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REVIEW

Mesothelioma among Motor Vehicle Mechanics: An Updated Review and Meta-analysis

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ABSTRACT

Background: We published a meta-analysis of the association between work as a motor vehicle mechanic and mesothelioma in 2004. Since then, several relevant studies on this topic have been published. Thus, to update the state-of-the-science on this issue, we conducted a new systematic review and meta-analysis.
Methods: A comprehensive PubMed literature search through May 2014 was conducted to identify studies that reported relative risk estimates for mesothelioma among motor vehicle mechanics (in general), and those who were engaged in brake repair (specifically). Studies were scored and classified based on study characteristics. Random-effects meta-analyses generated summary relative risk estimates (SRREs) and corresponding 95% confidence intervals (CI). Heterogeneity of results was examined by calculating *Q*-test *P*-values (*P-H*) and I^2 estimates. Sub-group and sensitivity analyses were conducted for relevant study characteristics and quality measures.
Results: Ten case-control studies, one cohort study, and five proportionate mortality ratio (PMR)/standardized mortality odds ratio (SMOR) studies were identified and included in the quantitative assessment. Most meta-analysis models produced SRREs below 1.0, and no statistically significant increases in mesothelioma were observed. The SRRE for all studies was 0.80 (95% CI: 0.61–1.05) with significant heterogeneity (P-H <0.001, I^2 = 62.90). A similar SRRE was observed among the five Tier 1 studies with the highest quality ratings (SRRE = 0.76, 95% CI: 0.46–1.25), with no heterogeneity

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among studies ($P\text{-}H = 0.912$, $I^2 = 0.00$). Meta-analysis of the Tier 2 ($n = 5$) and Tier 3 ($n = 6$) studies resulted in SRREs of 1.09 (95% CI: 0.76–1.58) and 0.73 (95% CI: 0.49–1.08), respectively. Restricting the analysis to Tiers 1 and 2 combined resulted in an SRRE of 0.92 (95% CI: 0.72–1.29). The SRRE specific to brake work ($n = 4$) was 0.64 (95% CI: 0.38–1.09).

Conclusions: This meta-analysis of the epidemiologic studies provides evidence that motor vehicle mechanics, including workers who were engaged in brake repair, are not at an increased risk of mesothelioma.

KEYWORDS: asbestos epidemiology; auto repair; brake dust; cancer epidemiology; chrysotile; mesothelioma

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INTRODUCTION

Studies of motor vehicle repair activities and brake repair activities provide an opportunity to examine the risks of mesothelioma in settings in which chrysotile exposure is not accompanied by exposure to commercial amphibole products. Exposure to short chrysotile fibers can occur during installation and repair of asbestos-containing brakes, clutches, and gaskets. In the past, automobile brakes typically contained chrysotile asbestos embedded in a solid binder (Jacko *et al.*, 1975). In the USA, EPA banned the manufacture, importation, and processing of brake linings and pads containing asbestos in 1993 (EPA, 1989). Although the phase-out of asbestos-containing brakes likely began in the 1980s, brakes that were in place in 1993 continued to be replaced after the ban took effect. The process of brake replacement involves three potential opportunities for release of asbestos fibers: (i) small amounts of chrysotile asbestos (usually <1%) may be present in the brake wear debris (Lynch, 1968; Hickish and Knight, 1970; Anderson *et al.*, 1973; Jacko and DuCharme, 1973; Rowson, 1978; Williams and Muhlbaier, 1982; Cha *et al.*, 1983; NIOSH *et al.*, 1989), (ii) asbestos can be released during sanding, grinding, and beveling of new asbestos brake linings or pads, and (iii) asbestos can be released during handling of new brakes and packaging materials (Madl *et al.*, 2008).

Some authors (Freeman and Kohles, 2012; Lorimer *et al.*, 1976), regulatory agencies (EPA, 1986b), and trade organizations (World Trade Organization, 2000) have opined in the past that motor vehicle mechanics are likely to be at increased risk of asbestos-related disease, most notably mesothelioma. These opinions were based primarily on the assumed opportunity for asbestos exposure during brake work (Paustenbach *et al.*, 2004; Madl *et al.*, 2008; IARC, 2012) and on case reports of mesothelioma among brake repair workers (EPA, 1986a,b, 1989; Lemen, 2004). However, case reports and case series cannot quantify associations and are not adequate for assessing causality (Hennekens and Buring, 1987). Case reports and case series become even less informative in the presence of analytic studies.

When the EPA conducted its evaluation ~30 years ago (EPA, 1986a,b), the epidemiologic information on mesothelioma among vehicle mechanics was limited to only three studies (McDonald and McDonald, 1980; Teta *et al.*, 1983; Spirtas *et al.*, 1985). Our previous meta-analysis (Goodman *et al.*, 2004) included 11 studies. In the past 10 years, five additional epidemiologic studies (Rake *et al.*, 2009; Aguilar-Madrid *et al.*, 2010; Rolland *et al.*, 2010; Merlo *et al.*, 2010; Roelofs *et al.*, 2013) and four updates of previous studies (McElvenny *et al.*, 2005; Milham, 2011; NIOSH, 2011; Health and Safety Executive, 2013) have examined the risk of mesothelioma among motor vehicle mechanics or brake workers. Therefore, an updated systematic review is warranted.

Our objective was to conduct an updated systematic review and quantitative meta-analysis of the epidemiologic literature examining the relative risk (RR) of mesothelioma among workers engaged in motor vehicle repair and, when possible, among workers occupationally exposed to brake dust. The specific aims were to: (i) estimate summary relative risk estimates (SRREs) between motor vehicle mechanics and mesothelioma; (ii) conduct sub-group and sensitivity analyses by relevant study characteristics (e.g. study design and type of population) to identify potential sources of heterogeneity; (iii) estimate the influence of each study on the overall effect size; (iv) examine potential trends of associations for certain study factors (study quality, study period) using meta-regression; and (v) evaluate the potential for publication bias.

METHODS

Literature search and study selection

A comprehensive literature search was conducted using PubMed and Embase to identify studies evaluating mesothelioma risk among motor vehicle mechanics. The literature search was conducted through May 2014, with no lower date truncation. Keyword searches were conducted in PubMed and Embase for terms including 'mesothelioma', 'pleural neoplasms', 'pleura tumor', 'occupational exposure', 'occupational diseases', 'asbestos', 'motor vehicles', 'automobiles', 'automobile industry', 'mechanics', 'case control studies', 'odds ratio', 'risk factors', 'mortality/trends', 'registries', 'incidence', 'epidemiology', and 'population surveillance'. References from relevant studies, review articles, and previous meta-analyses were also screened. Additional electronic searches were conducted to identify relevant studies that were not published in the peer-reviewed literature, including government documents. When information was missing from published reports, attempts were made to contact the authors to obtain it. Search results were screened by two individuals to determine relevancy, with no discrepancies between reviewers (Fig. 1). To be included in the meta-analysis, studies were required to meet the following criteria: (i) cohort or case-control design reporting incidence or mortality, or studies based on analyses of proportions [proportionate mortality ratio (PMR)/proportional incidence ratio (PIR)/standardized mortality odds ratio (SMOR) analyses]; (ii) analysis of an adult human population; (iii) mesothelioma risk analyzed among subjects involved in motor vehicle repair (if a study reported results only on the broad category of general mechanics, it was not included in the meta-analysis); and (iv) mesothelioma RR estimates and variance measures either reported in the original publication or calculated based on the data obtained from the authors or reported in the papers.

