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Occupational exposure to asbestos and cardiovascular related diseases: A meta-analysis

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ABSTRACT

Asbestos has become one of the leading causes of death among occupational workers in the world. The association between asbestos and cardiovascular disease is less reported. We performed a meta-analysis to quantify the association between asbestos exposure and the mortality of cardiovascular related diseases. We performed a systematic review in the PubMed database before December 2014. All cohort studies citing the standardized mortality ratio (SMR) of cardiovascular related diseases in workers exposed to asbestos were collected. We then calculated the pooled standardized mortality ratios of such diseases. Sixteen studies were included. The combined results from all studies indicated the pooled SMR estimate for cardiovascular related diseases was 1.11 (95% CI, 1.01–1.22). This meta-analysis showed that asbestos exposure significantly increased the risk of cardiovascular related diseases in exposed workers.

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Contents

Introduction

Asbestos designates a group of naturally occurring silicate minerals used commercially for their desirable physical properties. The harmful effects of asbestos, however, have made it one of the world's leading causes of death among occupational workers. For example, asbestos is one the most important occupational carcinogens, causing about one half of all deaths from cancer linked to workplace exposure (Driscoll et al., 2005). Currently, approximately 125 million workers are exposed to asbestos worldwide and at least 107,000 of them die from asbestos-related diseases every year (Burki, 2009). Despite progressively more stringent regulations controlling occupational exposure to asbestos, the asbestos-related disease epidemic has not eased. It is well accepted that occupational exposure to asbestos predicts incidence of various diseases such as lung cancer, asbestosis, or mesothelioma (Selikoff & Seidman, 1991; Lotti, 2010) but the association

Abbreviations: SMR, Standard mortality ratio; SEs, Standard errors; CI, Confidence interval; CD, Circulatory diseases; IHD, Ischemic heart disease; ODH, Other diseases of the heart; PHD, Pulmonary heart diseases; AHD, All heart diseases.

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between asbestos and non-respiratory diseases such as cardiovascular disease is less clear.

Chronic inflammation processes plays an important role in the pathogenesis of cardiovascular diseases (Libby, 2006). A growing body of evidence suggests that long-term exposure to combustion particles is associated with atherosclerosis and cardiovascular diseases (Hassing et al., 2009; Hoek et al., 2013). In addition, silica, a non-combustion particle, has also been reported to increase mortality from cardiovascular diseases in a cohort study of 74,040 workers. The standardized mortality ratios of ischemic heart disease (1.65, 1.35–1.99) were significantly elevated among workers exposed to respirable silica concentrations equal to or lower than 0.1 mg/m^3 (Chen et al., 2012). Asbestos, a kind of silicate, can also induce a strong inflammatory reaction in animal models and promotes atherogenesis (Gardner et al., 1986; Dogra & Donaldson, 1995; Dostert & Petrilli, 2008; Cyphert et al., 2012). However, little attention has been given to adverse health effects of asbestos exposure on cardiovascular system. It could be hypothesized that asbestos may be a risk factor of cardiovascular events. Certainly, some cohort studies have suggested an association between the increased risk of cardiovascular diseases and exposure to asbestos (Loomis et al., 2009; Harding et al., 2012) but there are also quite a number of studies which provide negative results (Battista et al., 1999; Sichletidis et al., 2009). The mortality of cardiovascular events in these studies which focus on the major asbestos-related diseases, namely lung cancer or mesothelioma, was not studied in depth. The potential role of chance, confounding factors, and other forms of bias were not taken into account. For this reason, this meta-analysis of the epidemiologic evidence was conducted. Our objective was to quantify the association between asbestos exposure and the mortality of cardiovascular related diseases.

