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AMERICAN THORACIC SOCIETY DOCUMENTS

# The Occupational Burden of Nonmalignant Respiratory Diseases

## An Official American Thoracic Society and European Respiratory Society Statement

Paul D. Blanc, Isabella Annesi-Maesano, John R. Balmes, Kristin J. Cummings, David Fishwick, David Miedinger, Nicola Murgia, Rajen N. Naidoo, Carl J. Reynolds, Torben Sigsgaard, Kjell Torén, Denis Vinnikov, and Carrie A. Redlich; on behalf of the American Thoracic Society and European Respiratory Society

This Official Statement was approved by the American Thoracic Society May 2019 and the European Respiratory Society March 2019

**Rationale:** Workplace inhalational hazards remain common worldwide, even though they are ameliorable. Previous American Thoracic Society documents have assessed the contribution of workplace exposures to asthma and chronic obstructive pulmonary disease on a population level, but not to other chronic respiratory diseases. The goal of this document is to report an in-depth literature review and data synthesis of the occupational contribution to the burden of the major nonmalignant respiratory diseases, including airway diseases; interstitial fibrosis; hypersensitivity pneumonitis; other noninfectious granulomatous lung diseases, including sarcoidosis; and selected respiratory infections.

**Methods:** Relevant literature was identified for each respiratory condition. The occupational population attributable fraction (PAF) was estimated for those conditions for which there were sufficient population-based studies to allow pooled estimates. For the other conditions, the occupational burden of disease was estimated on the basis of attribution in case series, incidence rate ratios, or attributable fraction within an exposed group.

**Results:** Workplace exposures contribute substantially to the burden of multiple chronic respiratory diseases, including asthma (PAF, 16%); chronic obstructive pulmonary disease (PAF, 14%); chronic bronchitis (PAF, 13%); idiopathic pulmonary fibrosis (PAF, 26%); hypersensitivity pneumonitis (occupational burden, 19%); other granulomatous diseases, including sarcoidosis (occupational burden, 30%); pulmonary alveolar proteinosis (occupational burden, 29%); tuberculosis (occupational burden, 2.3% in silica-exposed workers and 1% in healthcare workers); and community-acquired pneumonia in working-age adults (PAF, 10%).

**Conclusions:** Workplace exposures contribute to the burden of disease across a range of nonmalignant lung conditions in adults (in addition to the 100% burden for the classic occupational pneumoconioses). This burden has important clinical, research, and policy implications. There is a pressing need to improve clinical recognition and public health awareness of the contribution of occupational factors across a range of nonmalignant respiratory diseases.

**Keywords:** occupational; workplace; nonmalignant respiratory diseases; interstitial fibrosis; sarcoidosis; respiratory infections; pneumonitis

## Contents



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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health.

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## Overview

Occupational exposures are important, frequently overlooked, and modifiable contributors to the burden of respiratory disease. Quantifying the occupational contribution to this disease burden is critical to preventing disease and improving lung health. To date, the question of the occupational burden in respiratory disease at the population level has been addressed primarily in relation to asthma and chronic obstructive pulmonary disease (COPD). This document reviews and synthesizes existing data to quantify the occupational contribution to the burden of nonmalignant respiratory diseases across a range of conditions frequently unrecognized as potentially work related.

### Key Conclusions

- A substantial evidence base indicates that the contribution of inhalational workplace hazards to the burden of nonmalignant lung diseases is substantial.
- Conditions for which the estimated occupational burden is 10% or more include asthma, COPD, chronic bronchitis, idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis (HP), other noninfectious granulomatous lung diseases (including sarcoidosis), pulmonary alveolar proteinosis (PAP), and community-acquired pneumonia (CAP).
- These findings highlight the need for greater awareness that work exposures contribute substantially across a range of respiratory diseases.
- Strategies are needed to improve the recognition and prevention of the substantial occupational burden of nonmalignant respiratory diseases.