Study quality scoring methodology

All studies retained for quantitative assessment underwent formal evaluation and were assigned a quality score according to their methodological strengths and limitations, based on the methods used in our previous

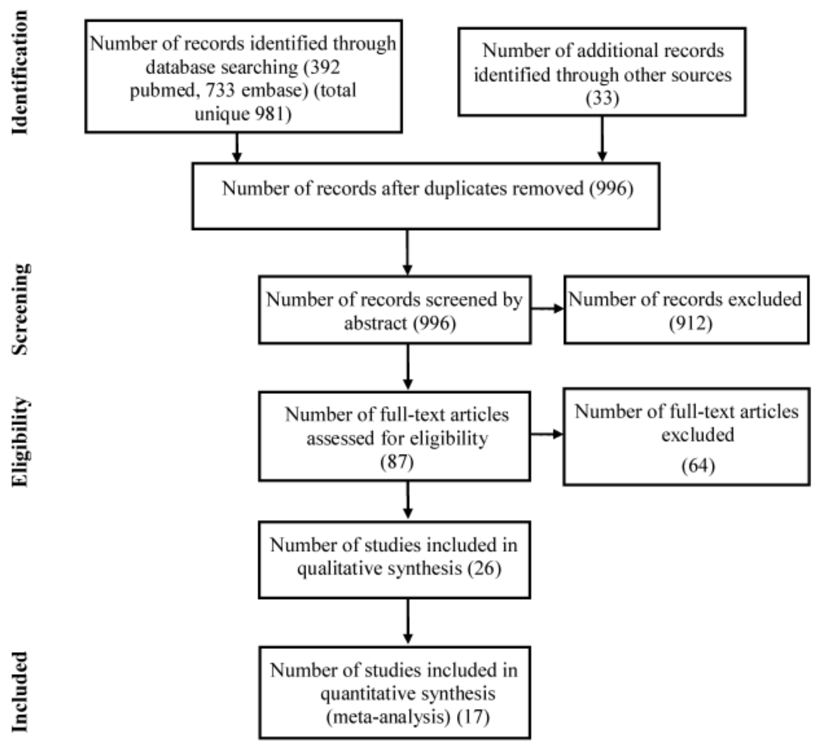

Figure 1 Flow diagram of study selection.

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paper (Goodman *et al.*, 2004) and those recommended in the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (Stroup *et al.*, 2000) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher *et al.*, 2009) guidelines. Each study was awarded a point for fulfilling each methodological criterion and a score of zero for failing to do so. The scoring used the following 12 criteria:

- Overall study design: PMR/PIR studies or death certificate-based SMOR studies = 0; else (cohort or case–control studies) = 1.
- Asbestos exposure: Job title based = 0 (e.g. 'car mechanic'); task specific = 1 [e.g. 'brake repairmen' or industrial hygiene (IH) based].
- Was age taken into account? no = 0; yes = 1.
- Lifetime asbestos exposure history obtained: no = 0; yes = 1.
- Did study methods or analysis address confounding in any way? no = 0; yes = 1.
- Exposure-response analysis performed? no = 0; yes = 1.
- Was latency taken into account? no = 0; yes = 1.
- For cohort studies, duration of follow-up: <30 years = 0; ≥30 years = 1.
- For case-control studies, response rate <80% or not reported: = 0; ≥80% = 1.
- Information bias: possible = 0; unlikely/addressed = 1 (e.g. in case–control studies using recorded occupational histories).
- Selection bias: possible = 0 (e.g. in hospital-based case-control studies); unlikely/addressed = 1 (e.g. in cohort studies or population-based case-control studies).
- Cases confirmed by pathologic review: no = 0; yes = 1.

Scoring was used as a formal approach to classify studies into three equal sized tiers. Studies with scores of seven or above were included in Tier 1 and considered to have the strongest study design and analysis and less opportunity for bias. Tier 2 included studies with a score of five or six, which were considered less informative due to methodological limitations. Tier 3 included studies that scored four or less. It should be noted that many of the scoring criteria related to inherent strengths or limitations of the study design and the underlying data, and not necessarily to the methodological decisions of the original investigators.

Data extraction and statistical analysis

Information extracted from each study using a standard form included first author, publication year, study design, nature of cohort, geographic location of study, exposure definition, source of cases, comparison group, sample size, number of cases, years of follow-up, population demographic characteristics, outcome classification, measures RR and 95% confidence intervals (CIs) for each relevant exposure group and worker classification, statistical adjustments, and the methodological factors on which scoring was based. If more than one article from the same study population was published, data from the publication with the longest follow-up and/or the most completely adjusted risk estimate was used.

Random-effects models were used to calculate SRREs and 95% CIs. The study weights were equal to the inverse of the variance of each study's effect estimate (DerSimonian and Laird, 1986). Measures of RR [e.g. odds ratios (ORs), rate ratios, standardized mortality ratios(SMRs)] and associated measures of variance (e.g. 95% CIs) were used as input parameters in the meta-analysis models. Four case-control studies (McDonald and McDonald, 1980; Woitowitz and Rodelsperger, 1994; Agudo *et al.*, 2000; Aguilar-Madrid *et al.*, 2010) did not report the results in terms of ORs but provided information from which ORs and 95% CIs could be calculated using SAS 9.3 (Cary, NC, USA). Two proportional mortality studies (Milham and Ossiander, 2001; NIOSH, 2011) did not report 95% CIs, but provided numbers of observed and expected cases, from which 95% CIs were calculated based on the Poisson distribution (Breslow and Day, 1987).

Primary meta-analysis models were used to generate SRREs for case-control and cohort studies of motor vehicle mechanics and mesothelioma overall and by study tiers. The base model included all eligible studies, and separate models were created for each study quality tier. Sub-group and sensitivity analyses were conducted to examine patterns of associations and to identify potential sources of heterogeneity overall and for groups of studies. These included analyses by study design, geographic location, and asbestos exposure history ascertainment. One-study-removed

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sensitivity analyses were conducted to determine the relative influence of each study on the overall model.

Heterogeneity was assessed quantitatively using the Cochran's *Q*-test with the corresponding *P*-value (*P-H*) and by calculating the I^2 statistic, which indicates the percentage of variation attributable to between-study heterogeneity (Higgins and Thompson, 2002). The presence of publication bias was assessed visually by examining a funnel plot measuring the standard error as a function of effect size, as well as performing Egger's regression method (Rothstein *et al.*, 2005). We generated forest plots for models of motor vehicle mechanics and mesothelioma by study quality tiers. Meta-regression analyses were performed to evaluate the patterns in summary effect sizes based on relevant factors (modeled as continuous variables), such as increasing study quality and study period. Statistical analyses were conducted using Comprehensive Meta-Analysis Software (version 2.2.046; Biostat, Englewood, NJ, USA), SAS 9.3 (SAS Institute, Cary, NC, USA), and STATA statistical software (Stata Corporation, College Station, TX, USA).

