

Original article

A meta-analysis on wood dust exposure and risk of asthma

Work-related asthma is the most common occupational respiratory disorder in the industrialized countries. It has been postulated that wood dust exposure may increase the risk of work-related asthma. The objective of this study was to assess, through a meta-analysis, the risk of developing work-related asthma associated with wood dust exposure. A systematic search of the literature was performed. Inclusion and exclusion criteria were applied and a quality scale used to measure the quality of the included studies was developed. Using standard meta-analysis techniques, studies were pooled using both random and fixed effects models. Nineteen studies were included which consisted of three cohort studies, twelve case-control studies and four mortality studies. The pooled relative risk (RR) of asthma among workers exposed to wood dust was 1.53 (95% CI 1.25–1.87). When the analysis was restricted to studies carried out on Caucasian populations, the pooled RR was 1.59 (95% CI 1.26–2.00) while the pooled RR of studies on Asian populations was 1.15 (95% CI 0.92–1.44). Wood workers present a higher risk of asthma. Future research should include careful evaluation of ethnicity and nativity as risk modifiers.

M. Pérez-Ríos^{1,2,3}, A. Ruano-Ravina^{1,2,4}, M. Etminan⁵, B. Takkouche^{1,2}

¹Department of Preventive Medicine, University of Santiago de Compostela, 15782 Santiago de Compostela; ²CIBER de Epidemiología y Salud Pública, CIBERESP; ³Epidemiology Section, Department of Public Health, Galician Regional Authority; ⁴Galician Agency for Health Technology Assessment, Galician Department of Health, Spain; ⁵Center for Clinical Epidemiology and Evaluation and Department of Medicine, University of British Columbia, Vancouver, BC, Canada

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Mónica Pérez-Ríos
Department of Preventive Medicine
University of Santiago de Compostela
15782 Santiago de Compostela
Spain

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Asthma is a chronic inflammatory condition that represents an important health problem in the developed world. It is the most common occupational respiratory disorder in the industrialized countries. Approximately, 250 specific substances at work are associated with the disease and about one-fifth of asthma cases is related to occupation (1). Recent data in the US show that the estimated number of workers potentially exposed to occupational triggers of asthma ranges from 8 to 20 million, which represent about 24% of the workforce, while the prevalence of the disease in the employed population is 6.5% (2).

Wood workers include different occupations such as carpenters, small boat constructors or sawmill workers, all of which are exposed to a certain amount of wood dust. They represent an important occupational group with more than one million people employed in Europe (3) and 370 000 in the US, a figure that will grow 3% through 2016 (4). An increased risk of asthma among wood workers would then cause an important public health concern given the large number of people employed in this sector.

The biological mechanism responsible for the effect of wood dust is not fully elucidated (5). Some studies have shown that abietic acid contained in the resin of some

trees may induce lytic damage to the bronchial epithelial cells (6). Further, terpenes contained in pine and other coniferous trees may cause increase bronchial responsiveness (7). IgE mediated sensitization is another plausible mechanism (8).

To date, results of epidemiologic studies have been inconsistent. Although several studies found an increase in the risk of asthma among wood workers, other studies failed to find any association (5, 9).

So far, no comprehensive meta-analysis is available. We, therefore, summarized the scientific evidence and carried out a meta-analysis on occupational exposure to wood dust and risk of asthma, following the MOOSE guidelines for meta-analyses of observational studies (10). Our study is limited to asthma occurring in an occupational setting.

Methods

Data sources and searches

We conducted a computerized Medline search from 1966 to August 2008 to identify potentially eligible studies. We applied the following algorithm both in Medical Subject Heading and in free text

words: (ASTHMA) AND (WOOD*) AND (CASE-CONTROL OR CASE-REFERENT OR RETROSPECTIVE OR COHORT OR FOLLOW-UP OR PROSPECTIVE). In order to check whether every article on the topic was retrieved, we performed a second search, introducing the words 'asthma' and 'wood' in an unstructured fashion. We used similar strategies to search Embase (1980–2008) and LILACS databases (Latin America and Caribbean). We searched meeting abstracts using the ISI Proceedings database from its inception in 1990–2008. We also examined the references of every article retrieved. We considered including any relevant article, independently of the language of the publication. Unpublished studies were not considered. All searches were carried out independently by two epidemiologists (MPR and BT) and results were merged.

