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Non-occupational exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis

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ABSTRACT

Objective To conduct an updated literature review and meta-analysis of studies of pleural malignant mesothelioma (PMM) risk among persons exposed to asbestos non-occupationally (household and neighbourhood)

Methods We performed a literature search for articles available in the National Center for Biotechnology Information's PubMed database published between 1967 and 2016 Meta-analyses were conducted to calculate pooled PMM risk estimates, stratifying for household or neighbourhood exposure to asbestos and/or predominant asbestos fibre type (chrysotile, amphibole or mixed)

Results Eighteen studies in 12 countries comprising 665 cases met the meta-analysis inclusion criteria We identified 13 estimates of PMM risk from neighbourhood exposures, 10 from household and one from mixed exposure, and combined the estimates using random-effects models The overall meta-relative risk (meta-RR) was 5 9 (95% CI 4 4 to 8 7) The meta-RRs for household and neighbourhood exposures were 5 4 (95% CI 2 6 to 11 2) and 6 9 (95% CI 4 2 to 11 4), respectively We observed trends in risk in relation to fibre type for both household and neighbourhood studies For chrysotile, mixed and amphibole fibres, respectively, meta-RRs for neighbourhood studies were 3 8 (95% CI 0 4 to 38 4), 8 4 (95% CI 4 7 to 14 9) and 21 1 (95% CI 5.3 to 84 5) and meta-RRs for household studies were 4 0 (95% CI 0 8 to 18 8), 5 3 (95% CI 1 9 to 15 0) and 21 1 (95% CI 2 8 to 156 0)

Conclusions PMM risks from non-occupational asbestos exposure are consistent with the fibre-type potency response observed in occupational settings By relating our findings to knowledge of exposure-response relationships in occupational settings, we can better evaluate PMM risks in communities with ambient asbestos exposures from industrial or other sources

What this paper adds

- It is well known that both occupational and non-occupational asbestos exposures, particularly amphibole asbestos, can increase the risk of pleural malignant mesothelioma (PMM). Earlier studies evaluating the risk of PMM due to non-occupational exposures observed elevated risks of PMM even though these exposures are generally much lower and more variable than occupational asbestos exposures. One previous meta-analysis of non-occupational asbestos exposures and PMM risk published in 2000 observed statistically significant risks that appeared dependent on fibre type. However, only eight studies were included in the original investigation published 17 years ago.
- Our updated review and meta-analysis included more than twice as many studies as the 2000 publication (n=18). We confirmed that non-occupational exposures to asbestos fibres are associated with an increased risk of PMM (household=5.4 (95% CI 2.6 to 11.2); neighbourhood=6.9 (95% CI 4.2 to 11.4)). Our updated meta-analyses also confirmed a fibre-type potency response for non-occupational exposures that is similar to the relationship observed in occupational settings.
- This study demonstrates more precisely a fibre-type potency response consistent with investigations of occupational asbestos exposures. By relating our fibre-type potency response findings to our knowledge of exposure-response relationships estimated in the occupational settings, we can better evaluate the risk of PMM in communities with ambient asbestos exposures from industrial or other sources.

INTRODUCTION

Asbestos is a fibrous hydrated magnesium silicate used extensively in building materials and insulation during the 20th century because of its indestructible nature, fire resistance and spinnability. Approximately 95% of world consumption has been chrysotile, a serpentine form of asbestos. Amphibole is the other asbestos fibre group comprising several types: amosite, crocidolite, anthophyllite, actinolite and tremolite. Exposure to asbestos can increase the risk of pleural malignant mesothelioma (PMM) and these risks appear to be considerably higher for amphiboles compared with chrysotile fibres.[1 3]

The increased PMM risks from occupational exposure to asbestos are well known. Some studies have shown that non-occupational (or environmental) exposures increase the risk of PMM in the general population. Two main types of non-occupational asbestos exposure are distinguished household (or domestic) and neighbourhood (or residential) exposure. Household exposures include the installation, degradation, removal, or repair of asbestos-containing products Moreover, household exposures include para-occupational exposures, which are those exposures taken home by asbestos workers or due to the use of asbestos-containing tools and products in the home. Neighbourhood exposures result from outside air pollution and include industrial emissions, natural outcroppings, or erosion of asbestos-containing

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building materials. Non-occupational asbestos exposures are usually much lower and more variable than exposures experienced by workers manufacturing or using products made with asbestos.[4]

Compared with studies of persons exposed to asbestos occupationally, relatively few studies have evaluated the relationship between non-occupational asbestos exposures and the risk of PMM. Numerous occupational and non-occupational studies, however, have evaluated the differential risk of PMM relative to fibre type. As early as 1972, the Occupational Safety and Health Administration (OSHA) indicated that chrysotile fibres were less harmful than crocidolite.[2] Hodgson and Darnton[3] conducted a systematic literature review that evaluated the quantitative risk of mesothelioma and lung cancer in relation to asbestos exposure. Based on occupational cohorts, the authors determined that the risk of mesothelioma due to exposure from chrysotile, amosite and crocidolite followed a 1 to 100 to 500 ratio, respectively. An updated analysis, which included additional studies, confirmed fibre potency differences associated with mesothelioma risk.[5] A meta-analysis of occupational studies, conducted by Berman and Crump,[1] evaluated fibre-type potency with regard to mesothelioma and found that chrysotile was between 0 and 1/200th as potent as amphibole asbestos.[1]