RESULTS

Ten case-control studies, one cohort study, and five PMR/SMOR studies published between 1980 and 2013 were included in the meta-analysis (Table 1). Since RRs could not be calculated for three cohort studies of motor vehicle mechanics (two from Sweden and one from Denmark) that provided information on mesothelioma (Jarvholm and Brisman, 1988; Hansen, 1989; Gustavsson *et al.*, 1990), these studies were not included in the meta-analysis. Five studies were of higher methodological quality (Tier 1), five studies were of moderate methodological quality (Tier 2), while six studies were of lower methodological quality (Tier 3) (Table 2).

Overview of studies included in meta-analysis

Tier 1

McDonald (McDonald and McDonald, 1980) compared histologically confirmed mesothelioma cases in the USA and Canada to matched controls that had pulmonary metastases from non-pulmonary malignancies. Lifetime occupational histories were obtained through interviews with relatives. Of the 156 cases and 156 controls who worked in occupations thought to entail asbestos exposure but not previously recognized as associated with mesothelioma risk, 11 cases and 12 controls were 'garage' workers, from which we calculated an OR of 0.91 (95% CI: 0.35–2.34). This study had a large sample size and a high next-of-kin response rate for both cases (95%) and controls (91%). Hospital-based cancer cases may not have been representative of the source population of cases (i.e. possible selection bias). However, the choice of controls with other cancers may have reduced recall bias. The use of the highest asbestos exposure to characterize each participant's occupational history likely decreased potential confounding by other asbestos exposures.

Teta (Teta *et al.*, 1983) compared pathologically confirmed cases from the Connecticut Tumor Registry and from a Veterans Administration hospital with controls from Connecticut death certificate files. Occupational histories were obtained from death certificates and city directories and did not include information specific to brake work. There were 147 total cases and 464 controls with 1 exposed case and 5 exposed controls included in the analysis. The OR for subjects employed in 'automobile repair and related service' was 0.65 (95% CI: 0.08–5.53). The choice of population controls, the completeness of occupational records (job titles were obtained for 98% of cases and 99% of controls) and the histological confirmation of cases were methodological strengths. Shortcomings were a lack of information on brake repair work and lack of control for confounding by other potential sources of asbestos exposure. The OR estimate was based on relatively few observations and did not take into account exposure-response or latency.

Hessel (Hessel *et al.*, 2004) updated a previous National Cancer Institute (NCI) case-control study (Spirtas *et al.*, 1985, 1994). Pathologically confirmed definite or probable mesothelioma cases in the Los Angeles County Cancer Surveillance Program, the New York State Cancer Registry (excluding New York City) and 39 Veterans Administration hospitals were included (n = 147). Controls included patients who died of causes other than cancer, respiratory disease, suicide, or violence (n = 358). Interviews requested lifetime occupational history and information specifically on brake lining installation or repair. Hessel calculated an OR of 1.04 (95% CI: 0.46–2.22) for the occupational category 'brake installation or repair'. However, after adjusting for any of eight occupations with potential asbestos exposure, the OR became 0.82

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Table 1. Summary of mesothelioma studies and corresponding RR estimates included in the meta-analysis.

First author	Year	Design	Exposure definition	Source of cases	Comparison group	RR estimate (95% CI)[a]
Tier 1 studies[b]						
McDonald	1980	Case-control	Garage workers	Hospital records	Non-pulmonary cancers	0.91 (0.35–2.34)
Teta	1983	Case-control	Automobile repair and related services	CT Tumor Registry	Connecticut decedents	0.65 (0.08–5.53)
Teschke	1997	Case-control	Vehicle mechanics	British Columbia's Cancer Registry	Randomly selected from voters lists	0.8 (0.2–2.3)
			Brake lining installation or repair			0.3 (0.0–1.4)
			Vehicle mechanics (ever employed in at-risk occupations excluded)			0.4 (0.0–3.2)
Hessel	2004	Case-control	Brake lining installation or repair, all other asbestos exposures controlled	NY Cancer Registry, LA County Cancer Surveillance Program, VA Hospitals	Deaths from causes other than cancer, respiratory disease, suicide or violence	0.82 (0.36–1.80)
Rake	2009	Case-control	Vehicle maintenance involving work with brakes or gaskets	Hospital records, National Cancer Research Network, healthcare providers	Randomly selected from Health Authority registers	0.4 (0.1–1.7)
Tier 2 studies[c]						
Agudo	2000	Case-control	Mechanics, motor vehicles	Hospital records	Patients with non-asbestos-related conditions	0.62 (0.11–2.36)
Hansen	2003	Case-control	Repair of motor vehicles and motorcycles	Danish Cancer Registry	All other occupations combined	0.8 (0.4–1.5)
Aguilar-Madrid	2010	Case-control	Automobile mechanics	Two hospitals	Randomly selected active and retired workers in the Mexican Institute of Social Security database	0.74 (0.08–6.68)

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Table 1. *Continued*

First author	Year	Design	Exposure definition	Source of cases	Comparison group	RR estimate (95% CI)[a]
Merlo	2010	Cohort	Bus maintenance workers	Employees of Azienda Municipalizzata Trasporti	Ligurian male population	1.27 (0.66–2.43)
Rolland	2010	Case-control	Motor vehicle mechanics	National Mesothelioma Surveillance Program	Randomly selected from the 1999 census	1.50 (0.76–2.95)
Tier 3 studies[d]						
Woitowitz	1994	Case-control	Motor vehicle repair workers	Not specified	Lung resection patients and population controls	0.87 (0.43–1.70)
			Definitely engaged in brake service			0.89 (0.31–2.47)
McElvenny	2005	Proportionate mortality	Motor mechanics	British mesothelioma register	General population of Great Britain	0.48 (0.37–0.62)
Milham	2011	Proportionate mortality	Automobile mechanics and repair workers	Washington State residents	All other occupations combined	0.73 (0.50–1.11)
NIOSH	2011	Proportionate mortality	Auto mechanics	National Occupational Mortality Surveillance database	All other occupations combined	0.82 (0.50–1.27)
Health and Safety Executive	2013	Proportionate mortality	Motor mechanics; auto engineers	British mesothelioma register	General population of Great Britain	0.41 (0.30–0.55)
Roelofs	2013	Standardized morbidity	Automobile mechanics	Massachusetts Cancer Registry	Patients with cancers not associated with asbestos	2.1 (1.1–4.0)

[a]RR estimates are shown as reported by each study or are rounded to two decimal places if they were calculated based on data obtained from the authors or reported in the papers.
[b]Studies of higher methodological quality.
[c]Studies of moderate methodological quality.
[d]Studies of lower methodological quality.

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Table 2. Quality scores of studies evaluating the association between mesothelioma risk and employment as a motor vehicle mechanic.