Inclusion and exclusion criteria

We included studies that presented original data from case-control, cohort or standardized or proportional morbidity or mortality studies (SMR or PMR). Studies were included if they: (1) had clear diagnostic criteria for asthma (either clinically diagnosed or self-reported through interview. Asthma-like disorders were not considered as asthma); (2) had explicitly described occupational exposure to wood; and (3) provided odds ratios (ORs) or relative risks (RRs) and 95% confidence intervals (CIs) or provided enough data to allow us to calculate these figures. If data were duplicated in more than one study, only the most recent or detailed publication was included. We made no restrictions on sample size or language. We also included studies that analyzed data on woodworkers as a sub-group analysis. When a study provided data from multiple countries, we used the average risk of all countries.

We excluded cross-sectional studies as such studies cannot provide useful information on a temporal relationship between the exposure and outcome. Mortality studies analyzing asthma as a cause of death without specifying its International Code of Disease (ICD) were excluded. Because they are beyond the scope of this meta-analysis, we excluded studies that used asthma-like symptoms or other manifestations of respiratory impairment as an outcome, such as wheezing and acute decline of lung function, and did not establish a diagnosis of asthma. For the same reason, we did not consider those studies that dealt with sensitization, when it was used by authors either as a proxy for exposure or as an outcome.

Data extraction and quality assessment

Data were abstracted by two independent reviewers using a standardized data sheet and differences were reconciled by consensus.

We assessed study quality based on a five-point scale which included elements of the Newcastle–Ottawa scale for observational studies, adapted to the needs of the present meta-analysis (11). Each study was scored according to the following five characteristics of methods and presentation of results applicable to all designs, labeled as 'yes' or 'no': (1) whether the target population was clearly defined (yes) or on the contrary, based on convenience sampling of subjects (no), (2) whether asthma diagnosis included clinical features and flow rate and/or reversal after treatment (yes) or was based on clinical examination only (no), (3) whether work exposure was thoroughly assessed through job matrix (yes) or only through questionnaire (no), (4) whether first asthma symptoms occurred clearly or not after the start of the occupation, and (5) whether or not results were adjusted by age, sex, and smoking.

The complete protocol for quality scoring is available upon request. For stratification purposes, studies that scored 2.5 or higher out of 5 were considered of high quality and the rest of low quality. Quality scoring was performed independently by two reviewers (BT and MP-R) and the average score between reviewers was assigned to the studies. Agreement was measured by a weighted Kappa coefficient, the value of which was 0.56 (P -value = 0.0001).

Data synthesis and analysis

We weighted the study specific adjusted log odds ratios for case-control studies and log relative risks for cohort studies by the inverse of their variance to compute a pooled relative risk and its 95% confidence interval. Odds Ratios were considered estimates of relative risks. We assumed that the person-time of the unexposed group is much larger than that of the exposed group and thus considered standardized mortality or morbidity ratios (SMRs) as equivalent to incidence rate ratios (12). We assessed incidence studies (case-control and cohort studies) and SMR studies separately in a first instance. We then pooled them together in a subsequent analysis. We presented both fixed and random effects pooled estimates but used preferentially the latter when heterogeneity was present. The fixed effects model assumes that there is no between-study variance, i.e. that the results of the studies used in the meta-analysis are homogeneous and that their variation is due to sampling only. The random effects model, on the contrary, assumes that study results are heterogeneous. The random effects model yields pooled results that are less precise in nature (have wider confidence intervals) but are closer to the true value in case heterogeneity exists.

We used a parametric bootstrap version (1000 replications) of the DerSimonian and Laird Q test to check for heterogeneity (13). The null hypothesis of the test is absence of heterogeneity. To quantify this heterogeneity, we calculated the proportion of the total variance due to between-study variance (R_i statistic) (13). To further explore the origin of heterogeneity, we restricted the analysis to subgroups of studies defined by study characteristics such as case-control/cohort design, adjustment factors, type of controls (hospital-based or population-based) and ethnicity.

We used funnel plots to assess publication bias visually. Because funnel plots have several limitations and represent only an informal way to detect publication bias (14), we carried out more formal testing using the test proposed by Egger et al. (15). All analyses were performed with the software HEPIMA, version 2.1.3 (16) and STATA version 8.0 (Stata Corp., College Station, TX, USA).

Results

Our search retrieved 281 articles. We finally included 19 studies that met our criteria. They were carried out in six countries and published between 1991 and 2008. We included 12 case-control studies, 3 cohort studies and 4 mortality studies (Table 1). As recommended by methodologic experts, proportional or standardized mortality studies were considered as a variant of the case-control design (17).