Bourdes *et al*[4] presented a literature review and meta-analysis by asbestos fibre type of the non-occupational studies of PMM risk available around the turn of this century. Two of the eight studies identified, published between 1965 and 1998 in six different countries, specifically investigated asbestos exposures associated with the Eternit asbestos cement factory located in Casale Monferrato, Italy.[6 7] The remaining studies were conducted worldwide and considered exposures to pure chrysotile, pure amphibole, mixed or unspecified fibre types.

The Bourdes *et al*[4] meta-analyses produced PMM risk effect estimates for neighbourhood and household asbestos exposures, respectively, that ranged from 1.5–4.0 for chrysotile, 6.7–8.2 for mixed or unspecified exposures, and 8.7–21.0 for amphiboles exposures. While the assessment of non-occupational asbestos exposures was generally less reliable than occupational exposure assessments, the results of the Bourdes *et al*[4] meta-analyses clearly supported the well known gradient in PMM risk by fibre type, or potency response, observed in the occupational studies.

Since the Bourdes *et al*[4] review in 2000, several new and updated studies have evaluated PMM risk by fibre type among persons exposed to asbestos non-occupationally. We conducted an updated literature review and meta-analysis aimed at providing more reliable overall estimates of PMM risks in relation to fibre type and non-occupational asbestos exposures. We report here the results of our updated and extended evaluation.

METHODS

Literature search

We conducted this study using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[8 9] We performed a literature search for articles available in the National Center for Biotechnology Information's (NCBI) PubMed database published between 1967 and 2016 using the following keywords: asbestos, environmental exposure, household exposure, neighborhood exposure, para-occupational exposure, mesothelioma and pleural mesothelioma. We conducted the literature search using the following operators. (((((household exposure) OR neighborhood exposure) OR para occupational exposure) OR environmental exposure)) AND ((asbestos) AND (((pleural mesothelioma) OR mesothelioma) OR peritoneal mesothelioma)). Additionally, we systematically searched the reference lists of all studies identified in our literature review, as well as published review papers and meta-analyses, in order to identify relevant studies not captured in the primary literature search. All abstracts and articles were reviewed by at least two scientists to determine if inclusion criteria were met.

We selected studies based on the following criteria:

1. Only published studies available in English.
2. Descriptive and analytical epidemiological studies, including ecological, case-control and cohort studies, were considered for inclusion. Case reports and case series were excluded
3. The medical condition of interest was defined as mesothelioma (identified as 'pleural mesothelioma' or 'mesothelioma'). Only studies that reported incidence and mortality outcomes of mesothelioma were included. Studies were excluded if the results were reported for peritoneal mesothelioma only or for pleural and peritoneal mesothelioma combined.
4. Exposures of interest were defined as non-occupational or environmental asbestos exposures (identified as 'environmental exposure'), which included household or domestic exposure (identified as 'household exposure' or 'para occupational exposure') and neighbourhood or residential exposure (identified as 'neighborhood exposure'). Household exposures included asbestos exposures from products contained within the home, or due to exposures associated with take-home asbestos from family members who potentially brought dust containing asbestos home from their jobs on their clothing. Neighbourhood exposures were associated with living in close proximity to industrial or environmental sources that released asbestos fibres into the air. The exposure descriptions provided by the authors of the included studies were used to categorise reported effect estimates into neighbourhood and household exposures. Studies were excluded if the study subjects had definitive occupational exposure or if occupational exposure was uncertain.
5. If there were multiple studies with the same or overlapping populations, only the most recent study was considered for inclusion in the meta-analysis.
6. Only studies that reported effect estimates or provided data that enabled the calculation of an effect estimate were considered for inclusion in this evaluation.

For all studies that met the above inclusion criteria, the following data were extracted. first author, publication year, study design, study location, outcome classification, asbestos exposure type and sources of exposure, the predominant asbestos fibre type, sex of the exposed subjects, number of cases and effect estimates (relative risk (RR), odds ratio (OR), standardised mortality ratio (SMR), standardised incidence ratio (SIR) and variance or confidence interval (CI)) for each relevant exposure group (table 1)

Meta-analysis

Meta-analyses were performed to calculate pooled risk estimates, specifically stratifying for: (1) household or neighbourhood exposure to asbestos, (2) predominant asbestos fibre type of the exposure (amphibole, chrysotile or mixed) and (3) asbestos fibre type by household and neighbourhood exposure The unspecified fibre type studies were only used in the analysis of all studies combined. In five of the publications that met the inclusion criteria, we manually calculated crude (unadjusted)