Quality criteria	Study															
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Overall study design: PMR/PIR/SMOR = 0; SMR/OR = 1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0
Asbestos exposure: Job title (e.g. 'car mechanic') = 0; Task specific (e.g. brake repairman or IH-based) = 1	0	0	1	1	1	0	1	0	0	0	1	0	0	0	0	0
Was age taken into account adequately?: no = 0; yes = 1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1
Lifetime asbestos exposure history: no = 0; yes = 1	1	1	1	1	1	1	0	1	0	1	1	0	0	0	0	0
Was any attempt made to control for confounding?: no = 0; unlikely/addressed = 1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0
Exposure-response analysis performed? no = 0; yes = 1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
Was latency taken into account? no = 0; yes = 1	0	0	1	0	1	0	1	0	1	0	0	0	0	0	0	0
For cohort studies: follow-up <30 yr = 0; ≥30 years = 1									1			0	0	0	0	0
For case–control studies: response rate: <80% or not reported = 0; ≥80% = 1	1	1	1	0	0	1	1	0		0	0					
Information bias: possible = 0; unlikely/addressed = 1	1	1	0	0	1	0	1	1	1	1	0	1	1	1	1	0
Selection bias: possible = 0; unlikely/addressed = 1	0	1	0	1	1	1	0	0	1	0	0	1	1	1	1	0
Cases based on pathology review: no = 0; yes = 1	1	1	1	1	1	1	0	1	0	1	1	0	0	0	0	1
Total score	7	7	8	8	10	6	6	5	6	5	4	3	3	3	3	2

1, (McDonald and McDonald, 1980); 2, (Teta *et al.*, 1983); 3, (Teschke *et al.*, 1997); 4, (Hessel *et al.*, 2004); 5, (Rake *et al.*, 2009); 6, (Agudo *et al.*, 2000); 7, (Hansen and Meersohn, 2003); 8, (Aguilar-Madrid *et al.*, 2010); 9, (Merlo *et al.*, 2010); 10, (Rolland *et al.*, 2010); 11, (Woitowitz and Rodelsperger, 1994b); 12, (McElvenny *et al.*, 2005); 13, (Milham, 2011); 14, (NIOSH, 2011); 15, (Health and Safety Executive, 2013); 16, (Roelofs *et al.*, 2013).

(95% CI: 0.36–1.80). In addition, when cases and controls with a history of employment in any of these occupations were removed from the analysis, the OR for occupational brake installation and repair became 0.62 (95% CI: 0.01–4.71). An exposure-response analysis showed no evidence of increasing risk of mesothelioma with increasing duration of brake work. Subjects whose only brake work was non-occupational (i.e. do-it-yourself) were not at increased risk of mesothelioma. These NCI data have several important features: (i) exposure was defined specifically as brake installation and repair, (ii) confounding by other occupational exposures was addressed, and (iii) information on duration of employment allowed an exposure-response analysis. A limitation of this data set was the relatively low response rate (74% among cases' next-of-kin, 79% among controls' next-of-kin).

Teschke *et al.* (1997) compared pathologically confirmed mesothelioma cases from the British Columbia Cancer Agency to matched controls selected from voter registration lists. Lifetime occupational and exposure histories were obtained, whenever possible, directly from cases and controls. The OR for 'vehicle mechanics' was 0.8 (95% CI: 0.2–2.3). The OR for the

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category 'brake lining installation or repair' was 0.3 (95% CI: 0.0–1.4). After removing cases and controls with at-risk occupational asbestos exposures, the OR for 'vehicle mechanics' was 0.4 (95% CI: 0.0–3.2). The results did not change after taking into account 20+ years of latency and, in fact, the first exposure for all of the vehicle mechanics and brake workers was >20 years prior to diagnosis. Information bias is a concern in this study due to the difference in proportion of next-of-kin interviews among cases (33.3%) compared with controls (13.6%). Although fairly small in size, this study was methodologically strong because: (i) it considered other asbestos exposures, (ii) specified exposure as 'brake lining installation or repair', (iii) considered latency, and (iv) had a high response rate (88% among cases, 81% among controls).

Rake *et al.* (2009) conducted a case-control study of 622 mesothelioma patients (92% histologically confirmed) and 1420 age-matched population controls in England, Wales, and Scotland. Cases were identified through chest physicians, surgeons and nurses, the National Cancer Research Network, and English and Scottish hospital records. A postal questionnaire and telephone interview assessed lifetime occupational and residential history, do-it-yourself activities, and other possible environmental exposures for living cases and controls. This included work with gaskets and brake linings. The OR for vehicle maintenance involving work with brakes or gaskets was 0.4 (95% CI: 0.1–1.7). Though this study used only living cases and controls, the response rates differed between the cases (73%) and controls (60%). This study was methodologically strong because the authors accounted for the impact of other high-risk jobs and examined latency and duration of exposure.

Tier 2

In 1987, Olsen and Jensen published a proportionate incidence ratio (PIR) analysis that linked cases from the Danish Cancer Registry with occupational histories (Olsen and Jensen, 1987). There were no cases of mesothelioma for the occupational category 'repair of motor vehicles and motorcycles' or for the industry category 'garage'. The data were updated in a 2003 case-control study (Hansen and Meersohn, 2003). For the category 'repair of motor vehicles and motorcycles' the OR was 0.8 (95% CI: 0.4–1.5), based on 10 mesothelioma cases. Limitations of this study were lack of requirement of histological confirmation of mesothelioma diagnosis for study inclusion, inability to obtain a complete work history or detailed exposure history regarding work with brakes specifically, and lack of latency analysis for repair of motor vehicles specifically. Its strengths included large sample size and unlikeliness of reporting bias due to the coverage of all cancer cases in Denmark by the registry.

Agudo *et al.* (2000), in a hospital-based case-control study in Spain, compared pathology-confirmed cases of mesothelioma to population/hospital controls. A complete occupational history was collected, though information was not available on exposure to brake repair specifically. There were three cases and 14 controls in the category 'mechanics, motor vehicle'. The non-exposed category included 51 cases and 148 controls that had never worked in any of the at-risk occupations. The crude OR for 'mechanics, motor vehicle' was 0.62 (95% CI: 0.11–2.36). The comparison of motor vehicle mechanics that may have had other potential asbestos exposure to persons without exposure may have led to unmeasured confounding. Because 44% of cases and <1% of controls had next-of-kin interviews, information bias is possible. The study's high response rate, methods of control selection, and complete occupational histories were among its strengths.

Aguilar-Madrid (Aguilar-Madrid *et al.*, 2010) conducted a case-control study of 472 workers insured by the Mexican Institute of Social Security including 119 histologically confirmed incident mesotheliomas and 353 matched hospital controls. In-person interviews for both cases and controls assessed the complete employment history and para-occupational exposures including family members' occupations and likely environmental exposures though information was not available on brake work specifically. No next-of-kin interviews were conducted. There were one case and four controls whose most frequent occupation was 'mechanic, automobile', resulting in an OR of 0.74 (95% CI: 0.08–6.68). This OR estimate was based on relatively few observations, was not adjusted for potential confounding by other occupational or non-occupational exposures, and did not take into account exposure-response or latency.