Table 2 shows that, globally, the risk of asthma was higher among woodworkers than among the general population (random effects pooled RR: 1.53, 95% CI: 1.25–1.87). Although heterogeneity was high when all studies were pooled together, the random effects

estimate and the fixed effects estimate were close to each other and showed a significant and substantial increase in the risk. Cohort studies showed a pooled relative risk that was lower than that of case control studies (RR = 1.34, 95% CI: 1.01–1.78 for cohort studies and RR = 1.74, 95% CI: 1.19–2.56 for case-control studies). Except for population-based case-control studies, heterogeneity did not subside when we stratified our analysis by study design. The three hospital-based case-control studies show an important increase in the risk that was statistically significant in spite of the reduced number of studies. Incidence studies (cohort and case-control studies) showed a higher risk increase than mortality studies. Stratification by gender shows that the risk is higher among female workers than among males.

When we restricted the analysis to those studies that adjusted for smoking status, we observed that heterogeneity subsided and that the risk increase mitigated although it remained statistically significant (pooled RR: 1.19 95% CI: 1.02–1.39).

Interestingly, stratification by ethnic origin shows that Caucasians present a higher risk than other ethnic groups (random effects pooled RR: 1.59, 95% CI: 1.26–2.00).

Stratification by quality score shows that good quality studies do not harbor any heterogeneity and that their pooled relative risk is slightly smaller than that of lower quality studies.

The two studies by Mastrangelo et al. (18) recruited their population among patients suspected of work-related asthma. This may have introduced some bias in the risk estimation. We, therefore, carried out an additional analysis in which we excluded these two studies. The random effects pooled RR after exclusion was 1.36, 95% CI: 1.16–1.59.

The studies by Flodin et al. (19, 20) included subjects exposed to unspecific dust, including wood dust. To measure the influence on the global pooled estimate exerted by these studies, we repeated the analysis excluding them. The random effects pooled RR after exclusion was 1.50, 95% CI: 1.20–1.87.

The funnel plot (Fig. 1) seems to be slightly skewed to the right. However, we could not find any further evidence of publication bias through Egger's regression test ($P = 0.63$). To further evaluate the possibility of publication bias in case-control studies, a design that is more probably disregarded by authors and editors in case of null or statistically nonsignificant results, we recalculated our pooled estimates under the following extreme assumptions: (1) published case-control studies are only half of the studies of occupational wood dust exposure and asthma ever conducted, (2) all unpublished studies found an RR of 1, (3) the unpublished studies included as many cases and controls as the average of the published studies. Under these assumptions, the pooled estimates still show a

significant increase in the risk: RR = 1.19 (95% CI: 1.07–1.34).

Discussion

The results of this meta-analysis and their consistency across designs and settings provide evidence that exposure to wood dust may increase the risk of work-related asthma. The magnitude of the risk increase is substantial (approximately 50%) when all studies are analyzed together and does not subside after stratification by design for cohort and case-control studies.

This risk increase relies on strong biologic grounds. Several studies have long provided evidence of a relationship between exposure to wood dust and asthma (21, 22). Some agents, such as terpenes, abietic acid and plicatic acid, contained in different types of wood are potentially implicated in the occurrence of asthma by inducing increased bronchial responsiveness or by damaging the bronchial epithelial cells (6, 7, 23).

The substantially higher risk of asthma among European and American studies than among Asian studies deserves further consideration. The fact that ethnicity and nativity may be strong predictors of the risk of asthma was recently reported for subjects of Hispanic origin in Chicago (24). This suggests the existence of interactions between genetic susceptibility to asthma and environmental factors.

Nevertheless, alternative explanations for the risk increase deserve careful examination. Publication bias may have distorted the results as studies that had not found any risk increase of asthma in this occupational group may have failed to be published. However, this distortion is unlikely to explain the magnitude of the risk increase as, first, no evidence of publication bias was detected through statistical testing, and second, our sensitivity analysis showed that, even under extreme assumptions of publication bias, the results of this meta-analysis are robust.

Confounding by tobacco consumption is a noncausal explanation that might be argued to explain our results. However, our analysis shows that, although the pooled relative risk is lower among studies that did not adjust for smoking or failed to provide information, it remained significantly elevated in the more homogeneous group of studies that did adjust for smoking. Furthermore, to act as a confounder, smoking has to be more prevalent among woodworkers. Danish data have shown recently that woodworkers are more likely to be nonsmokers than employees of other industries and that the prevalence of heavy smoking is lower both among male and female woodworkers (25). Nevertheless, residual confounding (confounding from unknown variables that is not eliminated by adjustment) may have distorted the results as in any meta-analysis of observational studies.