Table 1 Studies on non-occupational exposure and pleural mesothelioma

Authors	Year	Country	Outcome	Exposure type	Source of exposure	Fibre type	Sex	Cases (n)	Effect estimate (95% CI)
Ecological studies									
Camus et al[18]	*1998*	*Canada*	*Mortality*	*Neighbourhood*	*Asbestos mines or mills*	*Chrysotile*	*F*	*7*	*SMR=7 6 (3 1 to 15 7)**
Fazzo *et al*[21]	2014	Italy	Incidence	Neighbourhood	Industrial—asbestos processing plant	Unspecified	M+F	30	SIR=1 7 (1.1 to 2.4)
Mensi *et al*[22]	2015	Italy	Incidence	Household	Industrial—asbestos processing plant	Mixed	M	5	SIR=2 0 (0.7 to 4 7)
				Neighbourhood			M+F	72	SIR=6 6 (5.2 to 8 3)
Metintas *et al*[17]	2002	Turkey	Incidence	Neighbourhood	Geological	Mixed	M+F	24	SIR=87.0 (32 5 to 233.0)†
Case-control studies									
McDonald and McDonald[10]	*1980*	*Canada/USA*	*Incidence*	*Household*	*Industrial—asbestos processing plant*	*Chrysotile*	*M+F*	*8*	*OR=4.0 (0 8 to 18 8)‡*
				Neighbourhood	*Asbestos mines or mills*		*M+F*	*1*	*OR=0 2 (0.02 to 2 2)‡*
Madkour *et al*[11]	2009	Egypt	Incidence	Neighbourhood	Industrial—asbestos processing plant	Chrysotile	M+F	83	OR=26 7 (5 7 to 581 0)‡
Lacourt *et al*[23]	2014	France	Incidence	Mixed non-occupational	Unspecified/various	Chrysotile	M+F	22	OR=3.8 (1.6 to 8 9)†
Maule *et al*[29]	2007	Italy	Incidence	Household	Industrial—asbestos processing plant	Mixed	M+F	75	OR=1 8 (1.1 to 2 8)
				Neighbourhood			M+F	60	OR=6 1 (3 6 to 10 5)†
Ferrante *et al*[24]	2016	Italy	Incidence	Household	Industrial—asbestos processing plant	Mixed	M+F	33	OR=2.4 (1.3 to 4 4)
Luce *et al*[25]	2000	New Caledonia	Incidence	Neighbourhood	Geological	Tremolite	Unspecified	14	OR=40 9 (5 2 to 325 0)
Yazicioglu et al[12]	*1980*	*Turkey*	*Incidence*	*Household*	*Geological*	*Tremolite*	*M+F*	*22*	*RR=21 1 (2 8 to 156 0)‡*
Newhouse and Thompson[13]	*1965*	*UK*	*Incidence*	*Household*	*Unspecified/various*	*Mixed*	*M+F*	*7*	*OR=25 7 (3 0 to 220 0)‡*
				Neighbourhood	*Industrial—asbestos processing plant*		*M+F*	*11*	*OR=5 5 (1 7 to 17 3)‡*
Howel et al[19]	*1997*	*UK*	*Mortality*	*Household*	*Industrial—asbestos processing plant*	*Unspecified*	*M+F*	*17*	*OR=5 8 (1.7 to 19 2)*
				Neighbourhood			*M+F*	*5*	*OR=6.6 (0.9 to 50 0)*
Magnani *et al*[26]	2000	Various (Italy, Spain, Switzerland)	Incidence	Household	Unspecified/various	Unspecified	M+F	30	OR=3 7 (1 6 to 8 7)†
				Neighbourhood			M+F	25	OR=8 6 (1 7 to 42 2)†
Cohort studies									
Hansen *et al*[14]	1998	Australia	Incidence	Neighbourhood	Asbestos mines or mills	Crocidolite	M+F	27	SIR=12 3 (1 9 to 79 8)†‡
Magnani et al[6]	*1993*	*Italy*	*Mortality*	*Household*	*Industrial—asbestos processing plant*	*Mixed*	*F*	*3*	*SMR=7 7 (1 6 to 21.9)*
Ferrante *et al*[27]	2007	Italy	Incidence	Household	Industrial—asbestos processing plant	Mixed	F	11	SIR=25 2 (12 6 to 45.1)
			Morality						
Kurumatani and Kumagai[28]	2008	Japan	Mortality	Neighbourhood	Industrial—asbestos processing plant	Mixed	M+F	73	SMR=4.3 (3.4 to 5.4)

*Disease was specified as pleural cancer or as a pleural tumour

†Effect estimates were combined together using DerSimonian and Laird random effects models[15 16]

‡Crude (unadjusted) effect estimates and/or 95% CIs were calculated from the raw data provided in the study Technical details provided in online supplementary appendix