In Genoa, Italy, Merlo *et al.* (2010) conducted a historical cohort mortality study among 9267 male public transport workers of which 2073 were bus

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maintenance workers. Nine deaths from pleural mesothelioma were observed among bus maintenance workers, resulting in an SMR of 1.27 (95% CI: 0.66–2.43) when compared to the regional male population. This study did not obtain a lifetime asbestos exposure history, control for potential confounding by other exposures, assess exposure specific to brake work, require pathologic review of cases, or perform exposure-response analyses. This study did, however, have a long duration of follow-up (1 January 1970 to 31 December 2005) and took latency into account in the overall cohort but not among the bus maintenance workers specifically. Reporting or selection bias was unlikely as the authors identified all subjects ever employed at the public transport company in Genoa.

Rolland *et al.* (2005, 2010) conducted a population-based case-control study of primary malignant pleural tumors, nested within France's National Mesothelioma Surveillance Program (PNSM); 86.8% of the cases were pathologically confirmed. A self-administered survey and interviewer-administered questionnaire assessed lifetime residential, educational, and occupational history, including specific job tasks and do-it-yourself repair. No next-of-kin interviews were conducted. Of the 371 and 732 male cases and controls, 17 cases and 22 controls were motor vehicle mechanics. The OR for motor vehicle mechanics was 1.50 (95% CI: 0.76–2.95). The authors did not control for multiple occupational exposures despite the fact that this information was included in the questionnaire. The response rate was low, with overall participation under 50%.

Tier 3

Woitowitz and Rodelsperger (1994) compared lifetime occupational histories of 324 pathology-confirmed mesothelioma cases in Germany with two groups of controls: 315 hospital control patients who underwent lung resection and 182 population controls. Lung resection controls were used in order to obtain lung tissue for fiber analysis. Sixteen cases, 16 hospital controls and 12 population controls were listed as 'motor vehicle repair workers'. These data yielded an OR of 0.97 (95% CI: 0.45– 2.12) using hospital controls and an OR of 0.74 (95% CI: 0.32–1.75) using population controls. For people definitely engaged in brake service, the OR was 0.75 (95% CI: 0.25–2.23) using hospital controls and 1.32 (95% CI: 0.30–6.51) using population controls. The use of hospital controls that were largely lung cancer patients raises the possibility of confounding, whereas the population controls were not subject to this issue. When the two types of controls were combined for a larger sample size, the OR was 0.87 (95% CI: 0.43–1.70) for motor vehicle mechanics and 0.89 (95% CI: 0.31–2.47) for persons definitely engaged in brake servicing. (These calculations were based on updated numbers provided by the authors, Prof. H.-J. Woitowitz and Dr K. Rödelsperger, Justus-Liebig University Giessen, Germany.) The strengths of this study were its ability to examine the association with brake repair and its high response rate. The most important shortcomings included the lack of adjustment for age and an inadequate description of subject selection.

Roelofs *et al.* (2013) conducted a standardized morbidity odds ratio (SMOR) analysis using incident mesothelioma cases in the Massachusetts Cancer Registry (MCR) from 1988 to 2003. A total of 80 184 cancer controls were used to compute SMORs for each occupation and industry, controlling for gender and age. Of the 564 mesothelioma cases coded for occupation, 10 were identified as automobile mechanics, resulting in an SMOR of 2.1 (95% CI: 1.1–4.0). Although there were 1424 total cases of mesothelioma in the MCR during the time period of interest, only 564 (40%) were able to be coded for 'usual' occupation. The majority of cases were identified as retired, of unknown occupation, or disabled, and were excluded. The authors did not obtain a lifetime asbestos exposure history or brake work-specific exposure information, did not perform exposure-response analysis, and did not take latency into account. When calculating the risk estimate for each occupation, they omitted subjects with occupations known to carry an increased risk from the non-exposed group; however, similar at-risk individuals could not be excluded from the exposed group (only the usual occupation was coded). Thus many occupations, including vehicle mechanics, showed elevated risk estimates. The authors noted that it was not possible to determine if the cases in their study resulted from exposure to the reported usual occupation.

Four studies included in this review and meta-analysis were PMR analyses. Two of these studies took place in Great Britain (McElvenny *et al.*, 2005; Health and Safety Executive, 2013) and two in the USA

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(Milham, 2011; NIOSH, 2011). These studies did not collect task-specific asbestos exposure histories (i.e. brake repairman versus automobile mechanic) or lifetime asbestos exposure histories. The PMR studies did not control for confounding by other asbestos exposures and the reference group for each occupation was the general population, which included those with known risk-related exposures to asbestos. These studies did not assess exposure-response or latency. The cases of mesothelioma in these studies were not necessarily based on pathologic review.

Meta-analysis results

Primary meta-analyses

Meta-analysis of all 16 eligible studies (all tiers combined) of mesothelioma risk among motor vehicle mechanics resulted in an SRRE of 0.80 (95% CI: 0.61–1.05), with statistically significant heterogeneity [*Q*-test *P*-value (*P-H*) < 0.000, I^2 = 62.90] (Table 3, Fig. 2). Meta-regression by study quality did not yield a statistically significant effect (Fig. 3). The patterns of associations across tiers were relatively similar with overlapping CIs (Fig. 2). All five Tier 1 studies reported no increased risk of mesothelioma among motor vehicle mechanics resulting in an SRRE = 0.76 (95% CI: 0.46–1.25), with no heterogeneity between studies (*P-H* = 0.912, I^2 = 0.00) (Table 3, Fig. 2). In this model, the study by Hessel contributed the most relative weight (38.18%), while the study by Teta contributed the lowest (5.51%). Meta-analysis of the five Tier 2 studies produced a non-significant SRRE of 1.09 (95% CI: 0.76–1.58) with little heterogeneity (*P-H* = 0.637, I^2 = 0.00). Three of the individual study ORs in this model were below 1.0 and two were above 1.0 (none of which was statistically significant) and all CIs overlapped. Meta-analysis of the Tier 3 studies resulted in an SRRE of 0.73 (95% CI: 0.49–1.08), with statistically significant heterogeneity (*P-H* < 0.000, I^2 = 81.39). Of the six Tier 3 studies, five reported point estimates ranging between 0.41 and 0.87, while one study (Roelofs *et al.*, 2013) reported a point estimate of 2.10. The study by Roelofs *et al.* was identified as an outlier (overall and within the Tier 3 model) based on visual inspection of a funnel plot of standard error by log OR. Removal of this outlier study in a sensitivity analysis modified the Tier 3 effect size to 0.59, which was statistically significant (95% CI: 0.44–0.79).

Combination of the Tier 1 and Tier 2 studies produced a non-significant SRRE (0.96, 95% CI: 0.72–1.29) with no heterogeneity (*P-H* = 0.845, I^2 = 0.00). The Tier 1 studies provided ~36% of the relative weight in this model. This model was robust to the influence of any single study as reflected by our one-study-removed sensitivity analyses where SRREs ranged between 0.87 (Rolland removed) and 1.01 (Hansen removed).

Four studies reported data specific to brake work; meta-analysis of these studies resulted in an SRRE = 0.66 (95% CI: 0.39–1.10), with no appreciable heterogeneity (*P-H* = 0.472, I^2 = 0.00) (Table 3, Fig. 4). All four studies reported ORs below 1.0.