Materials and methods

Search strategy

All published studies citing the SMR of cardiovascular diseases in workers exposed to asbestos were collected by conducting a search on PubMed before December 2014. The following key words were used: “cardiovascular diseases,” “heart diseases,” “mortality,” “incidence,” “asbestos,” “crocidolite,” “chrysotile,” “amphibole,” and “amosite.” In addition, we searched all the references of collected studies to identify additional relevant reports. Individual studies and the data extracted were reviewed independently by two authors using a standardized form. We screened titles first and then a second screening on abstracts and full-text was considered. Only English language full-text papers were included that reported either SMR or observed and expected deaths in cohort study. The studies were excluded if there were not sufficient data to provide for the determination of standardized mortality ratio and confidence interval. If different opinions on including or excluding one paper appeared, the disagreement was resolved by voting among all authors. If a study made a stratified analysis based on gender, type of cardiovascular related diseases or kind of asbestos exposed, the results of stratification analysis were set as new literatures to be included. Each study was reviewed critically and the following data was extracted: (1) Author of the paper and year of publication, (2) Type of cardiovascular related disease, (3) Country of origin, (4) Type of industry and asbestos exposed in the study, (5) Number of the cohort and the information of gender, (6) Follow-up of study participants, (7) The SMR and the confidence interval for the SMR, (8) Assessment of asbestos exposure and (9) All-cause mortality. Details of the papers were summarized in Table 1.

Statistical analysis

Statistical analysis was conducted on natural logarithm of the SMR, the ln-SMR, because its sampling distribution more closely approximates a normal distribution proves more useful analyzing a combination of papers on different participants. Based on the reported confidence interval, we calculated the standard errors (SEs) for the ln(SMR) given by the formula SE = [ln(upper limit) − ln(lower limit)] / 3.92. Overall pooled SMR estimates and corresponding 95% CIs were calculated using fixed-effects (Manel–Haenszel method) and random-effects (DerSimonian and Laird method) methods (Harris, 2008). Because of the significant amount of heterogeneity, we only presented the random-effects estimates. Meta-regression techniques were used to determine the extent to which variables following might explain heterogeneity: gender (male, female, or gender mixed), geographic region (United States vs. Europe), type of industry (textiles, mining, cement, mixed, or others) magnitude of the SMR for all causes (≤1.0 or >1.0), type of asbestos (crocidolite, chrysotile, amphibole, amosite, or mixed), type of cardiovascular diseases (circulatory diseases, ischemic disease, pulmonary heart disease, all heart diseases, or others), and follow-up period (<35 or ≥35 years). To assess heterogeneity not only among studies but also between sub groups, we used the I^2 and Q statistics. For I^2, a value >25% was considered a measure of heterogeneity; for the Q statistic, $P_Q < 0.10$ indicated significant heterogeneity(Higgins & Thompson, 2002). Paper bias was assessed by visual inspection of Begg's funnel plots and investigated using Egger's regression asymmetry method formally. We defined statistical significance as p-value < 0.05 for all analyses except for the heterogeneity. All meta-analyses were completed with Stata software (Version 10.0; StataCorp, College Station, TX).

Results

Literature search

A total 1124 unique citations were initially retrieved from the PubMed database. The majority of these were excluded after the first screening on titles or abstracts, mainly because they were not cohort studies or not English papers, no SMR of cardiovascular related diseases reported, or not relevant to our research. After review of 29 full-text papers, 10 studies were excluded because of incomplete confidence interval information. For three studies in which the data analysis of the cohort was updated, we chose the most recent (Musk et al., 2008; Pira et al., 2009; Harding et al., 2012) and excluded 3 papers from the previous report. Finally, 16 studies were included in our analysis (Fig. 1).

Study characteristics

The characteristics of the 16 studies included are given in Table 1. Nine of the studies were conducted in European countries (United Kingdom, Denmark, Italy, Lithuania, Greece), four in North America (United States, Canada), and one was carried out in China, Australia and South Africa respectively. Five of the sixteen studies included data stratified by gender (Gardner et al., 1986; Smailyte et al., 2004; Hein et al., 2007; Harding et al., 2012; Wang et al., 2013). Six cohorts only included female workers and eight cohorts only were conducted on male workers, seven included both males and females. Of the sixteen papers analyzed, nine reported circulatory diseases (CD), seven reported ischemic heart disease (IHD), two reported pulmonary heart diseases (PHD), four reported all heart diseases (AHD), and three reported other diseases of the heart (ODH). The industries of asbestos exposure involved in analysis included mining, manufacture of textiles, cement production and construction.