Italicised studies were included in Bourdes et al[4] meta-analysis

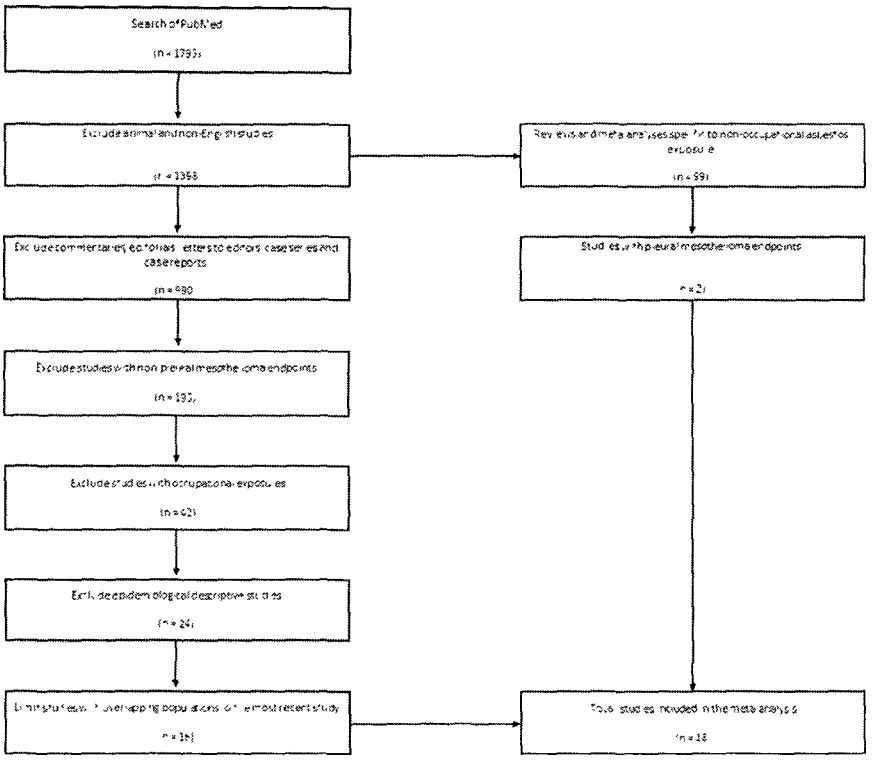

Figure 1 Flow diagram for included studies

effect estimates and corresponding CIs using data provided in the corresponding manuscript [10–14] The Appendix provides technical details of the data extraction and calculations performed to generate these estimates manually. In instances where more than one effect estimate was provided per stratification of interest (eg, separate estimates for men and women), but the predominant fibre type exposure was the same, effect estimates were combined together using Der Simonian and Laird random effects models[15 16] to determine an overall effect estimate.

Upon the extraction or derivation of all effect estimates and CIs from included publications, we performed fixed effects meta-analyses and the corresponding I^2 tests to assess the homogeneity of effect estimates from the studies. DerSimonian and Laird random effects models were subsequently performed on all iterations or stratifications described above.[15 16] The meta-analyses results are reported as meta-RR with corresponding 95% CI. Funnel plots were also created to evaluate the potential of publication bias. All statistical analyses were performed using StataMP V.14 (StataCorp, College Station, Texas, USA).

RESULTS

Literature search

Our PubMed literature search returned 1795 results (figure 1). Numerous search results were excluded because they did not meet the initial inclusion criteria: 314 research articles were written in languages other than English, 83 studies were conducted on experimental animals, 408 articles were commentaries, which included opinion letters and letters to the editor, and case series or case reports. When limiting the disease outcome to pleural mesothelioma, 797 studies were excluded. Limiting to non-occupational exposure excluded an additional 151 studies. Of the resulting 42 studies, 18 descriptive epidemiology studies were excluded. Cohorts were then limited to the most recent study, yielding 16 studies. Furthermore, 99 review articles were identified, specific to non-occupational exposures to asbestos. Two additional articles that specifically discussed PMM and met the rest of the inclusion criteria were referenced in the review articles.

Ultimately, 18 studies in 12 countries comprising 665 cases met the criteria for inclusion in the meta-analysis (table 1). Of these 18 studies, 11 reported effect estimates for PPM with either household or neighbourhood exposure. There were four ecological studies, 10 case-control studies and four cohort studies. Six papers reported effect estimates for both household and neighbourhood exposures, while one paper reported an effect estimate for a mixed non-occupational exposure. Overall, 24 effects estimates were reported, 13 due to neighbourhood exposures, 10 due to household exposures and one for mixed non-occupational exposures. Overall effect estimates ranged from an OR of 0.2 (95% CI 0.02 to 2.2) for neighbourhood exposures to chrysotile[10] to an SIR of 87.0 (95% CI 32.5 to 233.0) for neighbourhood exposures to geological sources of mixed asbestos fibres [17] Four of the reported effect estimates were not statistically significant. Only seven studies provided effect estimates for the risk of mesothelioma due to pure fibre exposures, with the majority being studies of mixed or unspecified fibre type.