Sub-group meta-analyses

Meta-analysis by study design generated SRREs <1.0 for both case-control and PMR/SMOR/cohort studies (Table 3). While no heterogeneity was apparent for the model including only case-control studies (*P-H* = 0.911, I^2 = 0.00), significant heterogeneity was found in the model including only studies that used PMR/SMOR/cohort methods (*P-H* = 0.000, I^2 = 83.86). Analysis of only PMR/SMOR studies resulted in an SRRE of 0.71 (95% CI: 0.46–1.10) with significant heterogeneity. Summary results of studies conducted in the USA/Canada (SRRE = 0.93, 95% CI: 0.69–1.27) differed slightly from the non-US/Canadian studies (SRRE = 0.70, 95% CI: 0.49–1.00), but the CIs largely overlapped and removal of Roelofs in the US/Canada model resulted in an SRRE of 0.79 (95% CI: 0.60–1.04). Analysis including only studies that controlled for confounding by other asbestos exposure resulted in an SRRE of 0.77 (95% CI = 0.46–1.28) with no apparent heterogeneity.

Publication bias assessment

Statistical testing for possible publication bias produced significant observations. Egger's regression test—a test for funnel plot asymmetry on a linear regression of a standard normal deviate—produced a *P*-value of 0.05. If a meta-analysis captured all relevant studies, it would be expected that the funnel plot would be symmetric, and that the studies would be dispersed equally on both sides of the overall effect (Rothstein *et al.*, 2005). Thus, the Duval and Tweedie trim and

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Table 3. Summary of meta-analysis results for mesothelioma among motor vehicle mechanics.

Model (number of studies)	SRRE	95% CI	P-value for heterogeneity, I^2	Notes
Primary analyses				
All studies (*n* = 16)	0.80	0.61–1.05	0.000, 62.90	Tier 1, 2, 3 studies included
All studies (*n* = 16), adjusted data from Teschke	0.79	0.60–1.05	0.000, 62.90	Teschke: Cases and controls removed if ever held at-risk occupations
All studies, Roelofs excluded (*n* = 15)	0.72	0.57–0.91	0.018, 48.44	Roelofs identified as an outlier study, and had the lowest study quality rating
Tier 1 studies (*n* = 5)	0.76	0.46–1.25	0.912, 0.00	Studies with the highest study quality rating
Tier 1 studies (*n* = 5), adjusted data from Teschke	0.74	0.43–1.26	0.885, 0.00	Teschke: Cases and controls removed if ever held at-risk occupations
Tier 2 studies (*n* = 5)	1.09	0.76–1.58	0.637, 0.00	Studies determined to be of moderate quality
Tier 3 studies (*n* = 6)	0.73	0.49–1.08	0.000, 81.39	Studies determined to be of low methodological quality[a]
Tier 1 and 2 studies combined (*n* = 10)	0.96	0.72–1.29	0.845, 0.00	Tier 1 and 2 studies included
Studies specific to brake work (*n* = 4)	0.64	0.38–1.09	0.486, 0.00	Analysis of studies that reported data specifically for brake work
Sub-group analyses				
Case-control studies (*n* = 10)	0.89	0.66–1.20	0.911, 0.00	Analysis of case-control studies only
SMOR/PMR/cohort studies (*n* = 6)	0.77	0.51–1.18	0.000, 83.86	Analysis of SMOR/PMR and cohort studies
SMOR/PMR studies (*n* = 5)	0.71	0.46–1.10	0.000, 84.30	Analysis of SMOR/PMR studies
Studies conducted in the USA/Canada (*n* = 7)	0.93	0.69–1.27	0.253, 23.12	Studies conducted in the USA/Canada
Studies conducted in the USA/Canada (*n* = 6), Roelofs excluded	0.79	0.60–1.04	0.998, 0.00	Roelofs identified as an outlier study, and had the lowest study quality rating
Non-US/Canadian studies (*n* = 9)	0.70	0.49–1.00	0.004, 64.60	Studies conducted in Europe, with the exception of one (Mexico)

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Table 3. *Continued*

Model (number of studies)	SRRE	95% CI	P-value for heterogeneity, I^2	Notes
Studies that controlled for confounding by other asbestos exposures ($n = 4$)	0.77	0.46–1.28	0.809, 0.00	Analysis of studies that controlled for confounding due to asbestos exposure outside of motor vehicle repair
Lifetime asbestos exposure history ascertained ($n = 9$)	0.92	0.66–1.28	0.868, 0.00	Analysis of studies that obtained information on prior history of potential asbestos exposure

[a]These studies were determined to be of lower quality but provided risk estimates for motor vehicle mechanic workers and mesothelioma, and were evaluated in the context of 'results consistency' with other studies.

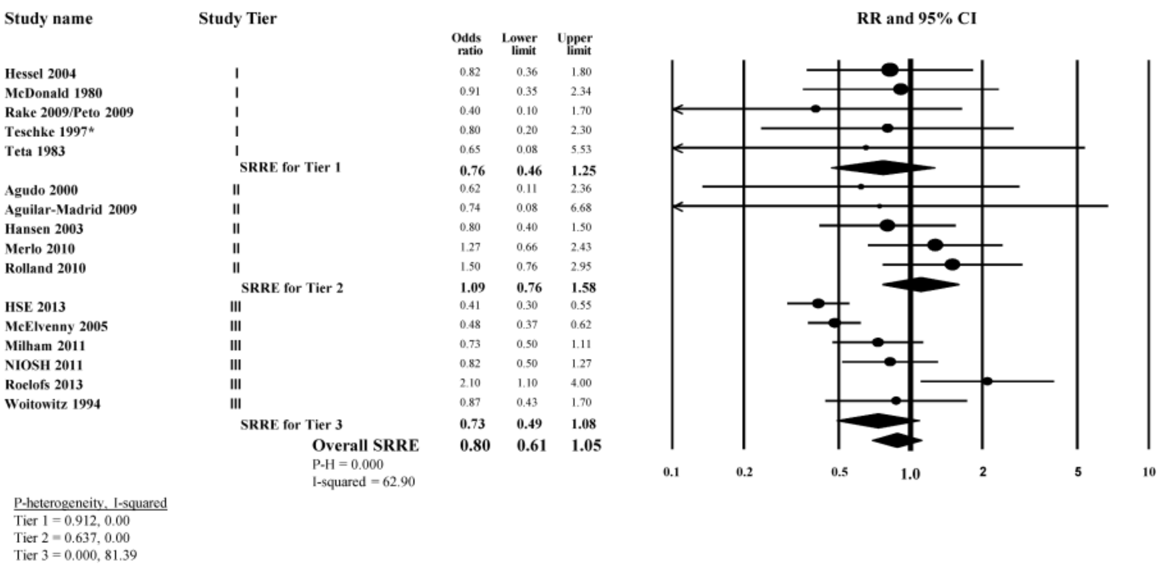

Figure 2 Meta-analysis of mesothelioma risk among motor vehicle mechanics by study tier.

fill method (Duval and Tweedie, 2000) imputes data to account for variable results between studies. Eight data points were imputed using this method, resulting in a change of the overall model SRRE from 0.80 (95% CI: 0.61–1.05) to 0.52 (95% CI: 0.39–0.69), further reinforcing the evidence of lack of an increased risk of mesothelioma among motor vehicle mechanics (Supplementary Fig. S1).

