Review

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Occupational chronic obstructive pulmonary disease: a systematic literature review

by Omland Ø, Würtz ET, Aasen TB, Blanc P, Brisman J, Miller MR, Pedersen OF, Schlünssen V, Sigsgaard T, Ulrik CS, Viskum S

This review on occupational chronic obstructive pulmonary disease (COPD) addresses some of the potential limitations of earlier assessments by restricting the studies included to high quality epidemiological analysis involving only spirometrically confirmed air-flow obstruction as the outcome. The authors combined this with minimal requirements for exposure characterization allowing for analysis of population-based studies.

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Key terms: airflow obstruction; chronic obstructive pulmonary disease; COPD; dust; fume; gas; lung function measurement; occupational chronic obstructive pulmonary disease; occupational exposure; review; systematic review; vapor

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Occupational chronic obstructive pulmonary disease: a systematic literature review

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Objective Occupational-attributable chronic obstructive pulmonary disease (COPD) presents a substantial health challenge. Focusing on spirometric criteria for airflow obstruction, this review of occupational COPD includes both population-wide and industry-specific exposures.

Methods We used PubMed and Embase to identify relevant original epidemiological peer-reviewed articles, supplemented with citations identified from references in key review articles. This yielded 4528 citations. Articles were excluded for lack of lung function measurement, insufficient occupational exposure classification, lack of either external or internal referents, non-accounting of age or smoking effect, or major analytic inadequacies preventing interpretation of findings. A structured data extraction sheet was used for the remaining 147 articles. Final inclusion was based on a positive qualitative Scottish Intercollegiate Guidelines Network (SIGN) score (≥2+) for study quality, yielding 25 population-wide and 34 industry/occupation-specific studies, 15 on inorganic and 19 on organic dust exposure, respectively.

Results There was a consistent and predominantly significant association between occupational exposures and COPD in 22 of 25 population-based studies, 12 of 15 studies with an inorganic/mineral dust exposure, and 17 of 19 studies on organic exposure, even though the studies varied in design, populations, and the use of measures of exposure and outcome. A nearly uniform pattern of a dose–response relationship between various exposures and COPD was found, adding to the evidence that occupational exposures from vapors, gas, dust, and fumes are risk factors for COPD.

Conclusion There is strong and consistent evidence to support a causal association between multiple categories of occupational exposure and COPD, both within and across industry groups.

Key terms: airflow obstruction; COPD; dust; fume; gas; lung function measurement; occupational exposure; vapor.

Chronic obstructive pulmonary disease (COPD) represents serious morbidity and has emerged as a leading cause of death worldwide (1). Although tobacco smoking is the leading factor in the etiology of COPD, the disease may be caused by inhalation of different gases and aerosols among both smokers and non-smokers (2). Various occupational exposures have been associated with COPD often in combination with tobacco smoking. As much as 15% of prevalent cases have been attributed to occupational exposures (3).

Chronic airflow obstruction (or limitation) is the main defining characteristic of COPD. However, the terminology and diagnostic criteria of respiratory disease characterized by chronic obstruction has varied

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widely during recent decades (4). The Global Initiative on Obstructive Lung Disease (GOLD) has proposed that the criterion forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio <70% as an indication of the presence of COPD (5). The staging of the severity of COPD in GOLD is based on the reduction in FEV_1 (as percent predicted) but has obvious limitations in clinical prediction (6). Moreover, variation in diagnostic criteria makes comparison of studies from different time periods and countries problematic. Refinement of the FEV_1/FVC criterion by using the lower limit of normal (LLN) rather than a fixed ratio may increase the diagnostic specificity, but there is currently no "gold standard" for the diagnosis of COPD. Thus, the disease remains a heterogeneous condition encompassing different structural lesions.

The inhalation of gases and particulates may initiate local inflammatory processes in the airways and lungs, which lead to conditions such as chronic bronchitis, small airways disease, and emphysema. Long-term consequences are pulmonary hypertension and systemic inflammation (7). The induction time from exposure to the detection of early COPD is often long (decades). Identification and measurements of relevant exposures over a prolonged period of time are generally not performed and thus are unavailable for research with few exceptions (8).

The recognition and acceptance of occupational exposure as a cause of COPD has been impeded by variable terminology and case definitions of COPD, lack of reliable exposure data, and insufficient analytic inclusion of important confounders in particular tobacco. As early as 1985, however, Margaret Becklake concluded that occupational exposure to dust and/or dust and fumes may have a causal link to the pathogenesis of COPD, often relying on studies in which work-related factors were included as confounders to be adjusted for in an analysis of smoking effects (9, 10). Coggon and Newman Taylor (11) made an extensive analysis of the literature on airflow obstruction among coal miners, concluding there was a significant association between exposure to coal dust and the development of chronic airflow obstruction. Additional systematic reviews also concluded there is indeed a causal association between occupational exposure and COPD (12–16). By 2003, the American Thoracic Society (ATS) published a systematic review of the evidence accumulated to date and relevant to the role of occupational factors in the pathogenesis of obstructive airway diseases (asthma and COPD). This quantified the contribution of work-related risk to the burden of these diseases in the general population and concluded that approximately 15% of COPD could be attributable to workplace exposure (3). This has been amplified by a recently published review focusing on COPD among non-smokers estimating that 25–45% of persons with COPD are non-smokers (17). Furthermore, that review concluded that occupational exposure stood among the major risk factors for COPD among non-smokers, along with biomass smoke, indoor air pollution, prior pulmonary tuberculosis, chronic asthma, and poor socioeconomic status (17). A more recent ATS official statement on COPD among non-smokers from 2010 concluded there was sufficient evidence to infer a causal relationship between occupational exposures and development of COPD (2).

We have reassessed the relationship between occupational exposure and the risk of COPD by building on previous analyses as well as taking advantage of new data that have emerged in the published literature. In addition, this review exclusively includes studies that have used ATS-/European Respiratory Society (ERS)-approved spirometric criteria for defining abnormalities in airflow obstruction and level of FEV_1 (18), albeit not requiring LLN-based definitions. The content of this review is derived from an analysis originally performed for the Danish National Board of Industrial Injuries and the Danish Occupational Diseases Committee on COPD and Occupational Exposure in 2010.

Methods

Expert panel members

The working group that performed the analysis on which this report is based was originally convened to draft a scientific reference document for the Danish National Board of Industrial Injuries and the Occupational Diseases Committee on Occupational COPD. The ten panel members included occupational physicians, pulmonologists, and respiratory physiologists with expertise in the study question and originating from five countries (Denmark, Norway, Sweden, UK, and USA).

Data sources and searches

We carried out a series of computerized librarian-assisted searches utilizing the databases PubMed and Embase (from February 2003 to May 2005, with updates in April 2008 and August 2009). The search strategy was intended to be broad in order to maximize the capture of citations of peer-reviewed publications relevant to the epidemiology of occupational risk factors for COPD. The PubMed searches were carried out using the following algorithm of MeSH (Medical Subject Heading) terms: (i) COPD AND (occupation* OR work* OR workplace* OR employment OR industry OR dust* OR fume* OR airborne*) (ii) Loss of lung function AND (occupation* OR work* OR workplace*

OR employment OR industry OR dust* OR fume* OR airborne*) (iii) (Social class AND COPD) OR (Social Class AND loss of lung function). This search strategy initially yielded 2667 hits in total. A parallel search utilizing Embase yielded 2912 hits in total. We further supplemented the citation pool through the manual assessment of the reference lists accompanying other published systematic reviews of COPD and occupation. In addition, the expert panel bought forward a limited number of other relevant publications for further review.