Meta-analysis

Fig. 2 presents the SMR and 95% CIs of individual studies and the pooled SMR results from the random-effects model. The average pooled SMR for cardiovascular related diseases among asbestos exposed

workers was 1.11 (95% CI, 1.01–1.22) which was statistically significant ($P < 0.05$). Significant heterogeneity was investigated among the studies ($I^2 = 93.5\%$; $P < 0.01$). Visual inspection of Begg's funnel plots did not confirm substantial asymmetry (Fig. 3). The Egger linear regression test and the Begg rank correlation test showed no evidence of publication bias among papers included (Egger, P = 0.36; Begg, P = 0.83). Heterogeneity was further investigated to determine potential explanatory factors. Subgroup analyses were conducted by the following covariates: gender, type of asbestos, geographic region, type of industry, type of diseases, follow-up period in years and SMR for all causes.

The pooled SMR for studies in males and females were 1.10 (95% CI, 0.8–1.53) and 1.08 (95% CI, 0.92–1.25) separately with significant heterogeneity ($I^2 = 97.6$, $P < 0.01$; $I^2 = 72.6$, $P < 0.01$). The pooled SMR for studies with mixed gender was 1.15 (95% CI, 1.02–1.30), with significant heterogeneity ($I^2 = 91.4$, $P < 0.01$). The pooled SMR for studies on European populations was 0.88 (95% CI, 0.75–1.02) with significant heterogeneity ($I^2 = 92.3$, $P < 0.01$). For workers in USA, the pooled SMR was 1.20 (95% CI, 1.09–1.32) with significant heterogeneity ($I^2 = 83.4$, $P < 0.01$). The pooled SMR of results from other countries was 1.75 (95% CI, 1.17–2.60) with significant heterogeneity ($I^2 = 96.8$, $P < 0.01$). The results suggest that pooled SMR from cardiovascular related diseases in asbestos-exposed workers in the USA and other countries including South Africa, Australia and China was higher than that in the general population ($P < 0.01$).

The SMRs from cardiovascular related diseases varied in people exposed to different types of asbestos. Our results showed that SMRs from such diseases was higher in workers exposed to chrysotile and amphibole (1.23 〔95% CI, 1.07–1.41〕; 1.26 〔95% CI, 1.02–1.56〕) when compared with those exposed to crocidolite (0.80 〔95% CI, 0.74–0.86〕). The differences were statistically significant. The SMRs from cardiovascular related diseases in workers exposed to mixed asbestos was 0.81 (95% CI, 0.6–1.08). Except for crocidolite studies ($I^2 = 0$, $P = 0.45$), other three subgroups had significant heterogeneity.

The types of industry influence the SMRs from cardiovascular related diseases in asbestos-exposed workers. The SMR from such diseases of workers in textile (1.41 〔95% CI, 1.16–1.70〕) was significant higher than that of workers in cement (0.82 〔95% CI, 0.70–0.98〕). The results in both industries had significant heterogeneity. The pooled SMR were 1.13 (95% CI, 0.91–1.39) and 1.07 (95% CI, 0.88–1.30) separately for workers in mining and other industries with significant heterogeneity ($I^2 = 87.9$, $P < 0.01$; $I^2 = 93.2$, $P < 0.01$).

The SMRs from various cardiovascular related diseases were pooled in this study. Significantly elevated SMRs were observed from pulmonary heart diseases, (SMR 4.13, 95% CI, 1.55–10.98), and other heart diseases (SMR 1.32, 95% CI, 1.14–1.53). The SMRs from circulatory diseases, all heart diseases and ischemic heart diseases were 0.99 (95% CI, 0.88–1.11), 0.99 (95% CI, 0.86–1.14), and 1.04 (95% CI, 0.82–1.32) respectively. All of these pooled SMRs had significant heterogeneity.

Follow-up period in years was not a significant predictor of the pooled SMR, both studies with a follow-up time of less than 35 years and those following up after 35 years or more did not appear to be associated with an increase in cardiovascular related disease mortality (1.10 (95% CI, 0.98–1.24); 1.13 (95% CI, 0.98–1.31)) with significant heterogeneity. Studies that reported an SMR for all causes > 1 (1.20 (95% CI, 1.09–1.33)) compared with other studies (0.84 (95% CI, 0.68–1.05)) had a larger pooled SMR, a difference which was statistically significant.