## Introduction

Inhalation of vapors, gas, dust, or fumes (VGDF) in the workplace is common worldwide, and occupation is an important global contributor to the burden of respiratory disease (1). For asthma and COPD, the contribution of workplace exposures has been a particular focus of attention in previous American Thoracic Society (ATS) policy statements (2–4). Occupational exposures also contribute to the disease burden in a number of other conditions, including interstitial disease diagnosed as IPF, HP, other noninfectious granulomatous lung diseases such as sarcoidosis, other interstitial lung diseases, and selected respiratory infections (5–9).

We synthesized data from multiple sources to quantify the occupational contribution to the burden of nonmalignant respiratory disease. The occupational burden in thoracic cancer (lung and pleura) has been well characterized elsewhere (10–12). Of note, the classic pneumoconioses (including silicosis, coal workers' pneumoconiosis, and asbestosis) remain an important, unabating global health problem that is not addressed in this document because the occupational contribution to these conditions is essentially 100%. That does not detract, however, from their public health importance.

In this statement, we assess the occupational burden in four categories of respiratory conditions: airway disease (asthma, COPD, and chronic bronchitis), interstitial lung disease (IPF as well as PAP and other uncommon interstitial diseases), granulomatous processes (HP and other noninfectious granulomatous diseases, including sarcoidosis), and selected respiratory infections (tuberculosis [TB] and CAP).

## Methods

We searched the PubMed and Embase databases from their respective start dates through December 31, 2017, unless otherwise noted. A supplemental literature search was conducted covering January to September 2018. The search strategies, including start dates, rationale, and search terms, are shown in Table E1 in the online supplement. For asthma, COPD, and chronic bronchitis, searches took into account the previous ATS reports (2–4) and additional reviews (13–20). We also reviewed reference citations in identified publications to identify relevant papers. Except when stated explicitly, all data were population based and were not limited to a specific industry or exposure. For asthma, COPD, chronic bronchitis, and IPF, we estimated the occupationally related population attributable fraction (PAF) reported by or derived from case–control and cohort studies. When needed, we calculated the PAF using the odds ratio (OR) and proportion of cases exposed [PAF = pc(OR − 1)/OR, where pc is the proportion of cases exposed] (3). We limited the analysis of asthma to incident data. For PAP, HP, and sarcoidosis, we extracted data from cases series in which the proportion of occupationally related cases was available. For TB, we used World Health Organization and World Bank databases (21–23) for data on country-specific general population rates to estimate relative disease incidence by occupation. For CAP, we examined both PAF estimates and, within exposure cohorts, the attributable fraction (AF). We pooled published or derived PAF values (asthma, COPD, chronic bronchitis, and interstitial lung disease) and the occupationally attributable burden (PAP, HP, and sarcoidosis) to obtain weighted summary estimates using the metaproportion command in Stata 14.2 software (StataCorp). We used the exact method to compute the 95% confidence interval (CI) for each pooled estimate. Because we recognized that the heterogeneity among the studies was high, we calculated the pooled PAF or proportion using random effects modeling with case numbers informing the weights. We also estimated statistical heterogeneity using the $I^2$ statistic, which in each case was consistent with high heterogeneity, as we expected (values not presented). We also calculated the pooled estimate excluding the highest and lowest values in the group, as well as calculating the median of the observed PAF or occupational burden values. For TB and CAP, we did not calculate weighted pooled values, limiting summary data to the median values among the estimates considered. For consistency, we use the term "occupational burden" across the various disease outcomes analyzed, even though in some cases the burden was derived from PAF estimates, whereas in others the burden was derived from attribution in case series, incidence rate ratios (IRRs), or AF within a group.

## Occupational Burden of Asthma Incidence

Work-related asthma is now the most commonly reported work-related respiratory disorder in many industrialized countries. Work-related asthma comprises occupational asthma, defined as asthma "caused" by the workplace, and work-exacerbated (or aggravated) asthma, meaning preexisting asthma with work-related worsening (24).

Cross-sectional (prevalence) studies have dominated previous estimates of the occupational burden of disease. To build on earlier estimates, we limited our search to longitudinal, population-based studies that reported incident asthma and occupational risk factors.