Study selection

We used a multi-step, iterative process to reduce the initial pool of citations down to a final selection as shown in the flow chart illustrated in figure 1. Of 5579 citations from the initial PubMed and Embase search, 1129 were duplicates. The first author screened the remaining 4450 citations for further consideration by title, excluding 4150 and leaving 300 citations for the next stage of review together with 78 additional publications nominated by panel members. The full ten member expert panel, divided into five pairs (four pairs consisted of a pulmonary physician and a specialist in occupational medicine, while one pair consisted of a pulmonary physician and a respiratory physiologist) reviewed the abstracts of 378 publications (including foreign-language papers if there was an English language abstract). The criteria for exclusion at this detailed review stage were: (i) insufficient characterization of occupational exposure risks; (ii) no inclusion of either external or internal reference subjects (the latter could represent a gradient of exposure and did not require unexposed subjects); (iii) insufficient analysis testing the association between exposure and a lung function-defined outcome; (iv) absence of an analysis taking into account both subject age and cigarette smoking exposure; (v) lack of documented measurements of lung function; (vi) and exposures predominantly associated with asthma (eg, isocyanates or plicatic acid [Western red cedar]). For studies of exposures that could lead to either obstructive or restrictive decrements in lung function (eg, inorganic dusts such as from coal mining), we further required data on FEV_1/FVC ratios, excluding those solely reporting FEV_1.

Following this round of exclusions, the fulltexts of all the remaining articles (N=147) were made available to the expert panel and the same review pairs further evaluated each of the full papers. Of these, five publications were translated fully into English (three from Italian and one each from German and Polish). Each pair reviewed one fifth of the total of 147 articles. After the evaluation, all ten reviewers met for a final discussion of all 147 articles and a final decision was agreed in plenum.

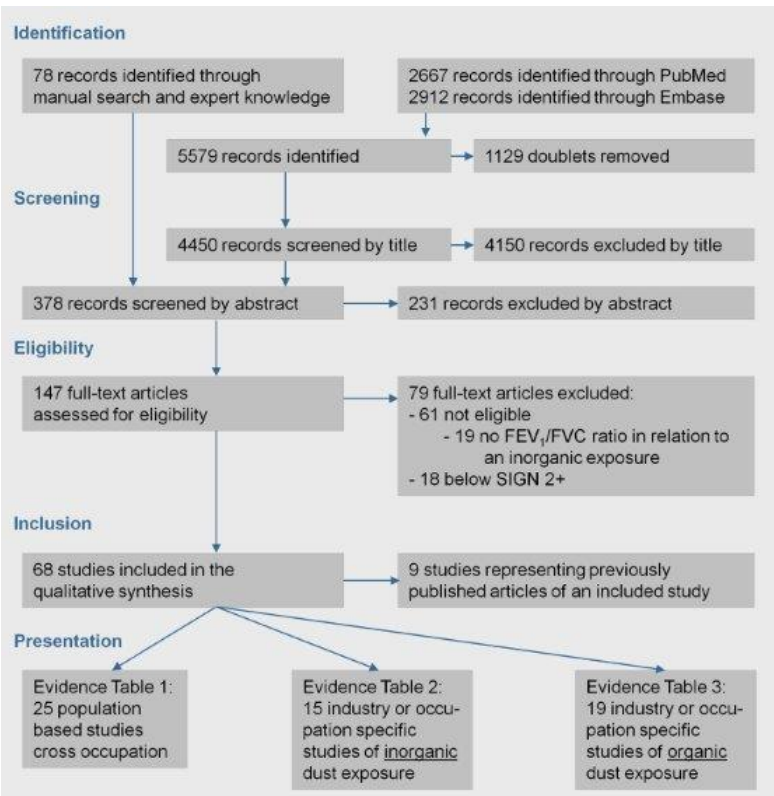

Figure 1. Flow chart of the number of articles in different stages of the selection strategy. FEV_1/FVC=forced expiratory volume in one second/forced vital capacity. SIGN=Scottish Intercollegiate Guidelines Network.

Data extraction and quality assessment

The quality score of the studies was assessed using a modified version of the ERS proposed data extraction sheet for "work-related asthma" previously developed for another systematic review (19). This approach provides for the systematic extraction of: study design and population; measurement of type, degree, and duration of exposure; quality of the exposure description; study limitations (eg, confounding and other potential biases); and key findings. A summary semi-quantitative assessment of the publication was then applied using the SIGN (Scottish Intercollegiate Guidelines Network) methodology to grade each study (20). SIGN requires: the guidelines must be developed by multidisciplinary groups, the assessment must be based on systematic review of the scientific evidence, and recommendations must be explicitly linked to the supporting evidence and graded according to the strength of that evidence. For case–control or cohort studies the grading has been set from 2–2++ where 2++ is the highest quality score. We set, *a priori*, a requirement of a score of ≥2+ (low risk of confounding/bias/chance).

Initially 68 articles were included, but 9 were based on data already represented by other articles, so ultimately 59 articles were included in the final analysis. Of these, 25 were population-based studies that crossed multiple industries and occupations while 15 were industry- or occupation-specific studies where the predominant exposure was inorganic/mineral dust and another 19 were industry- or occupation-specific studies of organic/biological dust exposures.

Certain studies of potential interest (11, 21–31) were omitted as we included only studies using ATS/ERS criteria for airflow obstruction, required that FEV_1/FVC ratios be reported for exposures that could lead to restrictive as well as obstructive decrements in lung function, and excluded studies of exposures predominantly associated with asthma. Even though these selected studies were excluded and did not contribute to the systematic review summarized in the core study tables, nonetheless they are addressed in a distinct supplemental section of the text. In a further additional section, we also summarized publications that only appeared after we carried out the systematic review upon which the core tables are based.

Statistical analysis

We relied on the statistical analyses reported in the published papers. We did not attempt to reanalyze data or derive additional measures of risk (eg, population attributable fractions). The selected studies were judged to be heterogeneous with regard to exposures and populations. This heterogeneity precluded a formal meta-analysis, which requires at least a number of studies to be similar to allow meta-analysis of subgroups.

Supplemental literature review

Our main systematic review was limited to publications appearing prior to September 2009. Because of an increased pace of recent publication in this area, we also wished to address interval reports in this review. In order to do so, two members of the original panel assessed such publications and summarized them as a supplement to the original review.

Results

The central analytic data are presented in three tables. Table 1 shows the population-based studies included in the analysis, table 2 industry- or occupation-specific studies of inorganic/mineral dust exposure, and table 3 industry- or occupation-specific studies of organic/biological dust.