Comparison to Bourdes *et al*.[4] Literature Search Results

The previous meta-analysis conducted by Bourdes *et al*[4] included eight papers.[6 7 10 12 13 18–20] Since the initial meta-analysis, 10 additional studies[11 17 21–28] and one update of a previously evaluated cohort[29] have been published that examined the risk of PMM following environmental exposure to asbestos. The overlapping studies included in Bourdes *et al*[4] and the current analysis are

Table 2 Random effects meta-analyses by asbestos exposure type and by fibre type

	Neighbourhood exposure			Household exposure		
	N	Meta-RR	95% CI	N	Meta-RR	95% CI
All studies*	13	6.9	4.2 to 11.4	10	5.4	2 6 to 11.2
Fibre type						
Chrysotile	3	3.8	0 4 to 38.4	1†	4 0	0.8 to 18.8
Mixed	6	8 4	4 7 to 14 9	6	5 3	1 9 to 15 0
Amphibole	2	21.1	5 3 to 84 5	1†	21.1	2.8 to 156.0

*In five of the publications, data reported in the manuscript were used to calculate crude (unadjusted) effect estimates and CIs See online supplementary appendix for technical details

†As reported by the sole study per category, Yazicioglu *et al*[12] and McDonald and McDonald [10]

Note Of the total 24 effect estimates included in this manuscript, 23 are presented in this table as one estimate pertained to a mix of both neighbourhood and household exposures [23]

italicised in table 1. Botha *et al*,[20] which was included in the earlier meta-analysis, was excluded from our analysis because the reported number of deaths from PMM and asbestosis could not be distinguished. Additionally, one study[14] was included in our meta-analysis, as it evaluated PMM due to neighbourhood exposure, but was not included in the Bourdes *et al*[4] meta-analysis. When accounting for the five studies[10–14] where reported data were used to estimate risks and 95% CI, our calculations were consistent with those reported by Bourdes *et al*,[4] except for those calculated from the data reported in Newhouse and Thompson.[13] Here, our calculated OR was similar, but the 95% CI was larger than that reported in Bourdes *et al*.[4]

Meta-analysis

Table 2 presents results of the random effects meta-analyses models and corresponding 95% CIs, by neighbourhood or household exposure type, fibre type, and neighbourhood or household exposure and fibre type concomitantly. When fixed effects models were run on all subgroups, only two subgroups failed to reject the null hypothesis of homogeneous effect estimates used from the studies: amphibole total and neighbourhood amphibole, both of which demonstrated an I^2 of 0 and *p-values of 0.70 and 0.40, respectively Of note, the results of* the random effects analyses on these two subgroups were not markedly different from those found under fixed-effects models. In all other instances, the findings of fixed-effects models demonstrated p-values <0.0001 for an I^2 test, indicative of heterogeneity Therefore, to account for heterogeneity demonstrated across the strata, we present results from our random effects models exclusively. Forest plots were generated to graphically represent the meta-RR, variability and heterogeneity of those studies by type of exposure (figure 2).

When we considered effect estimates from all studies (n=24), the meta-RR was 5.9 and statistically significant (95% CI 4 1 to 8 7). However, because household exposures are generally not equivalent to neighbourhood exposures, the remaining analysis considered these two exposure scenarios separately (excluding one study that had mixed neighbourhood and environmental exposures combined).[23] When stratified by asbestos exposure type, the meta-RR for household exposure was 5.4 and statistically significant (95% CI 2.6 to 11.2). The meta-RR for neighbourhood exposure was slightly higher (6.9) and statistically significant (95% CI 4.2 to 11.4) (figure 2). We observed similar trends in asbestos fibre-type potency in relation to PMM risk for both household and neighbourhood studies (table 2). For household exposure studies with mixed fibre type, the random effects meta-RR was 5.3 and statistically significant (95% CI 1 9 to 15.0). Only one effect estimate was available for household studies with chrysotile or amphibole exposure, precluding the calculation of a meta-RR for these subgroups. For comparative purposes, we reported results from each of these studies in table 2 (*Amphibole:* as reported in Yazicioglu *et al*[12]: OR=21.1 (95% CI 2.8 to 156.0); *Chrysotile:* as reported in McDonald and McDonald[10]. OR=4.0 (95% CI 0.8 to 18.8)). For neighbourhood studies, the meta-RR for mixed fibre exposure was 8.4 (95% CI 4.7 to 14 9); the meta-RR for chrysotile exposure was 3.8 (95% CI 0.4 to 38.4); and the meta-RR for amphibole exposure was 21 1 (95% CI 5.3 to 84.5).

DISCUSSION

Overall, the results of our updated meta-analysis demonstrated that non-occupational exposure to asbestos fibres is associated with increased PMM risk. The risk of PMM between household exposures and neighbourhood exposures was comparable with an evaluation of all studies demonstrating a statistically significant increased risk of PMM (meta-RR=5.9; 95% CI 4.1 to 8.7). However, there was a pronounced effect of fibre type on the meta-risk estimates. For neighbourhood and household exposures, respectively, exposure to amphibole fibres alone had a meta-RR of PMM 2.5–3.2 times greater than those exposed to mixed fibres, and 5.3–5.6 times greater than those exposed to chrysotile fibres alone