To explain the heterogeneity, we conducted a meta-regression and found geographical region and type of asbestos might be effect factors ($P < 0.05$). However, the combination of these two subgroups did not solve the problem of heterogeneity. Thus, we mixed the two covariates to recombine again. The pooled SMR of chrysotile exposure in European studies, North American studies, and studies in other countries were 0.98 (95% CI, 0.92–1.04), 1.23 (95% CI, 1.18–1.28), and 0.80 (95% CI, 0.74–0.86) respectively with non-significant heterogeneity. Another four groups including studies on exposure to other asbestos types outside of Europe and North America, North American studies on exposure to other asbestos types, European studies on exposure to mixed asbestos and studies on exposure to chrysotile outside of Europe and North America still had significant heterogeneity, with pooled SMRs of 1.33 (95% CI, 1.05–1.68), 1.14 (95% CI, 0.77–1.69), 0.81 (95% CI, 0.60–1.08) and 3.13 (95% CI, 0.56–17.48) respectively. Based on the result of visual impression of heterogeneity across all the studies, a study by Musk et al. (2008), conducted in Australia, and a study by Menegozzo et al. (2011) were the biggest contributors to inter-study variation. The pooled SMR for cardiovascular related diseases excluding these two studies was 1.17 (95% CI, 1.07–1.28). We mixed geographical region and type of disease to group when excluding the two studies above mentioned. Heterogeneity was eliminated except the groups of ischemic heart diseases in Europe and North America.

Discussion

The investigation of this meta-analysis showed that asbestos exposure could increase the risk of cardiovascular related diseases in exposed workers. The possible biological mechanisms might be indirect toxic effect of persistent inflammatory reaction induced by inhaled asbestos fibers in lung tissues. Some inflammatory mediators could enter blood vessel and transfer to heart. In addition, impaired lung function could lead to episodes of hypoxemia which would increase the risk of mortality from cardiovascular related diseases (Boor et al., 2009; Lee et al., 2011). However, there was significant heterogeneity in the papers included in the analysis. This may be explained by the differences in study designs, the nature of the cohort population, methodologies of exposure assessment, and other differences. The results from our studies clearly showed that geographical region and type of disease might be what affected the heterogeneity the most.

The risk of cardiovascular related diseases varied in workers exposed to different type of asbestos. Among studies involving chrysotile, the highest risks of cardiovascular related disease mortality were seen among asbestos textile workers compared to the lower risks which were observed among workers of mining and cement production. This could be explained by the higher concentration of exposure in textile manufacturing (Hughes & Weill, 1986). In addition, some samples of chrysotile from the mines contained contaminations of fibrous silicate, which has some characteristics in common with crocidolite, including the oxidant activity and cell toxicity (Turci et al., 2005). This is consistent with the result that exposure to crocidolite asbestos might not increase the risk of cardiovascular related diseases mortality. For studies investigating chrysotile, workers had shown lower rates of cancer than those exposed to other types of asbestos (Ohlson & Hogstedt, 1985). However, cardiovascular disease, a kind of chronic disease, was not like cancer and had longer survival, which could explain why SMRs of cardiovascular related diseases in chrysotile studies were higher.

Although the SMRs in the studies on chrysotile-exposed workers were generally higher in studies on other asbestos types, the effects of chrysotile exposure in different geographical regions were not the same. The studies conducted in developing countries like South Africa and China obtained a higher SMR compared to those in Europe or North America. There are several possible explanations. First of all, the protective measures were quite different. In developed countries, industries have enough economic ability to provide a greater degree of occupational safety and workers may be more conscious about safe production practices. It is therefore not surprising that fewer deaths occurred in these groups. The second explanation is the different exposure dose. In developing countries, the fiber concentrations in working environments were quite high (Sluis-Cremer et al., 1992). Another important factor for explaining the geographical difference in cardiovascular related disease mortality is the type of chrysotile. There was less than

Table 1
Study characteristics.