Population-based studies

Of the 25 population-based studies of occupational exposure to vapors, gas, dust, and fumes (VGDF) and COPD (table 1), 18 (32–49) were cross-sectional and 7 (50–56) were longitudinal with follow-up time between 5–25 years. The studies came from the US (32–35, 38, 41, 42, 48, 49, 51), Europe (36, 39, 40, 44, 46, 47, 50, 52–56), Australia/New Zealand (37, 43) and China (45). The studies comprised a total of 92 452 subjects. In some cases, a job-exposure matrix (JEM) was used to characterize the exposure (32–35), while others use JEM jointly with an expert opinion (35) or a questionnaire (32–34). Use of record-defined (16 occupational categories) description of exposure was limited (40), while in 20 studies (36–39, 41–56) the exposure was self-reported and questionnaire-based. The spirometric criteria included were non-uniform. The GOLD criteria were the most prevalent, with GOLD II+ (excluding GOLD I) dominating (32–34, 41, 42, 46, 50) and less frequent GOLD I+ (39). FEV_1/FVC ratio was used alone in 6 publications (37, 43, 44, 48, 52, 54) with different values of the ratio in the range of <0.6 (48) to ≤0.75 (43). FEV_1/FVC ratio <0.75 and FEV_1 <0.8 was the outcome only once (38). Some studies had dual outcomes, including either reduced FEV_1/FVC (FEV_1/VC) ratio (<0.8) or reduced FEV_1 value (<0.8) (47, 49, 53), while others assessed FEV_1/FVC% (36), FEV_1/FVC<LLN (35), and FEV_1 alone (40, 45, 51) (none of these in inorganic dusts that could cause a restrictive deficit, as noted previously). FEV_1 <0.65 or FEV_1 decline (55) and FEV_1

Table 1. Population-based studies. All studies included in the table have adjusted for smoking and age or otherwise taken smoking or age into account. [COLD=emphysema and/or chronic bronchitis; COPD=chronic obstructive pulmonary disease; ETS=environmental tobacco smoke-; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; GOLD=Global Initiative on Obstructive Lung Disease; ICD9=International Classification of Diseases 9th revision; JEM=job exposure matrix; LLN=lower limit of normal; OR=odds ratio; PAF=Population Attributable Fraction; PAR=Population Attributable Risk; RR=relative risk; VGDF=vapors, gas, dust or fumes; 95% CI=95% confidence interval]

Reference	Exposure	Study design	Population	Outcome	Measure of association
Cross-sectional studies					
Blanc et al, 2009 (32)	VGDF Questionnaire- or JEM defined	Case–control study	N=1843/1719 (1709/1652 referents) Age 55–75 yrs	COPD diagnosed: by a physician, excluding chronic bronchitis or GOLD II+	Physician (N=1843) Self-reported: Significant OR 2.1 (95% CI 1.4–3.0) and PAF of 25% JEM: Non significant. GOLD II+ (N=1719) Smoking (non-smoker/smoker) exposure (yes/no): Non-smoker/yes: Non significant. Smoker/no: Significant OR 4.9 (95% CI 2.3–10.4) Smoker/yes: Significant OR 8.5 (95% CI 3.8–18.8)
Blanc et al, 2009 (34)	Dusty/dirty jobs Questionnaire- or JEM defined	Ecological analysis	N=19 094 (referents; range 15–93%) Age at follow-up ≥40 yrs	COPD: GOLD II+	Significantly increased prevalence per 10% increase in exposure; 0.8 (95% CI 0.3–1.3) P=0.003
Blanc et al, 2009 (33)	VGDF Questionnaire- or JEM defined	Case–control study	N=1044 (302 referents) Age 40–65 yrs	COPD: GOLD II+	Self-reported: Significant OR 2.13 (95% CI 1.55–2.93) and PAF of 31% JEM high: Significant OR 2.33 (95% CI 1.45–3.72) and PAF of 14%
Weinmann et al, 2008 (35)	Mineral dusts, metal dust and fumes, organic dusts, irritant gases or vapors, sensitizers, organic solvents, diesel exhaust, and ETS Expert-defined JEM	Case–control study	N=744 (356 referents) Age ≥ 45 yrs	COPD diagnosis and FEV_1/FVC <LLN or COPD based on an algorithm developed for the study based on ICD9 MD diagnosis and medications	Overall (except ETS): Significant OR 1.5 (95% CI 1.1–2.1) and PAR of 24% Mineral dust: Significant OR 1.7 (95% CI 1.1–2.7) and PAR of 9% Organic dust: Non significant OR 0.99 (95% CI 0.7–1.4) and PAR of 0% Irritant gases and vapors: Significant OR 1.6 (95% CI 1.2–2.2) and PAR of 21% Diesel exhaust: Significant OR 1.9 (95% CI 1.3–3.0) and PAR of 12%
Jaén et al, 2006 (36)	Dust, fumes or gases Questionnaire defined	Cross-sectional study	N=576 (159 referents) Age 20–70 yrs	FEV_1/FVC%	Significant reduced in exposed ≥15 yrs compared with non-exposed 1.7% (95% CI 0.2–3.3)
Matheson et al, 2005 (37)	Biological dust, mineral dust, gases and fumes Questionnaire defined.	Two-phased cross-sectional study	N=1213 (550–814 referents) Age 45–70 yrs	FEV_1/FVC <0.70 ± symptoms.	Biological dust: Significant OR 3.19 (95% CI 1.27–7.97) Mineral dust: Non significant OR 1.40 (95% CI 0.56–3.51) Gases and fumes: Significant OR 2.81 (95% CI 1.01–7.77) Generally higher risk in females than males
Hnizdo et al, 2004 (41)	17 occupational and 17 industry categories Questionnaire defined	Cross-sectional study	N=9120 (2175 referents) Age 30–75 yrs	FEV_1/FVC <0.75 and FEV_1 <0.8	Caucasians: PAF of 21.0% African-Americans: PAF of 23% Mexican-Americans: PAF of 54.4%
de Marco et al, 2004 (39)	VGDF Questionnaire defined	Cross-sectional study	N=14 855 (approx. 8393 referents) Age 20–44 yrs	COPD: GOLD I+	Non significant
Mastrangelo et al, 2003 (40)	16 occupational categories Record defined	Case–control study	N=429 (72 referents) Age ≥45 yrs	FEV_1 <0.8	Biological dust; Significant OR 8.86 (95% CI 2.29–34.3) Gas/vapor/fume; Significant OR 5.83 (95% CI 1.82–18.6) Mineral dust; Significant OR 3.80 (95% CI 1.21-12.0)
Hnizdo et al, 2002 (38)	14 occupational and 16 industry categories Questionnaire defined.	Cross-sectional study	N=9495 (2277 referents) Age 30–75 yrs	COPD: GOLD II+	Work by occupation in all ethnic groups: Armed forces; Significant OR 2.0 (95% CI 1.1–3.6) Freight/stock/material handlers; Significant OR 2.2 (95% CI 1.3–3.7) Overall PAF 15.1% and among never smokers 25.6%
Mak et al, 2001 (42)	Gases, dusts, or fumes Questionnaire defined	Case–control study	N=517 (450 referents) Median age 57 yrs	COPD: GOLD II+	Significant OR 1.79 (95% CI 1.12–2.85) and PAR of 29.6%.

