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 extin-

guished (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 model of 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.