We identified nine studies with longitudinal data relevant to occupation and incident asthma for inclusion (25–33) (Table 1). Of these, six had been included in a previous review (20), including a study of Israeli military recruits (over 95% of the Jewish male population aged 18 yr) exposed across a range of vocations (30). Three newer studies have been published since the previous review (20). One study investigating asthma incidence among persons aged 13–44 years in Tasmania (Australia) reported a high cumulative incidence of asthma (37%) with a work-related job exposure matrix (JEM)-based PAF of 10% (26). A second study, using the RHINE (Respiratory Health in Northern Europe) adult study population aged 20–44 years, estimated a JEM-based PAF for occupation of 14% for males and 7% for females (28). A later reanalysis using a different JEM arrived at similar estimates (13% and 8% for males and females, respectively) (34). A third longitudinal study analyzed data from the United Kingdom. 1958 birth cohort limited to those without asthma by age 16 with later follow-up through age 42 (29). Using a JEM to assess exposure risk, the overall occupational PAF was 16%, with wide confidence intervals (95% CI, 3.8–27.1%).

Pooling data from all nine studies yielded an estimated PAF for the occupational contribution to incident asthma of 16% (95% CI, 10–22%) (Figure 1), which is comparable to prior estimates (2). Overall, longitudinal data from which inferences can be drawn on the occupational burden of incident asthma are limited. Of note, the studies considered were largely done in developed economic settings. Sex-stratified longitudinal data are even more limited; we identified only two such analyses, both with lower PAF estimates for women than for men.

## Occupational Burden of COPD and Chronic Bronchitis

Seven reviews published since the 2003 ATS statement (3, 13–16, 18, 19) identified 33 papers relating to the occupational contribution to COPD or chronic bronchitis. Of note, two of these found a median PAF for the occupational contribution to COPD of 15% (13, 15); one meta-analysis estimated a pooled OR of 1.43 for COPD related to VGDF exposures (18), whereas another meta-analysis observed minimal excess risks (1.04–1.15) for separate JEM-defined exposures (16). The additional literature search for publications published between 2014 and 2017 identified a further 15 relevant citations not among the 33 included in the reviews noted above.

We retained population-based studies that included a range of potential occupations or case–control studies that clearly reflected the general population. Studies were excluded if they lacked a clear definition of the disease endpoint (e.g., either COPD or chronic bronchitis) or when key data were missing (e.g., studies not presenting the number of subjects exposed that would have allowed for a PAF calculation). When a study reported multiple endpoints or measures of exposure, we preferentially considered risk estimates for COPD defined by spirometry (using lower limit of normal, if reported) over self-reported COPD, and, similarly, we considered JEM-defined risk over self-reported exposure. In studies stratified by smoking status, the ever-smoking stratum was the one used in the pooled analysis of PAF. When data from a never-smoking stratum were available (in some cases the entire cohort analyzed), we used these in a separate pooled analysis of PAF among never-smokers. Results presented only in a stratified manner (e.g., by sex) were considered as separate estimates of risk.

**Table 1.** Longitudinal Population-based Studies of Occupational Risk for Asthma

| First Author, Year, Location (Reference) | Study Type | Incident Cases (*n* [Total Population]) | Definition of Exposure | PAF (%) |
|---|---|---|---|---|
| Katz, 1999, Israel (30) | Population follow-up ages 18–21 yr at baseline | 588 (59,058) | Military exposure combat or maintenance vs. clerical | 44 |
| Karjalainen, 2001, Finland (31) | Population follow-up ages 25–59 yr at baseline | 49,575 (1,852,848) | Work-related compensation | 22 |
| Eagan, 2002, Norway (25) | Population follow-up ages 15–70 yr at baseline | 101 (2,723) | Self-reported dust and fume exposure at baseline | 14 |
| LeVan, 2006, Singapore (27) | Population follow-up ages 13–44 yr at baseline | 1,426 (52,325) | Occupations exposed to dust, smoke, or vapors | 8.6 |
| Kogevinas, 2007, international (32) | Population follow-up ages 20–44 yr at baseline | 133 (6,837) | Exposure to high-risk substances by JEM | 11 |
| Hedlund, 2006, Sweden (33) | Population follow-up ages 36–37, 50–52, and 66–67 yr at baseline | 271 (5,933) | Blue collar industrial workers vs. others | 9 |
| Lillienberg, 2013, international (28) | Population follow-up in RHINE population ages 20–44 yr at baseline | 129 males (5,933)<br>286 females (6,253) | Exposure to high-risk substances by JEM | 14<br>7 |
| Hoy, 2013, Australia (Tasmania) (26) | Population follow-up ages 13–44 yr at baseline | 290 (792*) | Exposure to high-risk substances by JEM | 10 |
| Ghosh, 2013, UK (29) | Population follow-up of birth cohort up to age 42 yr | 611 (7,088†) | Any asthma JEM >0 | 16.3 |