Continued

Table 1. Continued

Reference	Exposure	Study design	Population	Outcome	Measure of association
Fishwick et al, 1997 (43)	Fumes, gases, vapor, or dust Questionnaire-defined	Cross-sectional study	N=1132 (774 referents) Age 22–44 yrs	$FEV_1/FVC \leq 0.75$ + symptoms	Ever exposed to VGDF: Significant OR 3.13 (95% CI 1.07 – 9.12)
Isoaho et al, 1994 (44)	Dust Questionnaire-defined	Cross-sectional study	N=1191 (300 referents) Age 64–97 yrs	COPD: $FEV_1/FVC \leq 0.65$ or clinical findings.	Dust exposure and lower social class: Significant OR 2.3 (95% CI 1.1–4.8) and PAR of 19.6% Other combinations: Non significant
Xu et al, 1992 (45)	Dusts and gases/ fumes Questionnaire-defined	Cross-sectional study	N=1094 (530 referents) Age 40–69 yrs	FEV_1	Dust exposure: Significant deficit in FEV_1, $P<0.05$
Bakke et al, 1991 (46)	Asbestos, quartz, wood dust, metal gases (chromium, nickel, platinum), aluminium production and processing, welding, and soldering Questionnaire-defined	Two-phased cross-sectional study	N=706 (431/497 referents) Age 18–73 yrs	COPD: GOLD II+	Overall non significant. Persons >50 yrs: Exposed to asbestos: Significant OR 2.8 (95% CI 1.1–7.3) Exposed to quartz: Significant OR 3.7 (95% CI 1.2–11.0)
Viegi et al, 1991 (47)	Dusts, chemicals and/ or fumes, and not specified exposures Questionnaire-defined	Cross-sectional study	N=1635 (1218 referents) Age 18–64 yrs	COLD: emphysema and/or chronic bronchitis or Spirometry: $FEV_1/FVC < 0.7$ or $FEV_1 < 0.7$	COLD: Males, overall: Significant OR 2.31 (95% CI 1.10–4.86) Spirometry: Males, overall: Significant OR 1.45 (95% CI 1.03-2.05)
Lebowitz 1997 (49)	Occupational exposure or working in high-risk industry Questionnaire-defined	Cross-sectional study	N=1195 (518 referents) Age ≥18 yrs	Airways obstructive disease (AOD) grade 2: Physician-confirmed AOD or $FEV_1/FVC < 0.8$ or $FEV_1 < 0.75$	Significantly increased prevalence in exposed compared with referents 38.6% compared with 32.8%, $P<0.01$
Longitudinal studies					
Boggia et al, 2008 (50)	Welder smoke, gases or chemical irritants Questionnaire defined	Longitudinal study; 10 yrs	N=2017 (937 referents) Age 18–58 yrs	COPD: GOLD II+	Occupational exposure: Significant OR 2.62 (95% CI 2.02–3.41) Smoking: Significant OR 1.75 (95% CI 1.27–2.41 Interaction smoking-occupational exposure: Significant OR 2.51 (95% CI 1.97-3.20)
Harber et al, 2007 (51)	Fume and dust. Questionnaire defined.	Longitudinal study; 5 yrs	N=5335 (3846 referents) Age at baseline 34–67 yrs	FEV_1	Fume exposure in men compared with referents: Significantly associated with 0.25% reduction per year of post bronchodilator FEV_1
Sunyer et al, 2005 (52)	Biological dust, mineral dust, gas and fumes Questionnaire defined.	Longitudinal study; mean 8.9 yrs	N=6481(approx. 2823 referents) Age 20–45 yrs	$FEV_1/FVC < 0.7$	No significant difference in RR
Lindberg et al, 2005 (53)	Occupation based on 7 groups Questionnaire defined.	Longitudinal study; 10 yrs	N=1109 (183 referents) Age at baseline 36–67 yrs	COPD: $FEV_1/FVC < 0.70$ and $FEV_1 < 0.8$ or $FEV_1/FVC < 0.70$	Non significant but borderline results: Manual workers: OR 1.78 (95% CI 0.80–3.97)Low educational level: OR 1.73 (95% CI 0.98–3.04)
Humerfelt et al, 1993 (54)	Asbestos, quartz, ammonia, chlorine, nitrous gas, ozone, sulphur dioxide, aldehydes, anhydrides, diisocyanates, and metals (chromium, nickel, and platinum) Questionnaire defined	Longitudinal study; 20–25 yrs	N=911(518 referents) Age at baseline 22–54 yrs	$FEV_1/FVC < 0.65$	Only significant in high asbestos exposure compared with referents, $P<0.05$.
Krzyzanowski et al, 1986(55)	Dusts, variable temperature, high humidity, or chemicals Questionnaire defined	Longitudinal study; 13 yrs	N=1769 (1481–1670 referents) Age at baseline 19–70 yrs	COPD: $FEV_1 < 0.65$ or FEV_1 decline	Decline in FEV_1: Males exposed to dust: Significant decline in FEV_1 6.1 ml/yr compared with referents, $P<0.05$ Males exposed to chemicals; Significant decline in FEV_1 6.0 ml/yr compared with referents, $P<0.05$ Females exposed to variable temperature: Significant decline in FEV_1 6.1 ml/yr compared with referents, $P<0.05$ COPD: Non significant
Kauffmann et al, 1982 (56)	Dust, gases and heat Questionnaire defined	Longitudinal study; 12 yrs	N=556 (177 referents) Age at baseline 30–54 yrs	FEV1 slope (ml/yr)	Overall significant for at least one occupational hazard compared with referents, $P \leq 0.01$ Dust; Significant dose-response relation, $P \leq 0.01$.

slope (ml/yr) (56) were outcomes in longitudinal studies. Among 22 of the 25 population-based studies, there was a statistic significant association reported between COPD and exposure to VGDF, defined either predominantly by self-report or less frequently through JEM assignment of exposure likelihood. The JEM indicate the presence, intensity, frequency, and/or probability of exposure to a specific agent in a specific job. Lindberg et al (53) found a borderline association to manual work and low educational level and COPD. In 2 studies (39, 52) no statistically significant association between exposure to VGDF and COPD was observed, but both these articles were based on the European Community Respiratory Health Survey (ECRHS) cohort where the age of recruitment was 20–45 years, with a relatively short follow-up time and the outcome was mild COPD equivalent to GOLD stage I.

Industry- or occupation-specific studies of inorganic/mineral dust exposure

Of the industry- or occupation-specific studies of inorganic/mineral dust exposure and COPD (table 2), ten (57–66) were cross-sectional and five (67–71) longitudinal with follow-up time between 3.4–18 years. The studies came mostly from Europe (58, 59, 61–65, 71) and the US (67–70), followed by one each from Taiwan (57), China (60), and India (66). The studies comprised a total of 7332 subjects with exposures of welding, coal, coke, asphalt, silica, cement, tunnel work, cadmium, glass, and bleach. In a majority of studies (60, 62–64, 66, 69), personal sampling technique was used to define the exposure, both personal and area-level sampling technique were used in one (65) and area-sampling technique was used in two (57, 61) studies. The exposure was characterized by questionnaire in four studies (58, 68, 70, 71), while in two studies (59, 67) a record or workplace-defined strategy was used to assess exposure. The spirometric criteria included were non-uniform. The FEV_1/FVC ratio alone was the most prevalent (59, 65–68) together with FEV_1/FVC ratio with different values of the ratio (57, 61, 64, 69, 70) in the range of <0.65 (70) to <0.8 (69). GOLD criteria II+ defined COPD in two studies (60, 63) and FEV_1/FVC ratio ≤ LLN in two others (62, 71). In one study (58) there were a dual outcome both for obstructive (normal FVC and low FEV_1/FVC) and mixed pulmonary impairment (low FVC and low FEV_1/FVC).

In 12 of the 15 studies focusing on inorganic exposures, there was a statistic significant association reported between exposure and COPD. Among spot welders, there was a borderline association (P=0.08) with FEV_1 decline (57), among shipyard workers there was an increased risk of mixed pulmonary function impairment (58), and no significant association was found between cement dust exposure and COPD (63).