Study	Disease	Country	Industry type	Asbestos type	N	Follow-up time	SMR	95%CI	Exposure assessment	SMR of all causes
Gardner et al. (1986)	Circulatory diseases	United Kingdom	Cement	Chrysotile	1510 male	1941–1983	0.87	0.74–1.01	Occupational environment monitoring and assessment of industry job titles	0.94
	Circulatory diseases	United Kingdom	Cement	Chrysotile	657 female	1941–1983	1.16	0.87–1.51	Occupational environment monitoring and assessment of industry job titles	0.92
Raffn et al. (1989)	Circulatory diseases	Denmark	Cement	Chrysotile	8580 (7996 male, 584 female)	1928–1984	1.01	0.92–1.11	Occupational environment monitoring	1.18
Sluis-Cremer et al. (1992)	Ischemic heart disease	South Africa	Mining	Amphibole	7317	1946–1980	1.11	0.99–1.23	Occupational environment monitoring and assessment of industry job titles	1.37
	Pulmonary heart disease	South Africa	Mining	Amphibole	7317	1946–1980	2.24	1.07–4.12	Occupational environment monitoring and assessment of industry job titles	1.37
	Ischemic heart disease	South Africa	Mining	Amosite	3212	1946–1980	1.16	1.02–1.32	Occupational environment monitoring and assessment of industry job titles	1.42
	Pulmonary heart disease	South Africa	Mining	Amosite	3212	1946–1980	3.17	1.49–5.95	Occupational environment monitoring and assessment of industry job titles	1.42
	Ischemic heart disease	South Africa	Mining	Crocidolite	3430	1946–1980	0.99	0.84–1.77	Occupational environment monitoring and assessment of industry job titles	1.27
	Pulmonary heart disease	South Africa	Mining	Crocidolite	3430	1946–1980	1.15	0.2–3.61	Occupational environment monitoring and assessment of industry job titles	1.27
Levin et al. (1998)	All heart diseases	United States	Construction	Amosite	753 male	1954–1993	1.18	0.9–1.52	Environmental surveys and historical records	1.66
Germani et al. (1999)	Circulatory diseases	Italy	Mixed	Mixed (chrysotile and amphiboles)	631 female	1980–1997	0.89	0.7–1.12	Diagnoses of asbestosis as proxy for asbestos exposure	1.58
	Ischemic heart diseases	Italy	Mixed	Mixed (chrysotile and amphiboles)	631 female	1980–1997	0.53	0.28–0.93	Diagnoses of asbestosis as proxy for asbestos exposure	1.58
	Circulatory diseases	Italy	Textile	Chrysotile	276 female	1980–1997	0.93	0.65–1.3	Diagnoses of asbestosis as proxy for asbestos exposure	1.68
	Ischemic heart diseases	Italy	Textile	Chrysotile	276 female	1980–1997	0.43	0.12–1.09	Diagnoses of asbestosis as proxy for asbestos exposure	1.68
	Circulatory diseases	Italy	Cement	Mixed (chrysotile and amphiboles)	278 female	1980–1997	0.82	0.58–1.14	Diagnoses of asbestosis as proxy for asbestos exposure	1.43
	Ischemic heart diseases	Italy	Cement	Mixed (chrysotile and amphiboles)	278 female	1980–1997	0.69	0.3–1.35	Diagnoses of asbestosis as proxy for asbestos exposure	1.43
Battista et al. (1999)	Circulatory diseases	Italy	Construction	Mixed (chrysotile and crocidolite)	734 male	1945–1997	0.73	0.58–0.92	–	1
Smailyte et al. (2004)	Circulatory diseases	Lithuania	Cement	Chrysotile	1972 male	1978–2000	1	0.9–1.2	Occupational environment monitoring and assessment of industry job titles	1
	Circulatory diseases	Lithuania	Cement	Chrysotile	815 female	1978–2000	1	0.7–1.4	Occupational environment monitoring and assessment of industry job titles	1

(continued on next page)

Table 1 (*continued*)