While our meta-RRs for PMM are generally consistent with those observed in the earlier literature review and meta-analysis of Bourdes *et al*,[4] the variability associated with our estimates was similar or even greater for some subgroups considered, despite having included more than twice as many studies overall. These instances of increased variability are due to the heterogeneity of the effect estimates associated with the studies included in our update. These studies were conducted on populations located worldwide, and several different potential sources of asbestos were included: asbestos cement plants, asbestos textile facilities, asbestos mines and mills, and naturally occurring geological sources. The subpopulations evaluated also varied, with some studies including only men or women and some including both Depending on fibre type, the range in the reported risks of PMM in the individual studies was quite large For chrysotile-specific exposures the risk ranged from OR=0.2 (95% CI 0.02 to 2.2)[10] to OR=26.7 (95% CI 5.7 to 581.0).[11] Mixed fibre exposures reported PMM risks that ranged from OR=1 8 (95% CI 1 1 to 2.8)[29] to SIR=87.0 (95% CI 32 5 to 233 0).[17] There was roughly a threefold increased risk of PMM for amphibole exposures between the lowest (SIR=12.3; 95% CI 1.9 to 79.8)[14] and highest reported estimates (OR=40.9; 95% CI 5.2 to 325.0).[25] Moreover, a potential limitation is the inclusion of seven crude (unadjusted) effect estimates, which could have led to the large

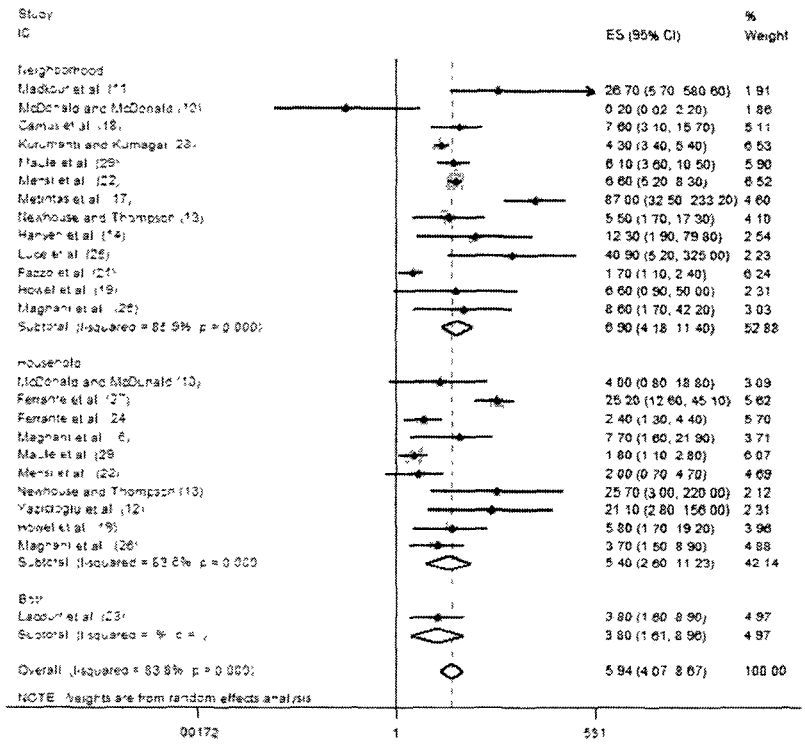

Figure 2 Forest plots of random effects models of household and neighbourhood exposures

range of reported effect estimates of PMM observed between studies.

Additional sources of the heterogeneity in meta-RRs include the overall mixture of asbestos fibre exposures and exposure levels to those fibres. The mixed fibre studies included asbestos cement plants,[6 22 24 27–29] geological deposits[17] and proximity to asbestos factories.[13] All of these sources emitted different amounts and different ratios of asbestos fibre types. Furthermore, only three studies[14 18 24] estimated actual exposure levels. Other studies considered distance from an asbestos emitting facility or mine, but the majority of the studies reviewed based the designation of exposure on general definitions of residential location or living with an individual who worked in an asbestos related industry. Another source of potential exposure misclassification could come in the form of recall bias. Only two of the case-control studies[11 23] directly interviewed the cases. The remaining case-control studies used family members to provide information on exposures or used proxy measures of exposure, such as residential location in relation to a potential asbestos source. The aforementioned exposure designations may have led to increased potential for exposure misclassification, which in turn increased the variability in the study findings and directly corresponded to the external inconsistencies observed between the evaluated studies.

Notably, six studies were conducted in Italy in locations adjacent to various asbestos cement product manufacturing facilities. The effect estimates for these studies ranged from a SIR of 1.8 (95% CI 1.1 to 2.8) for a hospital survey of new PMM cases diagnosed between 1 January 1987 and 30 June 1993, among residents living in Casale Monferrato[29] to a SIR of 25.2 (95% CI 12.6 to 45.1) for incident PMM cases for wives of workers employed at the same facility.[27] Thus, considerable internal inconsistency exists among the Italian observations as well as within the observations associated with the same asbestos emitting facility.