Industry- or occupation-specific studies of organic/biological dust

Of the industry- or occupation-specific studies of organic/biological dust exposure and COPD (table 3), nine (72–80) were cross-sectional and ten (81–90) longitudinal with follow up-time between 1–20 years. A majority of the studies came from Europe (72–77, 79, 80, 85, 86, 88) and the US (82, 83, 89, 90), with two each from China (81, 84) and South Africa (78, 87). The studies comprised a total of 16 856 subjects with exposures of cotton, flax, jute, farming, grain, wood, paper, and rubber. In eight of the studies (75, 77, 78, 80, 86–89), personal sampling technique was used to define the exposure; in one study (72), both personal and area-level sampling techniques were used, and in five studies (79, 81, 82, 84, 90), area-level sampling techniques alone were used. The exposure was characterized by questionnaire in four studies (73, 74, 76, 83), while in one study (85) employee records defined exposure. The spirometric criteria included were non-uniform. The FEV_1 alone was the most prevalent (72–74, 79, 81–86). GOLD criteria II+ was the outcome in two studies (76, 77), FEV_1/FVC ratio <0.7 in two others (78, 87), and FEV_1/FVC ratio alone in one (80). Decline in FEV_1 and/or FEV_1/FVC were assessed in three studies (88–90), while in one study the outcome was FEV_1/FVC< LLN (75).

Among 17 of the 19 studies focusing on organic exposures, there was a statistic significant association reported between exposure and COPD. In the Jacobsen et al study, the association was only found in subgroups (88). No association between past exposure to cotton dust and low FEV_1 was observed, but duration in the workplace and working in the waste room was associated with a low FEV_1 in the same study (72). The paper by Glindmeyer et al (89) is mostly a negative study, although difficult to interpret due to extensive stratification on exposure variables. Nonetheless, one of the measures (residual particulate) was indeed associated with COPD.

Studies of airway obstruction not included in the systematic analysis

Due to our study inclusion and exclusion criteria, only two studies (68, 69) of exposures to coal and gold dust in the mining industry were included in table 2 of industry- or occupation-specific studies. In their reanalysis of British coal miners, Marine et al (21) found an effect on FEV_1 of dust exposure alone when disentangling the pneumoconiotic effect of respiratory conditions. A comprehensive review (11) further supports the argument that coal mine dust might cause obstructive lung disease as do autopsy data from coal miners and non-miners where the cumulative exposure to respirable coal mine

Table 2. Inorganic exposures and occupational cohort studies. All studies included in the table have adjusted for smoking and age or otherwise taken smoking or age into account. [COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; GOLD=Global Initiative on Obstructive Lung Disease; ICD9=International Classification of Diseases 9th revision; JEM=job exposure matrix; LLN=lower limit of normal; OR=odds ratio; PAF=population attributable fraction; PAR=population attributable risk; RR=relative risk; VGDF=vapors, gas, dust or fumes; 95% CI=95% confidence interval]

Reference	Exposure	Study design	Population	Outcome	Measure of association
Welding					
Lou et al, 2006 (57)	Spot and arc welders Air sampling	Cross-sectional study	N=247 (130 referents) Age 22–56 yrs	FEV_1/FVC <0.75	Non significant. Borderline linear trend (P=0.08) to FEV1 decline and spot welding.
Gennaro et al, 1993 (58)	13 job categories in shipyard workers Questionnaire-defined	Cross-sectional study	N=657 (174 referents) Mean age 45.7 yrs	Obstructive pulmonary function: Normal FVC and low FEV_1/FVC Mixed pulmonary function impairment: Low FVC and low FEV_1/FVC	Obstructive pulmonary function: No significant association with job title Mixed pulmonary function: No significant association with job title Significant OR 2.52 (95% CI 1.15–5.53) for >20 yrs compared with <20 yrs experience for mixed impairment
Bogadi-Šare, 1990 (59)	Dust and fumes of stainless steel welding Defined by work place.	Cross-sectional study	N=186 (80 referents) Mean age exposed 38.5 yrs referents 36.9 yrs	FEV_1/FVC ratio	Significant lower FEV1/FVC ratio: Smokers: 79.2% compared with referents 84.4%, P<0.05 Non-smokers: 80.4% compared with referents 92.8%, P<0.01.
Wang et al, 1996 (67)	Dust exposure in steelworkers Record (steel corporation)-defined	Longitudinal study; 4–9 yrs	N=475 (internal referents) Age at baseline 20–61 yrs	FEV_1/FVC ratio	Significant reduce in FEV_1/FVC ratio of 0.03%/yr, P=0.02
Coal					
Seixas et al, 1993 (68)	Coal mine dust Questionnaire-defined.	Longitudinal study; 11–18 yrs	N=977 (internal referents) Mean age at follow-up 39.9 yrs	FEV_1/FVC ratio	FEV_1/FVC ratio change in significant association to mean exposure, P=0.02
Seixas et al, 1992 (69)	Coal miners Personal respirable dust samples. Cumulative exposure, mg/m³ yr: low exp <11; moderate exp 11 – 20; high exp >20	Longitudinal study; 15–18 yrs	N=1185 (internal referents with the lowest cumulative exposure) Mean age 40 yrs	FEV_1/FVC <0.8	Per increment of 1 mg/m³ yr: OR 1.05 (95% CI 1.01–1.09) 20 mg/m³ yr: OR 2.5
Coke					
Hu et al, 2006 (60)	Coke oven workers Personal air sampling benzene soluble fraction Cumulative exposure, µg/m³ yrs: low <630, moderate 630–1713, high ≥1714	Cross-sectional study	N=923 (211 referents) Mean age exposed 34.6–37.9 yrs referents 35.7 yrs	COPD: GOLD II	Moderate exposure: Significant OR 4.00 (95% CI 1.80–8.89) High exposure: Significant OR 8.22 (95% CI 3.76–17.97)
Asphalt					
Randem et al, 2004 (61)	Asphalt worker Exposure monitoring study	Cross-sectional study	N=259 (195 referents) Mean age exposed 37 yrs referents 40 yrs	COPD: FEV_1/FVC <0.7	Significant OR 2.8 (95% CI 1.2–6.5)
Silica					
Meijer et al, 2001 (62)	Dust and silica Personal air sampling (range of dust and silica 0.08-2.67 mg/m³ and 0.0003-0.186 mg/m³, respectively)	Cross-sectional study	N=254 (110 referents) Mean age exposed 35.9 yrs referents 35.5 yrs	FEV_1/FVC ratio COPD: FEV_1/FVC ≤LLN	Significant lower FEV_1/FVC ratio in exposed compared to referents, P=0.02 No significant association between exposure and COPD
Hertzberg et al, 2002 (70)	Silica exposure in foundry workers. Questionnaire defined	Longitudinal study; Ò 13 yrs	N=815 (internal referents) Mean age 58.7 yrs	Abnormal FEV_1/FVC ratio; <0.70 if age <60 yrs <0.65 if age ≥60 yrs	Significant relationship with increasing cumulative silica exposure, P=0.03 No association in nonsmokersSignificant trend in smokers P=0.01.
Cement					
Fell et al, 2003 (63)	Cement dust Personal sampling (range total dust 0.4–53.7 mg/m³, respirable dust 0.0–2.3 mg/m³, quartz ≤0.06 mg/m³).	Cross-sectional study	N=169 (50 referents) Mean age exposed 69.3 yrs referents 66.8 yrs	COPD: GOLD II+	No significant association between exposure and COPD
Tunnel work					
Ulvestad et al, 2000 (64)	Tunnel workers Personal samplings: Total dust 3.6 mg/m³ (GM), respirable dust 1.2 mg/m³ (GM), quartz 0.034 mg/m³ (GM), oil mist 0.5 mg/m³ (GM), NO_2 0.5 ppm (peak value)	Cross-sectional study	N=417 (205 referents) Mean age exposed 41 yrs referents 40 yrs	FEV_1/FVC <0.7	Significant OR 2.50 (95% CI 1.31–4.96). Significant association between FEV1/FVC <0.7 and workers employed 10–20 yrs compared with workers employed <10 yrs OR 2.56 (95% CI 1.13–6.32).