*Definition of abbreviations*: JEM = job exposure matrix; PAF = population attributable fraction; RHINE = Respiratory Health in Northern Europe; UK = United Kingdom.

The pooled estimated PAF for the occupational contribution to incident asthma was 16% (95% confidence interval, 10–22%).

*Subjects with asthma at baseline excluded.

†Total before subjects with childhood asthma were excluded.

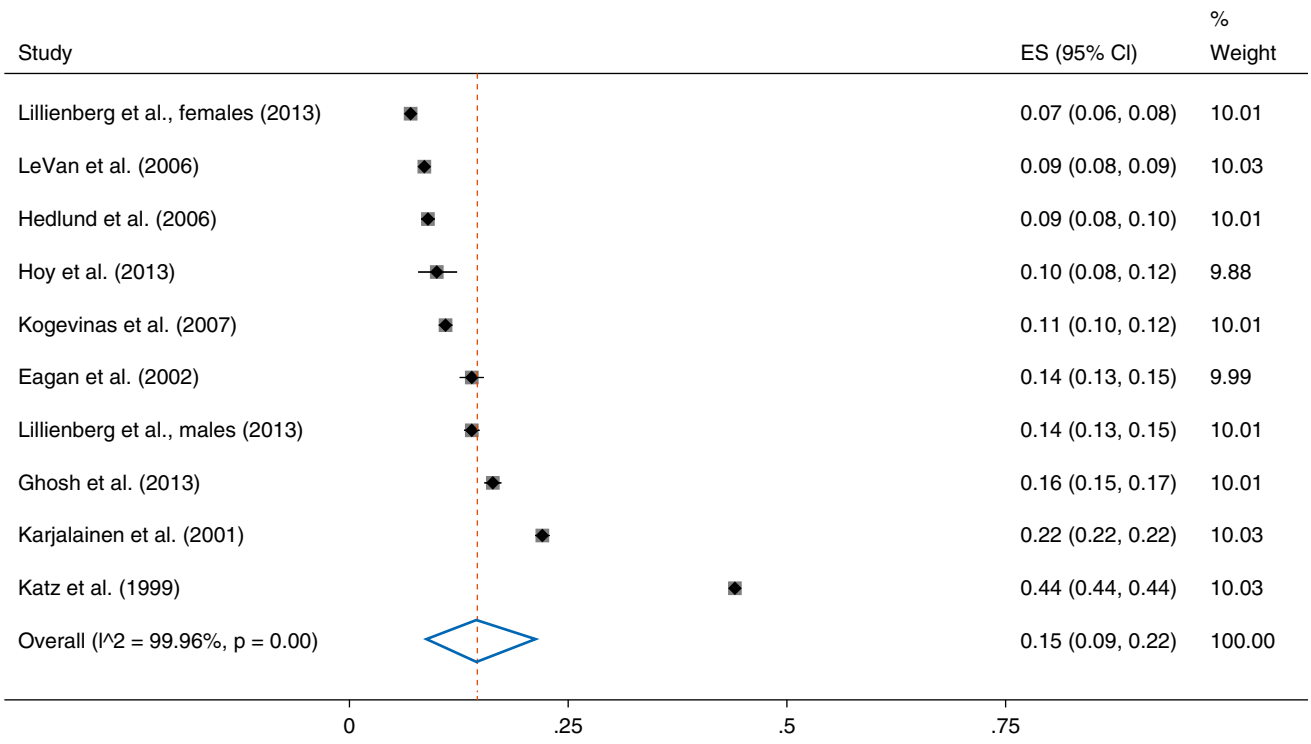


**Figure 1.** Asthma: population attributable fraction (PAF). Forest plot of studies relevant to estimating the occupational contribution to asthma. The estimated PAF, confidence interval (CI), and weighted contribution for each study, as well as the calculated pooled estimate (red dashed line) and 95% CI, are shown. For asthma, the pooled PAF for work exposures is 16% (95% CI, 10–22%). ES = effect size.