Study	Disease	Country	Industry type	Asbestos type	N	Follow-up time	SMR	95%CI	Exposure assessment	SMR of all causes
Hein et al. (2007)	All heart diseases	United States	Textile	Chrysotile	3072 (1807 male, 1265 female)	1940–2001	1.2	1.1–1.3	Occupational environment monitoring and assessment of industry job titles	1.33
	Ischemic heart diseases	United States	Textile	Chrysotile	3072 (1807 male, 1265 female)	1940–2001	1.2	1.1–1.32	Occupational environment monitoring and assessment of industry job titles	1.33
	Other diseases of the heart	United States	Textile	Chrysotile	3072 (1807 male, 1265 female)	1940–2001	1.27	1.01–1.58	Occupational environment monitoring and assessment of industry job titles	1.33
	Circulatory diseases	United States	Textile	Chrysotile	3072 (1807 male, 1265 female)	1940–2001	1.28	1.1–1.47	Occupational environment monitoring and assessment of industry job titles	1.33
	All heart diseases	United States	Textile	Chrysotile	1265 female	1940–2001	1.12	0.97–1.29	Occupational environment monitoring and assessment of industry job titles	1.29
	Ischemic heart diseases	United States	Textile	Chrysotile	1265 female	1940–2001	1.11	0.94–1.30	Occupational environment monitoring and assessment of industry job titles	1.29
	Other diseases of the heart	United States	Textile	Chrysotile	1265 female	1940–2001	1.34	0.92–1.88	Occupational environment monitoring and assessment of industry job titles	1.29
	Circulatory diseases	United States	Textile	Chrysotile	1265 female	1940–2001	1.25	0.99–1.56	Occupational environment monitoring and assessment of industry job titles	1.29
Musk et al. (2008)	Circulatory diseases	Astralia	Mining	Crocidolite	6943 (6498 male, 445 female)	1943–2000	0.79	0.73–0.85	Occupational environment monitoring and assessment of industry job titles	1.13
Sichletidis et al. (2009)	Circulatory diseases	Greece	Cement	Chrysotile	317	1968–2006	0.77	0.49–1.16	Occupational environment monitoring and assessment of industry job titles	0.71
Loomis et al. (2009)	All heart diseases	United States	Textile	Chrysotile	5770 (3975 male, 1795 female)	1950–2003	1.32	1.22–1.42	Occupational environment monitoring and assessment of industry job titles	1.47
Pira et al. (2009)	Ischemic heart diseases	Italy	Mining	Chrysotile	1056male	1946–2003	0.93	0.71–1.2	Occupational environment monitoring and assessment of industry job titles	1.43
Larson et al. (2010)	Ischemic heart diseases	Canada	Vermi-culite	Amphibole	1862	1946–2006	0.7	0.6–0.8	Occupational environment monitoring and assessment of industry job titles	1.3
	Other diseases of the heart	Canada	Vermi-culite	Amphibole	1862	1946–2006	1.5	1.2–1.8	Occupational environment monitoring and assessment of industry job titles	1.3
	Circulatory diseases	Canada	Vermi-culite	Amphibole	1862	1946–2006	1.4	1.2–1.6	Occupational environment monitoring and assessment of industry job titles	1.3
Menegozzo et al. (2011)	All heart diseases	Italy	Cement	Mixed (crocidolite, chrysotile and asmosite)	1247 male	1965–2005	0.57	0.48–0.68	Occupational environment monitoring and assessment of industry job titles	0.93
	Ischemic heart diseases	Italy	Cement	Mixed (crocidolite, chrysotile and asmosite)	1247 male	1965–2005	0.47	0.34–0.64	Occupational environment monitoring and assessment of industry job titles	0.93
Harding et al. (2012)	Ischemic heart diseases	United Kingdom	Mixed	Mixed	94403 male	16	1.28	1.24–1.32	Personal interview using questionnaire about occupational exposure to asbestos	1.42
	Ischemic heart diseases	United Kingdom	Mixed	Mixed	4509 female	1971–2005	1.61	1.38–1.87	Personal interview using questionnaire about occupational exposure to asbestos	1.42
Wang et al. (2013)	Pulmonary heart disease	China	Textile	Chrysotile	577 male	1972–2008	13.09	9.46–18.12	Occupational environment monitoring and assessment of industry job titles	1.31
	Pulmonary heart disease	China	Textile	Chrysotile	277 female	1972–2008	8.33	2.29–30.39	Occupational environment monitoring and assessment of industry job titles	0.82
	Other diseases of the heart	China	Textile	Chrysotile	577 male	1972–2008	0.87	0.52–1.43	Occupational environment monitoring and assessment of industry job titles	1.31
	Other diseases of the heart	China	Textile	Chrysotile	277 female	1972–2008	1.02	0.35–2.99	Occupational environment monitoring and assessment of industry job titles	0.82