Continued

Table 2. Continued

Reference	Exposure	Study design	Population	Outcome	Measure of association
Cadmium					
Davison et al, 1988 (65)	Cadmium workers. Static and personal sampling (range 34-600 μg/m^3) Cumulative exposure, μg/m^3 yrs: low <400 moderate 401–1600 high ≥1600	Cross-sectional study	N=189 (92 referents)	FEV_1/FVC ratio	Significant lower FEV_1/FVC ratio compared with referents, P<0.001 Significantly associated with 'year started exposure' (pre-1951, 1951-1970, post-1970) reduced 0.29%/(μg/m^3)/yr; P<0.001 Not significantly associated with cumulative exposure.
Glass bangle					
Rastogi et al, 1991 (66)	Glass bangle workers Personal dust sampling and air sampling.	Cross-sectional study	N=347 (127 referents) Mean age exposed 30.9 yrs referents 30.6 yrs	FEV_1/FVC ratio	Significant lower FEV1/FVC ratio 78% compared with referents 81%, P<0.001.
Bleach					
Mehta et al, 2005 (71)	Bleach workers. Questionnaire defined.	Longitudinal study; mean 3.4 yrs	N=232 (54 referents). Mean age 43.7 yrs	FEV_1/FVC <LLN	Significant prevalence ratio in: Pre-baseline ozone gassings: PR 4.3 (95% CI 1.2–15.7). Pre-baseline and interval ozone gassings: PR 5.5 (95% CI 1.1–28.0).

or coal dust retained in the lungs were significant predictors for emphysema severity (22). As with the studies of airway obstruction and coal mining, the studies on gold mining have the inherent challenge of disentangling the restrictive deficits associated with the dust exposure from obstructive deficits. The dust exposure with high silica concentration has been associated with different respiratory health outcomes: asthma (23), bronchial hyper-responsiveness (24), emphysema (25), silicosis-associated dysfunction, chronic airflow limitation, and chronic bronchitis (26), and studies among gold miners have found loss in lung function associated with pulmonary tuberculosis (27). The diversity in respiratory health outcome associated with the same exposure pinpoints a diagnostic uncertainty. However, published data (28) suggests an association between occupational exposures to dust and silica from gold mining. We also ultimately excluded studies where asthma was combined with COPD as a mixed obstructive endpoint. Nonetheless these data are relevant to the overall question at hand. Increased hazard ratios (HR) for incidence of chronic non-specific lung disease (CNSLD) among blue- compared to white-collar workers was found (29) in a Dutch longitudinal study The definition covers symptoms associated with asthma and COPD, as well as cases of asthma, chronic bronchitis, or emphysema. Standardized hospitalization ratio (SHR) for COPD were studied in three Danish cohorts (>2 000 000 males and females, aged 20–59 years). The risk ratio (RR) was 2.31 [95% confidence interval (95% CI) 2.13–2.51] for unskilled workers compared with senior salaried staff for men and 1.62 (95% CI 1.38–1.92) for women. SHR increased during the observational period for all classic high risk occupations apart from farming (30). COPD mortality, although beyond the scope of our core analysis, should also be noted. A Swedish study of mortality in COPD among construction workers comprised 317 629 subjects aged 15–67 years. There was a significant increase in mortality among subjects exposed to inorganic dust, gases and irritants, fumes, and wood dust [RR 1.12 (95% CI 1.03–1.22)], which was even higher among "never smokers" [HR 2.30 (95% CI 1.07–4.96)] (31).

Publications since the initial review

We identified eight relevant publications that appeared since the original literature review. Five of these (91–95) were cross-sectional and three (96–98) were longitudinal with a follow-up time between 5–13 years. Six studies came from Europe (91, 92, 94, 96–98) and one study each from the US (93) and South Africa (95). Three of the studies (91, 92, 96) focused on inorganic exposure (cement production and metal melting), one (97) analyzed the association between organic exposure (dairy farming) and COPD, while four studies (93–95, 98) were population-based. These studies comprised a total of 28 618 subjects. JEM alone defined exposure in four studies (91, 95, 96, 98); JEM with personal sampling technique was employed in one study (91), and JEM with questionnaire data in two studies (95, 98). The exposure was solely characterized by self-report in three studies (93, 94, 97) and one study defined exposure by area sampling (92). The spirometric criteria included were non-uniform. GOLD criteria II+ was the most prevalent (92–95). The FEV_1 and FEV_1/FVC were the outcome in two studies (91, 97), like FEV_1/FVC<0.7 and <LLN (96, 98). All eight studies found an association between airway obstruction/COPD and occupational exposure.

Table 3. Organic exposures and occupational cohort studies. All studies included in the table have adjusted for smoking and age or have otherwise taken smoking or age into account. [COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; GOLD=Global Initiative on Obstructive Lung Disease; ICD9=International Classification of Diseases 9th revision; JEM=job exposure matrix; LLN=lower limit of normal; OR=odds ratio; PAF=population attributable fraction; PAR=population attributable risk; RR=relative risk; VGDF=vapors, gas, dust or fumes; 95% CI=95% confidence interval]