We included 26 studies to estimate the contribution of occupational exposures to the burden of COPD (35–60) and 7 for the contribution to chronic bronchitis (39, 40, 50, 51, 61–63). Table 2 summarizes the 26 COPD studies considered, including 28 estimates of risk (taking into account sex-stratified data). The pooled PAF for the occupational contribution to the burden of COPD (including cohorts with mixed smoking status, adjusted for smoking) was 14% (95% CI, 10–18%) (Figure 2). The occupational PAF for COPD among never-smokers (not shown in table), estimated from six studies including stratified data (35, 47, 51, 64–66), yielded a pooled PAF of 31% (95% CI, 18–43%).

Table 3 summarizes the seven chronic bronchitis studies used (eight estimates of risk). The pooled PAF for chronic bronchitis was 13% (95% CI, 6–21%) (Figure 3). Only two studies allowed estimation of the occupational PAF for chronic bronchitis among never-smokers, yielding values of 8.3% (51) and 12% (67). Several publications excluded from the tables nonetheless warrant mention. Accelerated annual decline in $FEV_1$ in males with early COPD was observed in association with occupational exposures (68). An ecological analysis of three large international studies estimated a 0.8% increase in COPD prevalence per 10% increase in occupational exposures, taking into account the concomitant prevalence of smoking (43). Several large population-based studies have addressed the association between various occupations and COPD (11, 69, 70). Also of note, other researchers have investigated large occupational cohorts, including construction workers exposed to dust (71, 72).

In summary, an impressive body of new data on the occupational burden of COPD, and to a lesser degree chronic bronchitis, has been published since the original 2003 ATS statement. In aggregate, participant numbers are large and international in scope. The pooled estimates of the occupational PAF of 14% for COPD and 13% for chronic bronchitis are in line with those of the previous ATS statement and interval reviews. Moreover, the higher occupational PAF for COPD among never-smokers (31%) suggests that occupational exposures contribute more substantially to the burden of COPD in nonsmokers.

## Occupational Burden of IPF

IPF is a diagnosis of exclusion made in the presence of a usual interstitial pneumonia pattern on biopsy or with a consistent appearance on a high-resolution computed tomographic scan. The IPF diagnosis presumes that known causes of interstitial lung disease have been excluded (e.g., drug toxicity; connective tissue disease; and domestic, occupational, or environmental exposures) (73). Therefore, studies of cohorts with a diagnosis of IPF presumably already exclude persons with a recognized occupational cause of fibrosis, such as asbestosis.

We identified four reviews of occupational exposures in IPF (5, 74–76) that collectively included 10 relevant case–control studies. One of these, a meta-analysis of six studies, reported a PAF for several exposure categories ranging from 3.5% (silica) to 20% (agriculture) (5). Adding more recent citations ($n = 5$), we identified a total of 15 relevant case–control studies addressing the question of occupational exposures associated with IPF (77–91). Four of the 15 publications were not included in our PAF estimates: one because data were