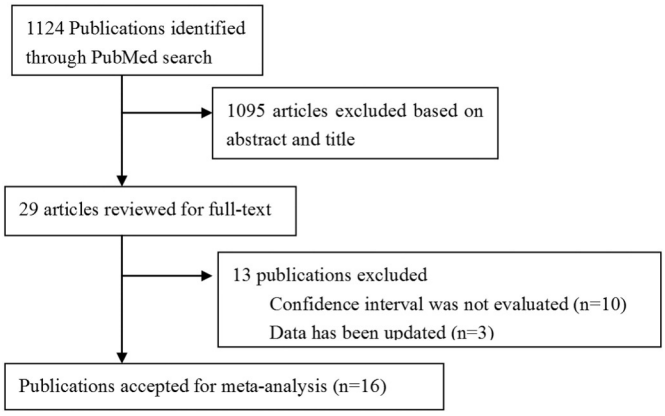

Fig. 1. Study flow chat.

10% tremolite in Russian chrysotile while 50% was found in a Canadian sample (Tossavainen et al., 2000). The chrysotile from Russia was much thicker than that from Canada and it could be cleared from the lungs within months. This Russian chrysotile seemed to be of lesser risk than other types of chrysotile. In developed countries, most asbestos industries used this chrysotile from Russia.

The analysis of disease subgroups showed a fairly high SMR of pulmonary heart disease. This may also help in explaining the biological mechanisms by which asbestos exposure could increase the risk of cardiovascular related diseases. Because all heart diseases include pulmonary heart disease, the SMR of all heart diseases was also above the national average with statistical significance. Additionally, cerebrovascular disease and hypertensive disease were inside the range of circulatory diseases and were strongly influenced by confounding factors such as genetic background and life habits. It has been reported that the mortality of cerebrovascular disease and hypertensive disease were not increased in cohort exposure to asbestos