Reference	Exposure	Study design	Population	Outcome	Measure of association
Cotton					
Fishwick et al, 1996 (72)	Cotton spinning mill workers Static air samplings of dust (range; 0.04–3.23 mg/m^3) Personal air samplings of dust (range; 0.14–24.95 mg/m^3)	Cross-sectional study	N=1043 (<430 internal referents) Mean age: exposed 33–44 yrs referents 31–37 yrs	FEV_1	No significant relation to FEV_1 deficit
Elwood et al, 1986 (73)	Ex-cotton textile workers Questionnaire-defined.	Cross-sectional study	N=886 (431 referents) Age 45–74 yrs	FEV_1	Men: Non significant Women: Significant deficit in FEV_1 compared with referents, P<0.05
Wang et al, 2008 (81)	Cotton textile workers Mean (SD) dust exposure 19.3 (13.3) mg/m^3/yr	Longitudinal study; 20 yrs	N=825 (417 referents) Mean age at baseline: exposed 37.1 yrs referents 36.1 yrs	FEV_1	15 yrs follow-up: Significant decline in FEV_1 9.7 ml/yr (95% CI 2.63–16.77) compared with referents 20 yrs follow-up: Non significant.
Glindmeyer et al, 1991 (82)	Cotton textile workers Area samplings of dust Mean (SD) cumulative dust exposure µg/m^3 yrs: Yarn manufacturing 2445 (3253) Slashing and weaving 6091 (5870)	Longitudinal study; 5 yrs	N=1817 (464 referents Mean age: exposed 39.3 yrs referents 36.5 yrs	FEV_1	Yarn manufacturing: Significant annual decline in FEV_1 16.20 ml/yr per 100 µg/m^3 average cotton dust exposure
Beck et al, 1982 (83)	Cotton textile workers Questionnaire-defined	Longitudinal study; 6 yrs	N=660 (277 referents) Age at baseline ≥45 yrs	FEV_1	Men: Significant decline in FEV_1 42 ml/yr compared with referents 25 ml/yr, P=0.02 Women: Significant decline in FEV_1 30 ml/yr compared with referents 14 ml/yr, P=0.001
Flax					
Elwood et al, 1986 (74)	Ex-flax workers Questionnaire-defined	Cross-sectional study	N=1896 (1267 referents) Age 40–74 yrs	FEV_1	Men: Significant deficit in FEV_1 compared with referents, P<0.05 Women: Significant deficit in FEV_1 compared with referents, P<0.01.
Jute					
Liu et al, 1992 (84)	Jute processing Area sampling (mean range 1.4–64.6 mg/m^3)	Longitudinal study; 5 yrs	N=75 (25 referents) Mean age: exposed 40.0 yrs referents 38.5 yrs	FEV_1	Men: Significant decline in FEV_1 90.0 ml/yr compared with referents 32.9 ml/yr, P<0.01
Farming					
Eduard et al, 2009 (75)	Farming Personal sampling: interquartile range for dust 0.24–1.6 mg/m^3	Cross-sectional study	N=4735 (21% referents, crop farmers) Mean age 49 yrs	COPD: FEV_1/FVC <LLN	Overall livestock farming: Significant OR 1.4 (95% CI 1.1–1.7) for COPD Organic exposure: Significant OR 1.2 (95% CI 1.0–1.4) for COPD for a 10-fold increase of exposure level
Lamprecht et al, 2007 (76)	Farming Questionnaire-defined	Cross-sectional study	N=1258 (970 referents) Median age 57 yrs	COPD: GOLD II+	Significant OR 1.8 (95% CI 1.2–2.8) for COPD GOLD II+
Monsó et al, 2004 (77)	Indoor air contaminants in animal confinement buildings Personal air sampling (interquartile range 2.3-9.4 mg/m^3)	Cross-sectional study	N=76 (referents, 1st and 2nd quartile exposure) Mean age 45.1 yrs	COPD: GOLD II+	High dust exposure (4th quartile): Significant OR 6.60 (95% CI 1.10–39.54) for COPD GOLD II+ Significant dose–response relationship
Dalphin et al, 1998 (85)	Dairy farmers Medical-file-defined	Longitudinal study; 6 yrs	N=328 (138 referents) Age at baseline 20–60 yrs	FEV_1	Significant decline in FEV_1 compared with referents, P=0.03
Grain					
Post et al, 1998 (86)	Grain processing and animal feed industry Personal dust samplings (range 2 – 20 mg/m^3).	Longitudinal study; 5 yrs	N=140 (referents, no and low exposure). Mean age at baseline 37.7 yrs	FEV_1	Estimated for a 40 yrs old non-smoker: High compared with low dust exp: 58.2 compared with 35.8 ml. annual decline in FEV_1, P<0.05.
Bachmann et al, 1991 (87)	Grain dust Personal air sampling (range 0-95.59 mg/m^3)	Longitudinal study; 6 yrs	N=159 (<38 referents, low exposure) Mean age 42.7 yrs	FEV_1/FVC <0.7	High exposure: Significant OR 3.09 (95% CI 1.35–7.07) for obstruction
Wood					
Shamssain, 1992 (78)	Wood dust Personal air sampling (mean dust concentration 3.82 mg/cm^3)	Cross-sectional study	N=297 (152 referents) Mean age: exposed 32.27–34.92 yrs referents 33.69–33.77 yrs	FEV_1/FVC <0.7	Significantly lower FEV_1/FVC in exposed compared with referents, p<0.01 Significant lower FEV_1/FVC in exposed employed ≥10 yrs compared with exposed employed <10 yrs, P<0.01.

Continued

Table 3. Continued

Reference	Exposure	Study design	Population	Outcome	Measure of association
Jacobsen et al, 2008 (88)	Wood dust Personal air sampling Median (range) 3.75 (0–7.55) mg*yr/m^3.	Longitudinal study; 6 yrs	Male: N=1031 (104 referents). Mean age at baseline 39 yrs Female: N=316 (131 referents). Mean age at baseline 38 yrs	Decline in FEV_1, FEV_1/FVC; New onset cases of FEV_1/FVC<0.70	Males: No significant decline in FEV_1, FVC, FEV_1/FVC or increase in new onset of COPD in relation to exposure Females: Dose-response relationship between exposure and % annual decrease in FEV_1; An additional reduction of 14.50 ml/yr and 27.97 ml/yr for medium and high exposed respectively. New onset COPD: 11% in fourth quartile of cumulative dust exposure, compared with 4% in first quartile of cumulative dust exposure, P=0.08
Glindmeyer et al, 2008 (89)	Wood dust Personal air sampling mg/m^3 GM (GSD) Inhalable dust: 1.45 (2.7)	Longitudinal study; 3.5–4.2 yrs	N=1164 (internal referents) Mean age at baseline 39–41 yrs	Decline in FEV_1, FEV_1/FVC	No significant decline in FEV_1, FEV_1/FVC, in relation to inhalable wood dust Residual particulate matter significant associated with annual decline in FEV_1 (milling and plywood sawmill) and FEV_1/FVC (milling) for the respirable dust fraction
Heederik et al, 1987 (79)	Paper Soft–paper dust Dust sampling, GM mg/m^3: Respirable dust: 4.9 Total dust: 5.8	Cross-sectional study	N=94 (48 referents) Mean age: exposed 35.7 yrs referents 42.6 yrs	FEV_1	Significant deficit in FEV_1 compared with referents, P<0.05.
Rubber					
Meijer et al, 1998 (80)	Rubber fumes and dust Personal air sampling (mean dust exposure 2.0 mg/m^3) Mean cumulative dust 32.5 mg/m^3 yrs	Cross-sectional study	N=139 (69 referents) Mean age: exposed 37.1 yrs referents 35.5 yrs	FEV_1/FVC ratio	Significantly lower FEV_1/FVC ratio in exp. compared with referents, 80 compared with 82%, P<0.05 Cumulative dust exposure significantly associated with reduced FEV_1/FVC ratio 0.04%/mg/m^3*yr; P<0.001.
Fine et al, 1976 (90)	Rubber workers. Environmental samples	Longitudinal study; 1 yr	N=233 (141 referents) Age >24 yrs	FEV_1/FVC ratio (cross-sectional) FEV_1 (longitudinal)	Decline in FEV_1/FVC ratio: Non significant In multiple regression: Exposure time (yrs) was significant to predict one year loss in FEV_1, P<0.001.
Endotoxin					
Eduard et al, 2009 (75)	Farming Personal sampling: interquartile range for endotoxin 19 000–63 000 EU/m^3	Cross-sectional study	N=4735 (21% referents, crop farmers) Mean age 49 yrs	COPD: FEV_1/FVC <LLN	Significant OR 1.2 (95% CI 1.0–1.5) for COPD for a 10-fold increase of exposure level.
Monsó et al, 2004 (77)	Indoor air contaminants in animal confinement buildings Personal air sampling (interquartile range 282.2–2203.0 units/m^3).	Cross-sectional study	N=76 (referents, 1st and 2nd quartile exposure) Mean age 45.1 yrs	COPD: GOLD II+	Non significant.
Wang et al, 2008 (81)	Cotton textile workers Mean cumulative endotoxin exposure 48 479.5 EU/m^3/yr	Longitudinal study; 20 yrs	N=825 (417 referents) Mean age at baseline: exposed 37.1 yrs referents 36.1 yrs	FEV_1	Endotoxin exposure not related to annual decline in FEV1.
Post et al, 1998 (86)	Grain processing and animal feed industry Personal samplings of endotoxin, mean (3–177 ng/m^3)	Longitudinal study; 5 yrs	N=140 (referents, no and low exposure) Mean age at baseline 37.7 yrs	FEV_1	Annual decline in FEV1 estimated for a 40 yrs old non-smoker: High endotoxin exposure: Non significant.