Table 1. Baseline characteristics and summary risk of studies included in the meta-analysis

First author, year	Country	Population	Year of the study	RR (CI 95%)	Type of controls*	Adjustment, matching and restriction factors	Case/Controls or exposed cases
Case-control studies							
Ng et al. 1994 (29)	Singapore	Adult patients	Not given	1.79 (0.93–3.45)	H	Age, sex, race, smoking, atopy	787/1591
Flodin et al. 1996 (19)	Sweden	Patients receiving beta-agonists	1990	2.5 (1.3–4.8)	P	Age, sex, municipality	79/304
Mastrangelo et al. 1997 (18)	Italy	Patients with occupational disease	1989–1993	6.8 (2.3–19.6)	H	Age, sex, calendar year of diagnosis	387/387
Mastrangelo et al. 1997 (18)	Italy	Patients with occupational disease	1974–1978	8.3 (2.7–19.1)	H	Age, sex, calendar year of diagnosis	325/325
Lipscomb et al. 1998 (30)	USA	Carpenters	1989–1992	1.5 (0.65–2.6)	P	Age, sex, time in the union, smoking	109/225
Toren et al. 1999 (9)	Sweden	General population	1996	0.6 (0.2–1.4)	P	Age, sex, smoking	321/1459
Toren et al. 1999 (31)	Sweden	General population	1996	0.9 (0.5–1.8)	P	Age, sex and year of diagnosis	251/2044
Vermeulen et al. 2002 (32)	Netherlands	General population of an industrial city	1987–1993	1.01 (0.28–3.67)	P	Age, sex, smoking, socio-economic status	274/274
Jaakkola et al. 2003 (33)	Finland	General population	1997–2000	1.72 (0.71–4.17)	P	Age, sex, smoking	521/932
Flodin et al. 2004 (20)	Sweden	General population of an industrial city	1996–1997	1.5 (0.96–2.2)†	P	Age, sex	43/156
Schlünssen et al. 2004 (5)	Denmark	Employees of the furniture industry	1997–1998	0.82 (0.25–2.71)	P	Age, sex, smoking, previous jobs, sideline occupation, education, lung diseases	222/129
Krstev et al. 2007 (34)	China	Women of Shanghai aged 40–70	1997–2000	1.83 (0.65–5.21)	P	Age, sex, smoking, education, family income, bronchitis	1050/4200
Cohort studies							
Heikkilä et al. 2001 (28)	Finland	All employed Finns	1985–1998	1.50 (1.35–1.66)	–	Age, sex	1475
LeVan et al. 2006 (35)	Singapore	General population of Singapore (Chinese ethnicity)	1999–2004	1.09 (0.85–1.38)	–	Age, sex, dialect, smoking	75
Kogevinas et al. 2007(1)	Europe	General European population aged 20–44	1990/1995 1998/2003	2.22 (0.69–7.17)	–	Age, sex, smoking, center	3
Mortality studies							
Toren et al. 1991 (36)	Sweden	Swedish men aged 20–64	1971–1980	1.19 (0.79–1.78)	–	Age, sex, smoking	31
Schenker et al. 1993 (37)	USA	General population of California	1960–1989	3.6 (1.6–6.9)	–	Age, sex, race	9
Robinson et al. 1996 (38)	USA	White males employed as carpenters	1987–1990	0.99 (0.68–1.4)	–	Age, sex, race	32
Toren et al. 1997 (39)	Sweden	Swedish men aged 20–64	1981–1992	1.19 (0.67–1.72)	–	Age, sex, smoking	20

*H = hospital controls; P = population controls.

†Exposure to dust from paper, textile, wood and flour.