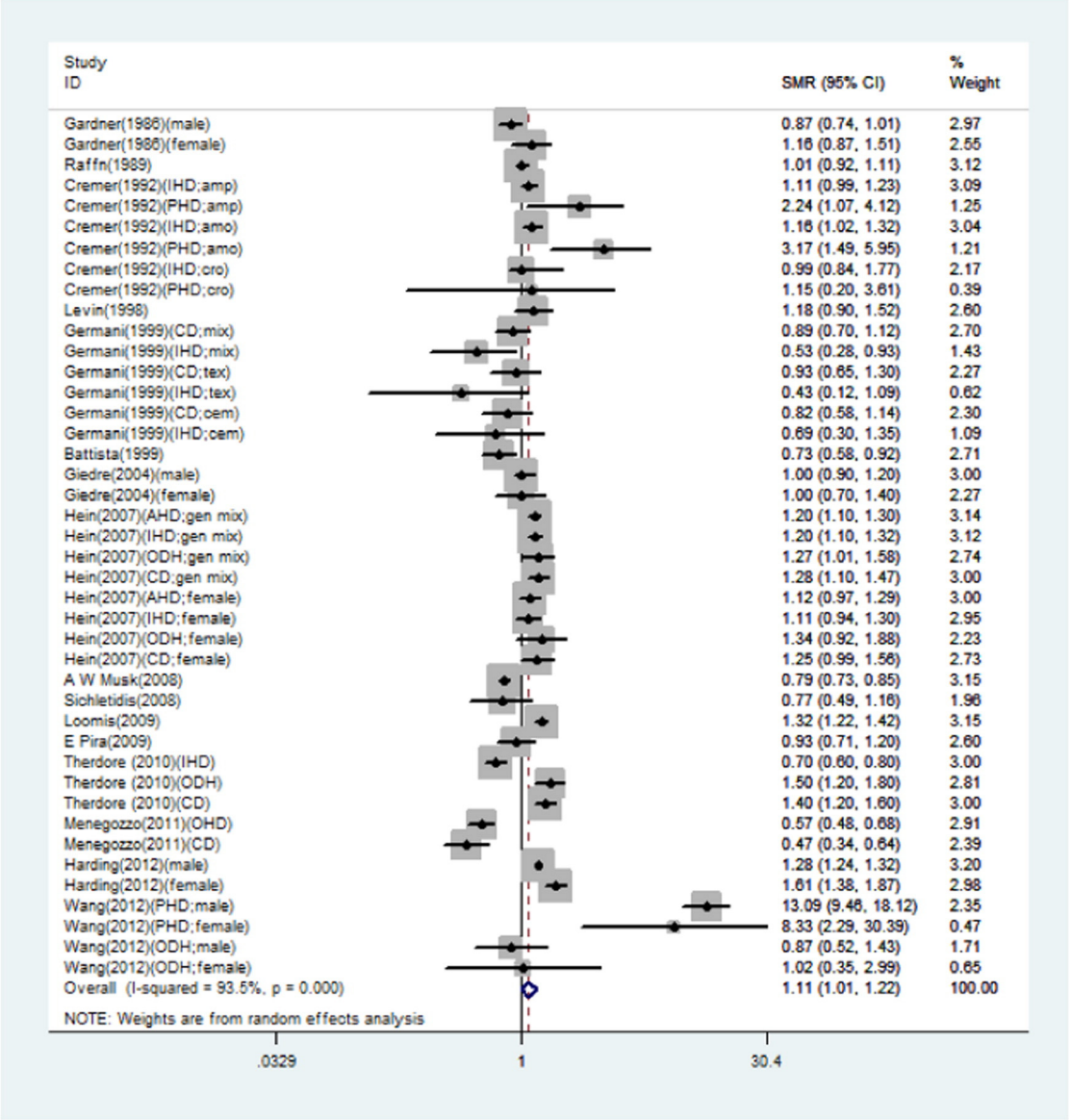

Fig. 2. Forest plot shows association between cardiovascular related diseases and occupational exposure to asbestos. Each triangle in box represents an individual SMR estimate with the size of the box being proportional to the weight given to the study. Weights are from random-effects model. The lines represent the 95% CI for the point estimate in each study. The pooled SMR is displayed as a diamond.

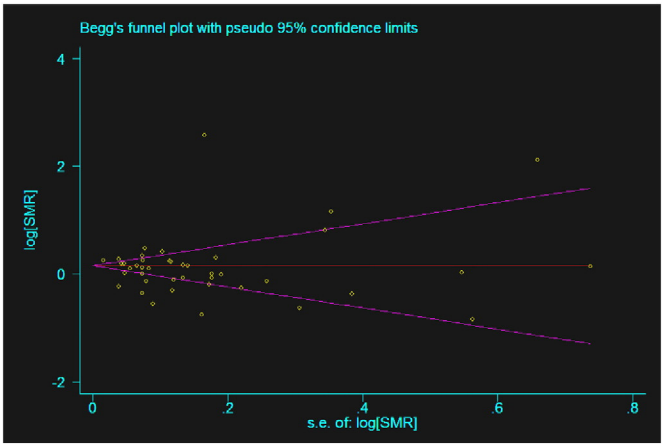

Fig. 3. Begg's funnel plot with pseudo 95% CIs.

(Germani et al., 1999). Our results also indicated that there was no explicit relationship between asbestos exposure and mortality of ischemic heart diseases.

Our meta-analysis has a number of limitations need to be taken into account when investigating the association between asbestos exposure and cardiovascular related diseases. These limitations depend on the information that papers include in the analysis. A number of studies lacked details of exposure assessment. When studies used job titles to classify exposure, misclassification is a possibility. In addition, differences in the definitions of exposure duration and latency of asbestos exposure measures could prevent a unified evaluation of a dose-response relationship. Moreover, personal interview using questionnaires (Harding et al., 2012) were more likely to be influenced by individual biases, as cases tended to report their exposures more precisely. Other unknown occupational hazards might be not accounted for in the individual studies and could overestimate the risk of asbestos exposure. A further limitation was its inability to assess nonoccupational risk factors for cardiovascular related diseases like smoking status, living habits, diet, alcohol use or medications. Finally, some published studies regarding asbestos exposure failed to report cardiovascular related diseases or only reported the results for SMRs of diseases but no CIs. These studies could be a potential concern.

Conclusion

This meta-analysis showed that asbestos exposure significantly increased the risk of cardiovascular related diseases in exposed workers.

Conflict of interests

All authors are involved in performing the study and reviewing the final version of manuscript. There are no conflicts of interests.

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