Discussion

A modified version of the ERS proposed data extraction sheet for "work related asthma" and SIGN system were used to assess the quality of all studies, ensuring ≥2+ value on a quality scale and consequently low risk of confounding/bias/change. In 29 studies, spirometric criteria of airflow obstruction other than GOLD were used, 21 studies used GOLD criteria and 10 used LLN criteria. In 16 studies, change in FEV_1 or FEV_1/FVC over time was the outcome. There have been relatively few studies using LLN criteria with the GOLD criteria being more frequent in recent years, although this has changed in favor of LLN criteria. The distribution of the criteria used thus reflects temporal trends in publishing rather than a selection bias per se. We found a consistent association between airflow obstruction/COPD and a wide variety of occupational exposures in this systematic literature analysis. This reaffirms the findings of previous reviews but also addresses some of the potential limitations of earlier assessments by restricting the studies included to high quality epidemiological analysis involving only spirometrically confirmed

airflow obstruction as the outcome, combining this with minimal requirements for exposure characterization (eg, reported internal or external referents). The 59 publications included in the core analysis, supplemented by 8 more recent studies, comprise both population-based and industry-specific approaches and represent a global database.

Consistency, strengths, and temporality of association

The included studies originated from Europe, America, Asia, and Africa, albeit dominated by the former two regions. The exposure variables were multi-dimensional and heterogeneous and described, evaluated, or measured differently. The industry-specific studies often involved with direct exposure measurements were constructed to analyze for associations while the population-based studies did not benefit from such data. Exposure was assessed by means of questionnaire, JEM, occupational- and industrial categorizations, and personal- and area measurements. It is interesting to observe that the findings from the population-based studies, which were not designed to analyze for an association between exposure and COPD (that is, occupation was of interest as a confounder), did not differ in either strength or direction of the association from the industry-specific studies designed for that purpose. Multiple study designs were used and the size of the population analyzed varied substantially. The outcomes in the analyses were not uniform and similar outcomes were defined differently among the studies. Yet, despite these heterogeneous attributes, there is a pattern of consistency in the association observed between exposure and COPD. This diversity in design but consistency in findings supports the conclusion that occupational exposure plays a causal role in the development of COPD. The findings of COPD among non-smokers (17, 99) further underscore the importance of exposures other than smoking in the etiology of the disease.

The odds ratios (OR) for COPD (GOLD I+ and II+) were calculated for 18 studies. Among the population-based studies (33–36, 39, 42, 43, 47), OR ranged from 1.08–2.13, and among the studies on inorganic exposure, the OR was 1.70–3.80 (35, 40, 61, 64) and <1 (37), Among the studies on organic exposure, OR ranged from 1.20–8.86 (37, 40, 75, 76) and <1 (35). The data support a "robust" more than a "very strong" (high point estimate of risk) association, but do not contradict a causal relationship. In all of the included studies, the exposure occurred prior to the health outcome (eg, temporally consistent). Finally, the relationship of exposure to VGDF and COPD is certainly biologically plausible given the physicochemical heterogeneity that characterizes cigarette smoke as the best established cause of this disease.

Dose–response data from selected industries

In addition to the consistency of the association between occupation and COPD, during the last two decades dose–response data have lent further support to a causal relation. These include analyses showing effects across a gradient of exposures to cotton textile (82, 83), jute processing (84), farming (85), grain and animal feed (86), wood workers (88), welding (67), foundry work (70), coal mining (68, 69), and non-mining industrial dust (56). The consistent finding of a dose–response relationship despite the diversity of exposures adds to the evidence that occupational exposure from VGDF is a risk factor for COPD.

Biological plausibility and experimental data

COPD is a heterogeneous disease with diverse involvement of both large and small airways (in relation to emphysema in particular), the alveoli, and lung parenchyma. Several pathological pathways are thought to be involved. An abnormal inflammatory response in the lungs to toxic particles and gases inhaled from tobacco smoke, air pollution, and occupational exposure is thought to be the central event in the pathogenesis of COPD (100). However, the pathophysiological mechanisms that link the inflammatory response in the lung with accelerated loss in FEV_1 are not wholly understood and may also involve factors related to genetic factors, immune regulation, and mechanisms related to cellular repair and the resolution of inflammation (101). Even the effect of smoking, the main risk factor for COPD, is not fully understood (14). There are published data that show pathological similarities in the COPD "phenotype" associated with tobacco smoke exposure and occupational exposure to particles and gases. Smoking-induced COPD is characterized pathologically by the development of emphysema, chronic bronchitis, and small airways disease in varying degrees in different individuals. The effect of occupational exposure is studied less than smoking exposure but published data supports an association between emphysema and occupational exposure to cadmium (65) and, to a lesser extent, coal (102) and silica (103). Similarly, exposures to cadmium, coal, endotoxin, and silica in animal models have all been shown to cause emphysema (104). Among α1-antitrypsin-deficent subjects, there is clear biological support for the association between occupational exposure and COPD. Although tobacco smoke is the major cause of a classical gene-environment interaction in α1-antitrypsin, deficiency studies have shown an increased risk of chronic cough, lower FEV_1, and lower FEV_1/FVC among subjects with phenotype Pi*Z and occupational exposure, an association independent of tobacco smoke (105, 106).

Strengths and limitations

This review emphasizes standard spirometric criteria for airway obstruction/COPD and does not systematically consider chronic bronchitis. Removing the latter diagnostic category increases the specificity of the association we observed although it does limit generalization of our findings beyond airflow obstruction to chronic productive cough. COPD populations defined on the basis of FEV_1/FVC alone may be heterogeneous with respect to etiological risk factors and clinical progression of disease, including disability risk. For example, longstanding asthma causing irreversible airways obstruction cannot be differentiated from COPD based on spirometry alone, even with bronchodilator administration. However, in most of the studies we included, persons with self-reported asthma were excluded, while studies with high-risk asthma exposures (ie, isocyanates) were also avoided.

The non-uniform spirometry-based definitions of COPD in the studies we analyzed introduce possible misclassification and limit the comparison of the prevalence/incidence of COPD among studies. In most of these, moreover, especially the older studies, there was no information about post bronchodilator spirometry for subjects with FEV_1/FVC ratios <0.7. The frequently used GOLD criterion introducing a fixed FEV_1/FVC of <0.70 is prone to overestimation of obstruction among older or male subjects, while, among the young or female subjects, the GOLD criteria will tend to underestimate the true prevalence because FEV_1 /FVC declines with age as we noted earlier (107). Indeed, defining COPD solely on the criterion of FEV_1/FVC <0.7 is no longer accepted in the European Respiratory Journal (6). This misclassification, however, would most likely influence the estimate of the proportion of subjects with disease rather than skew the association between disease and exposure. It must also be kept in mind that the airflow limitation (whether by GOLD criteria or defined by LLN) is present not only among persons with appropriately diagnosed clinical COPD but also among a subset of persons who have gone undiagnosed. Therefore, a spirometry-based definition of abnormality may not be wholly generalizable to clinical disease.

Concluding remarks

The studies we analyzed were of varying design, derived from different populations, and applied differing measures of exposure and outcome. Nonetheless, across these studies there was a consistent association between occupational exposures and COPD, providing epidemiological support for this association. Furthermore, these associations were dose-dependent for both organic and inorganic exposures in multiple longitudinal studies, and data from animal studies support biological plausibility. Central criteria for evidence of causation (108) including strength, consistency, and temporality of association together with documented biological gradient, plausibility, and coherence have all been documented. We therefore conclude that there is strong evidence for a causal association between various types of occupational exposures and COPD.

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