Table 2. Pooled relative risks (RR) and 95% confidence intervals (CI) of asthma among woodworkers*

	Number of studies	RR (95% CI) fixed effects	RR (95% CI) random effects	Ri†	Q test P-value
All studies	19	1.43 (1.33–1.55)	1.53 (1.25–1.87)	0.76	0.0001
Cohort studies	3	1.43 (1.30–1.57)	1.34 (1.01–1.78)	0.85	0.04
Case-control studies (all)	12	1.67 (1.36–2.04)	1.74 (1.19–2.56)	0.69	0.0003
Population based	9	1.40 (1.13–1.75)	1.37 (1.05–1.80)	0.27	0.24
Hospital based	3	4.53 (2.68–7.67)	4.56 (1.66–12.51)	0.73	0.027
PMR studies	4	1.24 (1.02–1.52)	1.39 (0.91–2.13)	0.76	0.007
Case-control + PMR studies	16	1.44 (1.25–1.66)	1.63 (1.22–2.17)	0.71	0.0001
Incidence studies‡	15	1.47 (1.35–1.60)	1.61 (1.26–2.05)	0.79	0.0001
Male only	6	1.32 (1.16–1.52)	1.30 (1.12–1.51)	0.09	0.36
Female only	3	1.51 (1.33–1.71)	1.51 (1.33–1.71)	0.00	0.89
Smoking adjusted	11	1.19 (1.02–1.39)	1.19 (1.02–1.39)	0.02	0.64
Smoking non adjusted	8	1.53 (1.40–1.67)	2.05 (1.41–2.98)	0.92	0.0001
Caucasians	16	1.48 (1.36–1.61)	1.59 (1.26–2.00)	0.81	0.0001
Asians	3	1.15 (0.92–1.44)	1.15 (0.92–1.44)	0.00	0.45
Quality score <2.5	13	1.44 (1.32–1.56)	1.63 (1.24–2.15)	0.86	0.0001
Quality score ≥2.5	6	1.41 (1.13–1.76)	1.41 (1.13–1.76)	0.00	0.80

*RR, relative risk; CI, confidence interval; PMR, proportional mortality ratio.

†Proportion of total variance due to between-study variance.

‡Incidence studies: Cohort studies + case-control studies (PMR studies are excluded).

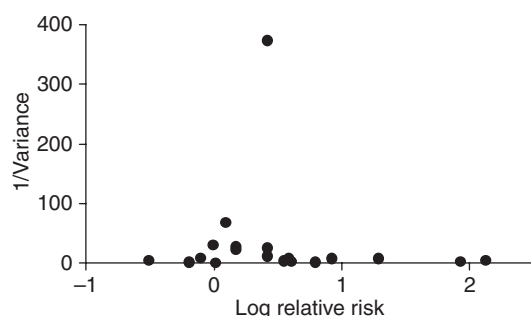


Figure 1. Funnel plot of the studies of occupational exposure to wood and asthma.

A potential limitation of this meta-analysis, is the fact that misclassification of the outcome may exist in instances in which true asthma diagnosis overlaps with that of asthma-like disorders. Asthma-like disorders present the same clinical features as asthma but without persistent hyperresponsiveness and eosinophilia (26). However, these disorders are observed mainly in occupational exposure to grain or textile dusts such as cotton, jute and flax, and wood exposure has not been included among frequent triggers of asthma-like manifestations (27). If ever misclassification of the outcome exists in the studies included in this meta-analysis, it is more likely to be nondifferential (occurs independently of exposure status). This would then bias the results towards the null, which implies that the association between occupational exposure to wood and asthma is even stronger than the one we observed.

Similarly, recall bias may also have played a role in case-control studies as exposure to biological dusts may

have been reported more frequently through self-reporting than through job-exposure matrix (1). In our meta-analysis, case-control and cohorts pooled estimates were close to each other, which indicates that recall bias was unlikely to distort the results in a meaningful fashion.

Our meta-analysis is also limited by the fact that we could not assess the existence of a dose-response gradient as data on duration of employment or exposure intensity were available in two studies only (5, 28). In the first one, limited data were available on dust concentration, and in the second one data were available on duration of exposed employment. From these studies, it is difficult to appreciate a dose-response gradient.

Finally, as in every meta-analysis of observational studies, the quality of the individual studies may largely influence the results of the review. In this work, we observed that high quality studies yielded a slightly smaller risk estimate than low quality studies. Further, as no universally validated quality scale exists, ours was based on items the selection of which was based on common sense only. It is then possible that a different scale could possibly yield other results.

In summary, the relatively large number of studies included, the magnitude of the associations found, the consistency of the results through settings and the existence of mechanisms that give strong biological plausibility to the relation provide evidence that occupational exposure to wood dust may increase the risk of asthma. Future research should include careful evaluation of ethnicity and nativity as risk modifiers and assess duration and intensity of exposure to wood dust.

Contributors

ME, BT and MP-R initiated the project. MP-R and ME screened and extracted the data. BT analyzed the data. All authors participated in discussing the results and writing the paper.

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