**Table 2.** Population-based Studies of Occupational Risk for Chronic Obstructive Pulmonary Disease

| First Author, Year, Location (Reference) | Study Type and Population | Total (*N*) | Number of Cases | Definition of COPD | Exposure Information | PAF (%) |
|---|---|---|---|---|---|---|
| Hnizdo, 2002, USA (35) | Population based | 9,823 | 693 | COPD = $FEV_1$/FVC <0.7 and $FEV_1$ <80% (pre-BD) | Occupational groups | 19.6 |
| Trupin, 2003, USA (36) | Population based | 1,932 | 377 | Self-reported doctor's diagnosis | Self-reported | 20.0 |
| de Marco, 2004, international (37) | Population based | 14,318 | 1,751 | COPD = $FEV_1$/FVC <0.7 (pre-BD) | Self-reported exposure to dust, gas, and fumes | 17.4 |
| Lindberg, 2005 Sweden (38) | Population based (longitudinal) | 1,109 | 83 | COPD = $FEV_1$/FVC <0.7 and $FEV_1$ <80% (pre-BD) | Socioeconomic classification (manual worker in industry) | 15.0 |
| Sunyer, 2005, international (39) | Population based (longitudinal), females | 3,279 | 53 | COPD = $FEV_1$/FVC <0.7 (pre-BD) | VGDF by JEM (high exposure) | 1.0 |
| Sunyer, 2005, international (39) | Population based (longitudinal), males | 3,202 | 61 | COPD = $FEV_1$/FVC <0.7 (pre-BD) | VGDF by JEM (high exposure) | 0 |
| Jaén, 2006, Spain (40) | Population based | 497 | 73 | COPD = $FEV_1$/FVC <0.7 (post-BD) | Self-reported (any exposure to dust, gas, and fumes) | 9.0 |
| Zhong, 2007, China (41) | Population based | 20,245 | 1,668 | COPD = $FEV_1$/FVC <0.7 (post-BD) | Self-reported (any exposure to dust, gas, and fumes) | 3.9 |
| Weinmann, 2008, USA (42) | Case–control | 744 | 388 | COPD = $FEV_1$/FVC below LLN or by algorithm | JEM | 24 |
| Blanc, 2009, USA (43) | Case–control | 1,504 | 1,202 | COPD = $FEV_1$/FVC <0.7 (pre-BD) | VGDF by JEM (high exposure) | 14.0 |
| Blanc, 2009, USA (44) | Case–control | 1,788 | 79 | COPD = $FEV_1$/FVC <0.7 | VGDF self-reported | 17.0 |
| Melville, 2010, UK (45) | Population based | 841 | 84 | COPD = $FEV_1$/FVC <70 and $FEV_1$ <80% (post-BD) | Self-reported occupational exposure at risk of COPD | 50.0 |
| Idolor, 2011, Philippines (46) | Population based | 722 | 141 | COPD = $FEV_1$/FVC <70 (post-BD) | Self-reported exposure in a dusty job | 5.2 |
| Mehta, 2012, Switzerland (47) | Population based (longitudinal) | 1,958* | 43* | COPD = $FEV_1$/FVC below LLN stage II+ (pre-BD) | VGDF by JEM (high exposure) | 23* |
| Lam, 2012, China (48) | Population based | 8,216 | 461 | COPD = $FEV_1$/FVC below LLN (pre-BD) | Self-reported (any exposure to dust, gas, and fumes) | 10.4 |
| Darby, 2012, UK (49) | Population based | 571 | 197 | COPD = $FEV_1$/FVC <70 (pre-BD) | Self-reported VGDF exposure | 20 |
| Hansell, 2014, New Zealand (50) | Population based | 750 | 83 | COPD = $FEV_1$/FVC below LLN (pre-BD) | VGDF by JEM (high exposure) | 2.7 |
| Doney, 2014, USA (51) | Population based | 3,508 | 196 | COPD = $FEV_1$/FVC below LLN and $FEV_1$ below LLN (pre-BD) | Self-reported (severe exposure) | 38.8 |
| de Jong, 2014, Netherlands (52) | Population based (LifeLine cohort), | 11,851 | 1,754 | COPD = $FEV_1$/FVC <0.7 (pre-BD) | VGDF by JEM (high exposure) | 4.3 |
| de Jong, 2014, Netherlands (52) | Population based (Vlagtwedde-Vlaardingen cohort) | 2,364 | 639 | COPD = $FEV_1$/FVC <0.7 (pre-BD) | VGDF by JEM (high exposure) | 9.7 |
| Pallasaho, 2014, Finland (53) | Population based (longitudinal) | 4,080 | 140 | Self-reported | Self-reported | 23.6 |
| Scholes, 2014, UK (54) | Population based | 7,603 | 1,032 | COPD = $FEV_1$/FVC below LLN (pre-BD) | Job classification as routine occupation | 9.1 |
| Paulin, 2015, USA (55) | Population-based cohort of smokers | 1,075 | 721 | COPD = $FEV_1$/FVC <0.7 (post-BD) | VGDF by JEM (intermediate/high risk) | 12.0 |
| Würtz, 2015, Denmark (56) | Population based | 4,132 | 279 | COPD = $FEV_1$/FVC below LLN (pre-BD) | VGDF by JEM (high exposure) | 10.3 |
| Obaseki, 2016, Nigeria (57) | Population based | 875 | 67 | COPD = $FEV_1$/FVC below LLN (post-BD) | Self-reported (dusty jobs) | 14.9 |
| Tagiyeva, 2017, UK (58) | Population based | 237 | 63 | COPD = $FEV_1$/FVC below LLN (post-BD) | VGDF by JEM | 0 |
| Sinha, 2017, India (59) | Population based | 1,203 | 122 | COPD = $FEV_1$/FVC <0.7 (post-BD) | Self-reported | 34.6 |
| Torén, 2017, Sweden (60) | Population based | 1,052 | 50 | COPD = $FEV_1$/FVC <0.7 + dyspnea, wheezing, or chronic bronchitis | Self-reported | 37 |