DISCUSSION

Our results indicate that mesothelioma risk is not associated with either motor vehicle repair or with brake repair work. The SRREs of mesothelioma showed no trend either upward or downward according to study quality. There have been a number of studies published since 2004, when we last reviewed this topic, including four studies in Tiers 1 and 2 (Rake *et al.*, 2009; Aguilar-Madrid *et al.*, 2010; Merlo *et al.*, 2010; Rolland *et al.*, 2010), a new study in Tier 3 (Roelofs *et al.*, 2013), and updates to PMR studies (Milham, 2011; Health and Safety Executive, 2013). The addition of this substantial body of scientific evidence did not change the previously reported conclusion (Goodman *et al.*, 2004) of no association between mesothelioma and either motor vehicle repair or brake repair work. The single study that showed a significantly increased risk

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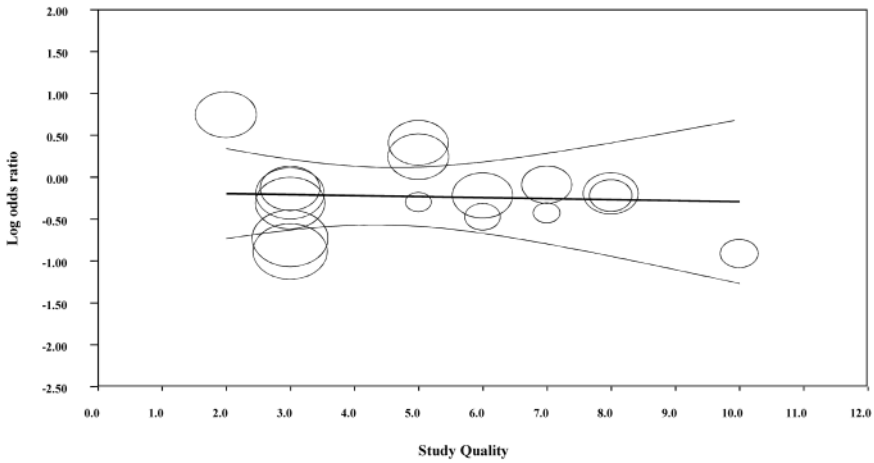

Figure 3 Regression of log odds ratio on study quality. The circle size represents the weight in the regression analysis.

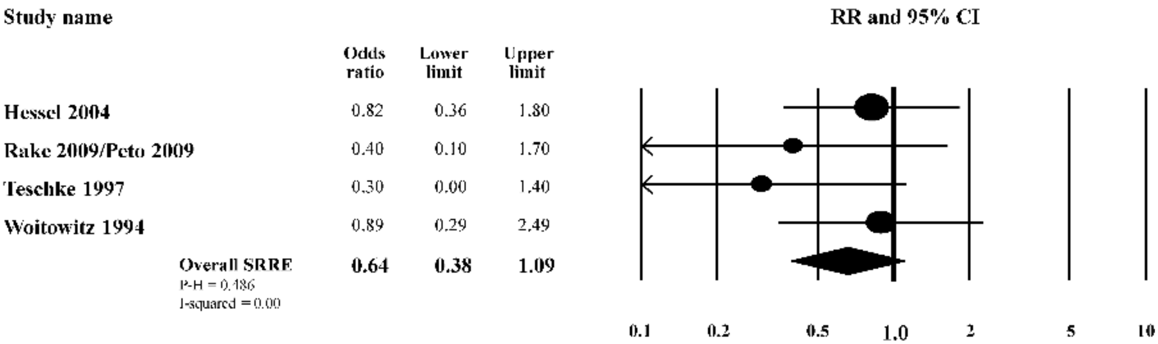

Figure 4 Meta-analysis of mesothelioma risk among workers involved with brake repair.

of mesothelioma (Roelofs *et al.*, 2013) had several methodological deficiencies and received the lowest quality score. Moreover, analyses of heterogeneity indicated that this study was appreciably different than the entire body of literature on this topic.

It should be emphasized that this body of research was conducted using different study designs, in different populations in Europe and North America, by different teams of researchers, and over a period spanning three decades. These different circumstances yielded consistent results with no appreciable heterogeneity. Although it can be argued that not all motor vehicle mechanics are engaged in brake repairs, clearly many are. While in theory exposure misclassification at the occupational title level could miss an association if the exposure was low level or of low frequency, we sought to minimize this possibility by focusing on studies that reported brake, clutch, and gasket repairs specifically and on studies that examined duration of exposure. Moreover, the studies that examined brake repairs specifically (Woitowitz and Rodelsperger, 1994; Teschke *et al.*, 1997; Hessel *et al.*, 2004; Rake *et al.*, 2009) provided results that were not appreciably different than the results for motor vehicle mechanics across all studies. Thus, the lack of association seen in the studies specific to exposure to brakes was not meaningfully different than studies that were less specific. This was not unexpected as brake repair is a very common activity among vehicle mechanics. Similarly, vehicle mechanics were commonly exposed to asbestos from clutch and gasket repairs. The lack of mesothelioma risk across studies indicates that vehicle mechanics' work with asbestos-containing clutches and gaskets does not increase the risk for mesothelioma. It is unlikely that the healthy worker effect biased the results. A number of the studies compared

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Table 4. Summary of mesothelioma studies and corresponding RR estimates not included in the meta-analysis.

First author	Year	Design	RR estimate	95% CI	Reason for exclusion
Malker[a]	1985	Cohort	2.4 ($P < 0.01$)	NA	Exposure defined as 'mechanics'
Jarvholm	1988	Cohort	NA (1 case)	NA	Unable to calculate relative risk
Schiffman	1988	Case-control	0 (no cases, 2 controls)	NA	Exposure defined as 'mechanics'
Hansen	1989	Cohort	NA (1 case)	NA	Unable to calculate relative risk
Gustavsson	1990	Cohort	NA (2 cases)	NA	Unable to calculate relative risk
Pan[b]	2005	Case-control	1.02	0.66 – 1.57	Exposure defined as 'mechanics, not specified'
Welch	2005	Case-control	1.50	0.43 – 5.26	Exposure defined as 'Tire or brake lining work'

CI, confidence interval; NA, not available; RR, estimate of relative risk.
[a]Of the 16 mechanics with mesothelioma in this study, only one was likely to be an auto mechanic (W. Blot, personal communication, 2003).
[b]Mechanics were not restricted to motor vehicle mechanics (D. Garabrant, personal communication, 2014).

vehicle mechanics to other working populations or were case-control studies. Moreover, mesothelioma has a very long latency and is often diagnosed after the exposed workers have retired—it is difficult to imagine a healthy worker effect exists 40+ years after starting work and into retirement.