Only two studies we evaluated provided PMM effect estimates by estimated level of non-occupational exposure to asbestos.[4 24] Hansen *et al*[14] evaluated the risk of PMM due to environmental crocidolite exposures among residents of Wittenoom, Australia. As we noted in a recent letter to the editor,[30] the highest exposure groups considered by Hansen *et al* had cumulative exposures of at least 20 f/mL-years (fibers/mL-years), with RRs ranging from 3.6 to 6.3 depending on the type of censoring.[14] In contrast, Ferrante *et al*[24] found an OR of 23.3 (95% CI 2.9 to 186.9) for their highest non-occupational cumulative exposure category of 10.0 f/mL-years to 24.2 f/mL-years. Thus, the higher exposure levels estimated by Hansen *et al*[14] yielded PMM risks 3.0-fold to 6.5-fold lower than those reported by Ferrante *et al*.[24] This inconsistency was exacerbated by the fact that subjects in Ferrante *et al*[24] were exposed to mixed chrysotile/amphibole fibres, whereas the residents of Wittenoom were exposed to pure crocidolite fibres. This finding conflicts with the established view that PMM risks are higher for exposure to amphibole fibres than other fibre types.[1–3]

The Ferrante *et al*[24] study also contained internal inconsistencies in PMM effect estimates relative to asbestos exposure. For example, Boffetta[31] recently noted that the ORs for environmental asbestos exposure appeared to be higher for the same

level of exposure than the corresponding ORs for occupational asbestos exposure. This was particularly evident in the category of highest exposure (≥10 f/mL-years) despite exposure levels being lower on average in that category (15 f/mL-years vs 260 f/mL-years). It is difficult to estimate how these inconsistencies may have influenced this analysis as overall effect estimates from each study were calculated and used in the reported meta-analysis, rather than risks reported by exposure levels.

The numerous inconsistencies and considerable variability we observed for asbestos related PMM effect estimates across and within the individual studies are due in part to limitations associated with these studies and the corresponding meta-analysis. For one, the overall quality of the studies is mixed. Seven effect estimates from the 18 studies were based on 10 or fewer PMM cases, giving rise to less precise individual and combined effect estimates. Five studies did not confirm the diagnosis of mesothelioma histologically.[6 12 14 18 21] Misdiagnosis of mesothelioma could lead to inflated risk estimates and ultimately result in meta-RRs that are higher than expected. Relatively few studies evaluated non-occupational exposures to pure asbestos fibre types. Also, as stated above, the potential for exposure misclassification and related study bias is high for many studies because of the lack of quantitative exposure estimates. Furthermore, as indicated by Bourdes *et al*,[4] the pooled risk estimates from this most recent meta-analyses most likely overestimated PMM risk due to non-occupational exposures as the evaluated groups experienced higher levels of exposures than individuals living in countries without specific sources of exposure.

The quality of the included studies and the control or comparison groups used by the individual studies could also influence the results of this meta-analysis. Several studies calculated effect estimates by comparing the exposed population to national[28] or world[14 17] standardised populations. Due to the varying rates of PMM across an individual country or the world, reported effect estimates could be biased. For example, Delgermaa *et al*[32] compared mesothelioma rates across the world and showed that the UK had age-adjusted mortality rates 5.6-fold higher than Japan. A review article of incident mesothelioma rates showed that Australia had the highest incident rate, followed by Great Britain and Belgium while South Korea, Morocco and Tunisia had the lowest, approximately a 30-fold difference.[33] For countries with high mortality and incidence rates, comparison to the global population would overestimate the risk. Conversely, a country with lower incidence and mortality rates that compares to the world population may underestimate their risk estimates. Moreover, rates of mesothelioma have also been shown to vary considerably across regions within individual countries. An evaluation of mortality rates in Italy showed that standardised rates can vary by more than sevenfold for the total population, depending on the location of interest.[34] Historical evaluations of pleural mesothelioma deaths in USA have shown that rates are higher in north-eastern USA, Colorado, Wyoming, Florida, Illinois and the Pacific Coast than in other regions of USA.[35] Similar to the use of global standardised rates, comparison to national rates could also lead to biased risk estimates. Studies that were able to draw comparison groups from populations in the surrounding region may have been able to minimise this potential source of bias.

Another limitation of the presented analysis is the inclusion of ecological studies. We understand that these are not usually included in meta-analyses due to the limitations associated with exposure assessment and the lack of adjustment for confounding factors. In this instance, we felt it was appropriate to include the ecological studies because all individuals were selected based on their potential exposure to asbestos rather than their case status. Furthermore, the exposures for some of the ecological studies were equivalent, and in some instances, better than the proxy measures of exposure reported in some of the case-control studies. For instance, Camus *et al*[18] used historical records of asbestos use, ambient asbestos air concentrations recorded by the government, and asbestos fibre concentrations in the air reported by the asbestos industry. This historical information, along with information on the duration of residency, allowed for the estimate of cumulative exposure levels. Metintas *et al*[17] collected soil samples and indoor and outdoor air samples to confirm exposure to naturally occurring asbestos. Furthermore, it is unlikely that confounding factors contributed to the development of mesothelioma because the primary risk factor for the development of mesothelioma is exposure to asbestos.