*Definition of abbreviations*: BD = bronchodilator; COPD = chronic obstructive pulmonary disease; JEM = job exposure matrix; LLN = lower limit of normal; PAF = population attributable fraction; UK = United Kingdom; USA = United States; VGDF = vapors, gas, dust, or fumes.

The pooled PAF for the occupational contribution to COPD was 14% (95% confidence interval, 10–18%). The pooled PAF for the occupational contribution to COPD in nonsmokers (references not in table [35, 47, 51, 64–66]) was 31% (95% confidence interval, 10–18%).

*Ever-smokers.

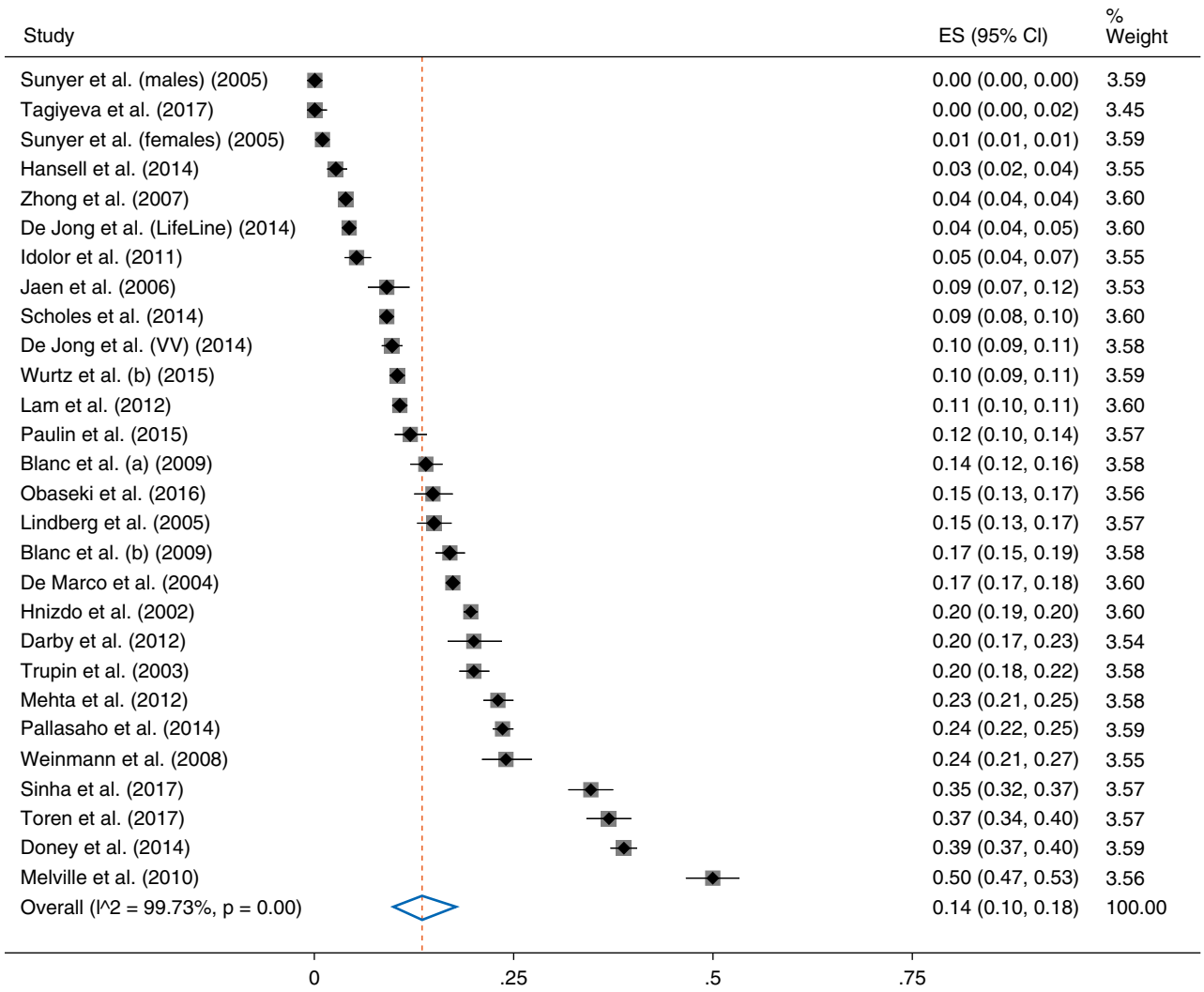


**Figure 2.** Chronic obstructive pulmonary disease (COPD): population attributable fraction (PAF). Forest plot of studies relevant to estimating the occupational contribution to COPD. The estimated PAF, confidence interval (CI), and weighted contribution for each study are shown, as well as the calculated pooled estimate (red dashed line) and 95% CI. For COPD, the pooled PAF for work exposures is 14% (95% CI, 10–18%). ES = effect size.

not available on the proportion of cases with specific occupational exposures (78), two because of methodological issues in exposure assignment (85, 86), and one because of overlap with an included study (90). We initially included one publication that appeared in abstract form only (92), because we were aware that the full paper was forthcoming (89). The remaining 11 case–control studies provided data permitting analysis of occupational exposures in five exposure categories: VGDF, metal dust, wood dust, silica dust, and agricultural dust. For the IPF analysis, VGDF represents an inclusive category combining any of multiple exposures, defined variously by each study.