Although some of the individual studies had limited power to detect a statistically significant association, the meta-analysis had greatly increased study power as reflected in the narrow CIs. Furthermore, the SRREs indicated associations near and slightly below 1.0. Thus, power to detect a statistically significant positive association in individual studies was irrelevant.

In general, the relevant exposure periods of the study populations coincided with the timeframe in which chrysotile asbestos was used in brakes. In addition, the studies had adequate elapsed time from first exposure to case identification to detect mesothelioma if this outcome had been causally related to brake exposures. This is of particular importance because of the long latency period of mesothelioma. For example, in Woitowitz (Woitowitz and Rodelsperger, 1994), the median first date of exposure was 1949 for both cases and controls, and case ascertainment occurred between 1988 and 1994. In the study by Teschke *et al.* (1997), where latency was considered, all of the vehicle mechanics and brake workers began their exposures prior to the minimum latency period (i.e. 20 years).

Both study design and statistical heterogeneity are important considerations in a rigorous meta-analytic approach. Indeed, we made an effort to conduct an objective and transparent study quality scoring exercise based on recommendations by the MOOSE (Stroup *et al.*, 2000) and PRISMA (Moher *et al.*, 2009) guidelines. This facilitated several additional meta-analyses based on parameters such as study design, potential bias, the influence of confounding, and the specificity of exposure designations. SRREs by study design, study quality, study region, and ascertainment of lifetime asbestos exposure were calculated. However, virtually all analyses produced the same results—no association between mesothelioma risk and either motor vehicle repair or brake repair. Some study designs are inherently weaker than others, such as PMR studies, which are not designed to include lifetime occupational histories, task-specific

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information, duration of employment, latency, or covariates for other sources of exposure. These types of studies received zero scores on all of these criteria, as they should. In the PMR studies, the results for motor vehicle mechanics are below 1.0 but sometimes are above other occupations. This likely reflects the fact that mechanics may be more likely than workers in other occupations (e.g. farmers, teachers, clerical workers) to have worked in other asbestos-exposed jobs. For this reason, we believe the analyses that controlled for other sources of asbestos exposure (Hessel *et al.*, 2004; Rake *et al.*, 2009) provide a more reliable estimate of RR and warrant great analytical weight.

There were seven potentially relevant studies that could not be included in the meta-analysis (Table 4). Three were excluded because no measures of association were provided or could be calculated. Jarvholm and Brisman (1988) reported a single case of mesothelioma in a cohort of 21 905 Swedish car mechanics born between 1890 and 1945, and followed through 1979. Hansen (1989) reported a single case of mesothelioma in a cohort of 21 800 Danish auto mechanics and followed from 1970 to 1980, accumulating 192 000 person years. Gustavsson *et al.* (1990) reported two cases of mesothelioma among 695 Stockholm bus garage workers followed from 1958 to 1994. Three other studies (Malker *et al.*, 1985; Schiffman *et al.*, 1988; Pan *et al.*, 2005) reported mesothelioma risks for 'mechanics', but could not be included in the meta-analysis because occupations were not restricted to motor vehicle mechanics (W. Blot and H. Malker, 2003, personal communication; D. Garabrant and M. Shenker, 2013, personal communication). The seventh study (Welch *et al.*, 2005), which compared cases of peritoneal mesothelioma to cases of appendiceal cancer, was excluded because it grouped brake installation and repair with tire installation and repair and did not report brake repair activities or work as a motor vehicle mechanic. These studies did not provide evidence of mesothelioma risks among motor vehicle mechanics.

The observed lack of association between work as a motor vehicle mechanic or brake mechanic and mesothelioma may result from several factors. First, the asbestos fibers found in dust and airborne samples of vehicle mechanics workplaces or simulated workplaces are generally short (<5 μm) chrysotile fibers (Hatch, 1970; Anderson *et al.*, 1973; Rohl *et al.*, 1976; Roberts and Zumwalde, 1982; Williams and Muhlbaier, 1982; Cha *et al.*, 1983; Rodelsperger *et al.*, 1986; Rodelsperger, 1987; NIOSH *et al.*, 1989). There appears to be increasing consensus that short fibers, particularly those <5 μm in length, are associated with little (if any) pathologic response, including risk of lung cancer and mesothelioma (Platek *et al.*, 1985; Eastern Research Group, 2003; Berman, 2011; Bernstein *et al.*, 2013). In an analysis of dust obtained from sanding brake drums manufactured with chrysotile, no significant pathological response was shown following short-term inhalation in rats (Bernstein *et al.*, 2014). Secondly, asbestos fibers in brake pads are embedded in resin (Weir and Meraz, 2001) and therefore are less likely to become airborne. Thirdly, much of the chrysotile in brake pads is transformed to forsterite during the braking process (Anderson *et al.*, 1973). Forsterite does not appear to have asbestos fiber properties and is not considered carcinogenic in humans (Wong, 1992). More importantly, Langer demonstrated that chrysotile's biological activity becomes virtually nil hundreds of degrees below the forsterite transformation temperature. Thus, complete transformation of the mineral is not required to result in loss of activity (Langer, 2003). A large body of IH literature indicates the mean time weighted average asbestos exposure during brake servicing was ~0.04 fibers per cubic centimeter during the post-1974 time period (Weil and Delpire, 1985).

Two studies addressed the risk of mesothelioma among bystanders (i.e. persons presumed to be indirectly exposed to asbestos) and do-it-yourself mechanics (Hessel *et al.*, 2004; Rake *et al.*, 2009). Both studies reported no association in these circumstances. If workers whose occupation involving low-level chrysotile exposure are not associated with an increased risk of mesothelioma, it follows that co-habitants of these workers also would not have an increased risk of mesothelioma (Goswami *et al.*, 2013). Take-home exposure from friction products has been estimated to be lower than the exposures of automobile mechanics (0.0001 f/cc versus 0.04 f/cc) (Goswami *et al.*, 2013).

An association between an exposure and a disease should clearly exist before a determination of causation is made (Hill, 1965). Even in the absence of an association between employment as a motor vehicle mechanic and mesothelioma, our meta-analysis allowed evaluating some key considerations of a causal relationship such as strength of association and consistency of

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findings. All of the studies with the exception of Roelofs *et al.,* 2013 provided homogeneous effect estimates showing no association. The SRREs do not support an increased risk of mesothelioma. Two studies evaluated the duration of work and neither found a positive association in the group with the longest duration of work (Hessel *et al.*, 2004; Peto *et al.*, 2009). Further, a positive dose-response pattern would be unlikely given the fact that few studies (and of lower quality) reported risks above 1.0. Finally, study-specific risk estimates were consistent across studies. We sought to find an effect by analyzing the data in a number of alternative ways to ensure that the results were not overly influenced by any single study or group of studies. Therefore, based on this comprehensive quantitative assessment of the totality of epidemiologic literature, neither work as a motor vehicle mechanic nor work in brake repair is associated with an increased risk of mesothelioma. This conclusion is clearly supported by the data reported in a large group of studies spanning decades of research across multiple study populations using a variety of study design and exposure assessment methods.

SUPPLEMENTARY DATA

Supplementary data can be found at http://annhyg.oxfordjournals.org/.

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