veterans Health in the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine. Before joining the National Academies, Dr. Butler served as an analyst for the U.S. Congress Office of Technology Assessment, was a research associate in the Department of Environmental Health of the Harvard T.H. Chan School of Public Health, and conducted research at Harvard's John F. Kennedy School of Government. He has directed several National Academies studies on military and veterans health, environmental health, and risk assessment topics, including ones that produced *Veterans and Agent Orange: Update 1998*, *Update 2000*, and *Update 11*; *Damp Indoor Spaces and Health*; *Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry*; *Future Uses of the Department of Defense Joint Pathology Center Biorepository*; and the report series *Characterizing the Exposure of Veterans to Agent Orange and Other Herbicides Used in Vietnam*. Dr. Butler earned his B.S. and M.S. in electrical engineering from the University of Rochester and his Ph.D. in public policy analysis from Carnegie Mellon University. He is a recipient of the National Academies' Cecil Medal for Research.

Elizabeth Barksdale Boyle, M.P.H., CIH, has more than 15 years of experience in environmental health and epidemiology. She recently joined the Health and Medicine Division as a program officer after serving within the

Division on Earth and Life Studies of the National Academies of Sciences, Engineering, and Medicine. Formerly she was an environmental health scientist at Westat, where she supported the Environmental Protection Agency, the National Institute of Child Health and Human Development, and the National Cancer Institute by completing other environmental epidemiology–related projects. Prior to her tenure at Westat, Ms. Boyle was a student epidemiologist at the Minnesota Department of Health and an industrial hygienist at a consulting firm in Cincinnati. She serves as the chair of the nominations committee for the International Society of Exposure Science. Ms. Boyle is a fellow of the Bloomberg American Health Initiative at the Johns Hopkins Bloomberg School of Public Health, where she is pursuing a doctorate of public health in environmental health.

Christina R. Samuel, M.P.H., is a research associate for the Board on Population Health and Public Health Practice in the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine. As a graduate student, Ms. Samuel worked at the Rutgers Center for Tobacco Studies, where she evaluated tobacco control initiatives, wrote technical summaries, and assisted with research projects. She has also interned at the Association of Schools and Programs of Public Health in Washington, DC, where she worked on undergraduate and graduate public health education initiatives. Prior to joining the National Academies, Ms. Samuel worked with the Nurses' Health Study team in the Channing Division of Network Medicine at Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health, where she helped assist and coordinate gut microbiome research among health care professionals. Ms. Samuel earned her B.S. in public health and her M.P.H. in epidemiology from Rutgers University in New Brunswick, New Jersey.

Rebecca F. Chevat is a senior program assistant in the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine. She was a recipient of a Health and Medicine Division Spot Award in 2019. Ms. Chevat graduated from American University in 2018. She received her B.A. in public health with concentrations in psychology and political science. During her undergraduate career, she worked in the Office of the Secretary and in the Office of Health Affairs at the Department of Homeland Security, where she examined public–private partnerships and their role on points of dispensing models during emergencies. Ms. Chevat also has experience working on Capitol Hill and on political campaigns. Additionally, she is a National Registered Emergency Medical Technician. She plans to pursue her M.P.H. in global health.

Anne N. Styka, M.P.H., is a senior program officer in the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine. Over her tenure, she has worked on more than 12 studies, and directed or co-directed 6 of them, on a broad range of topics related to the health of military and veteran populations. Studies have included mental health treatment offered in the Department of Defense and the Department of Veterans Affairs; designing and evaluating epidemiologic research studies of deployment-related exposures, including burn pits, dioxin, and other chemicals and the use of antimalarial drugs; and directing a research program of fostering new research studies using data and biospecimens collected as part of the 20-year Air Force Health Study. Before coming to the National Academies, Ms. Styka spent several years working as an epidemiologist for the New Mexico Department of Health and the Albuquerque Area Southwest Tribal Epidemiology Center, specializing in survey design and analysis of behavioral risk factors and injury. She also spent several months in Zambia as the epidemiologist on a study of silicosis and other nonmalignant respiratory diseases among copper miners. She has several peer-reviewed publications and has contributed to numerous state and national reports. She received her B.S. in cell and tissue bioengineering from the University of Illinois at Chicago and has an M.P.H. in epidemiology from the University of Michigan. Ms. Styka was the 2017 recipient of the National Academies' Division on Earth and Life Studies Mount Everest Award, the 2015 recipient of the Institute of Medicine and National Academy of Medicine Multitasker Award, and a member of the 2011 National Academies' Distinguished Group Award.

Kristin E. White is an associate program officer in the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine. Previously a medical writer and editor, she worked across numerous medical specialties and drug classes to create materials for, and resulting from, continuing medical education programs, international medical symposia, and drug and research advisory board meetings. She worked on programs at the annual meetings of the American Academy of Allergy, Asthma & Immunology; American College of Cardiology; American College of Gastroenterology; American College of Rheumatology; American College of Obstetricians and Gynecologists; American Diabetes Association; American Heart Association; European College of Cardiology; European Society for Sexual and Impotence Research; Heart Failure Society of America; and International Congress of Cardiology. She received an A.B. from Princeton University.

Rose Marie Martinez, Sc.D., has been the senior board director of the National Academies of Sciences, Engineering, and Medicine's Board on Population Health and Public Health Practice (BPH) since 1999. BPH has a vibrant portfolio of studies that address high-profile and cutting-edge issues that affect population health. It addresses the science base for population health and public health interventions and examines the capacity of the health system, particularly the public health infrastructure, to support disease prevention and health promotion activities, including the education and supply of health professionals necessary for carrying them out. BPH has examined such topics as the safety of childhood vaccines and other drugs; systems for evaluating and ensuring drug safety post-marketing; the health effects of cannabis and cannabinoids; the health effects of environmental exposures; population health improvement strategies; integration of medical care and public health; women's health services; health disparities; health literacy; tobacco control strategies; and chronic disease prevention, among others. Dr. Martinez was awarded the 2010 Institute of Medicine (IOM) Research Cecil Award for significant contributions to IOM reports of exceptional quality and influence. Prior to joining the National Academies, Dr. Martinez was a senior health researcher at Mathematica Policy Research (1995–1999), where she conducted research on the impact of health system change on public health infrastructure, access to care for vulnerable populations, managed care, and the health care workforce. Dr. Martinez is a former assistant director for health financing and policy with the U.S. General Accounting Office, where she directed evaluations and policy analysis in the area of national and public health issues (1988–1995). Her experience also includes 6 years directing research studies for the Regional Health Ministry of Madrid, Spain (1982–1988). Dr. Martinez is a member of the Council on Education for Public Health, the accreditation body for schools of public health and public health programs. She received the degree of doctor of science from the Johns Hopkins School of Hygiene and Public Health.