In order to evaluate how some of the limitations stated above may have impacted our overall findings, additional analyses were conducted. The potential for publication bias (figure 3) was also evaluated. We conducted sensitivity analyses to determine how the inclusion of the crude (unadjusted) estimates calculated by the authors and the inclusion of the ecological studies may have impacted our overall findings. Neither the exclusion of the crude (unadjusted) estimates nor the ecological studies changed our overall findings, with effect estimates remaining above 5 and heterogeneity unchanged. As shown in figure 3, the potential for publication bias appears limited for the neighbourhood studies. The household studies do not appear as equally distributed, however, any studies possibly omitted most likely would have had lower effect estimates and been weighted less than the reported studies. In this hypothetical scenario, inclusion of such

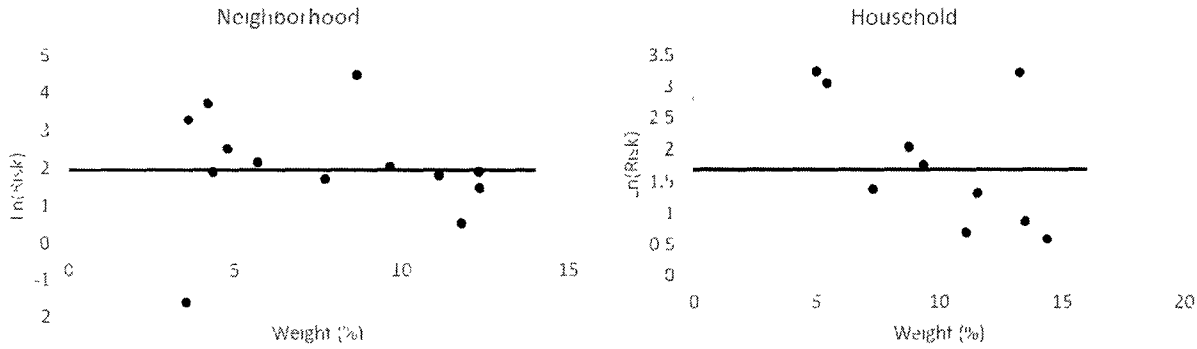

Figure 3 Plots to evaluate publication bias for neighbourhood (A) and household (B) studies that reflect the natural log of the reported effect estimates versus the weights used in the random effects meta-analysis for each group of studies separately

studies would not be expected to influence the overall results of the meta-analysis. The observed funnel plots are consistent with the neighbourhood exposure evaluation previously conducted by Bourdes *et al*.[4]

Another critical component of these studies is to ensure adequate latency for disease development. Six studies reported latency values of at least 20 years for a majority of, if not all, individuals diagnosed with PMM.[6 22 24 25 28 29] Mensi *et al*[22] observed a latency period of 54 years, on average, for those with familial exposure and a median of 50 years since first exposure for those with environmental exposure. Maule *et al*[29] accounted for latency in domestic or environmentally exposed subjects by excluding information about residential location for the last 20 years leading up to diagnosis. We used the reported effect estimate for women married to asbestos cement plant workers that had latency values between 20 years and 38 years.[6] An evaluation of individuals who lived near an industrial source of asbestos in Japan had an average latency of 43 years.[28] However, the remaining studies were not clear on the duration of time between exposure and disease diagnosis.

A strength of our evaluation was the systematic approach to locating and summarising relevant studies. In addition, our update included more than twice the number of studies included in the previous Bourdes *et al*[4] evaluation which included the most recent updates for cohorts that have been evaluated at numerous time points. The increased sample size of studies allowed for the evaluation of confirmed mixed fibres without the inclusion of unspecified fibre-type studies. We also calculated PMM effect estimates from the raw data provided in the publications when the requisite estimates for our meta-analysis were not provided by the authors. Finally, we were able to account for the observed heterogeneity in study design and population by using random effects analytical techniques.

Though limitations inherent to the studies included in this meta-analysis are evident (specifically with inadequate comparison groups, exposure misclassification, misdiagnosed mesothelioma and recall bias), these studies are the current literature available evaluating non-occupational exposures. Addressing this important potential source of bias in a formal way would require access to medical and pathology records, and to pathology specimens. It is unlikely that these sources are available. However, a discussion of this source of bias, including simulation-based sensitivity analyses using results of independent validation studies, would be useful. Future studies could benefit from implementing simulation-based sensitivity analyses, as well as more formal confirmation of medical diagnoses and non-occupational exposures.

CONCLUSIONS

We observed elevated risk of PMM for both neighbourhood and household exposures. The risk of PMM was directly related to asbestos fibre type, with chrysotile fibres not showing statistically elevated risk of PMM. However, PMM effect estimates observed across and within the 18 individual studies revealed considerable heterogeneity, and the sample sizes for the meta-analyses conducted by fibre type were small for pure fibre studies. Nevertheless, PMM risks from non-occupational asbestos exposure are consistent with the fibre-type potency response observed in occupational settings. By relating our findings to knowledge of exposure-response relationships in occupational settings, we can better evaluate PMM risks in communities with ambient asbestos exposures from industrial or other sources.

Contributors GMM had the idea for the manuscript and was responsible for the overall quality of the work. He also drafted the text and assisted with the biostatistical approach to the analysis. ASR, KAK and SMB reviewed the literature and confirmed the inclusion and exclusion of various studies. KAK and SMB were responsible for drafting the text and creating the figures. ASR was responsible for conducting the analyses and drafting the text.

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Non-occupational exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis

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