Thirty-nine risk estimates from 11 studies (1,229 IPF cases in total) contributed to these pooled PAF estimates (Table 4) (77, 79–84, 87, 88, 91, 92). The burden of each pooled exposure type was based on 5–11 individual risk estimates (Table 5). The pooled OR for agricultural work (five studies) was elevated but not statistically significant (OR, 1.6; 95% CI, 0.8–3.0), with a PAF of 4%. The pooled ORs for each of the remaining exposure categories were elevated and statistically significant. These pooled PAFs were as follows: silica (3%), wood dusts (4%), metal dusts or fumes (8%), and VGDF (26%). A forest plot for the estimates for VGDF, the broadest exposure category, is presented in Figure 4.

In summary, our findings suggest that occupational exposures contribute substantially to the burden of disease otherwise considered idiopathic and labeled "IPF." It is also interesting to note that in one Korean study, patients with IPF who had been occupationally exposed to dust had earlier onset of disease and worse prognosis (93). A major challenge in assessing the occupational burden of IPF disease is differentiating between disease misclassification (e.g., chronic HP or one of the classic pneumoconioses [e.g., asbestosis, silicosis] misdiagnosed as IPF) and a causative role of work exposures in usual interstitial pneumonia–like processes. Another important challenge is exposure misclassification, especially when estimating chronic inhalational work exposures over many years. For example, asbestos exposure was common in metal and wood industries and could have contributed to these exposure-associated PAFs for IPF.

**Table 3.** Population-based Studies of Occupational Risk for Chronic Bronchitis

| First Author, Year, Location (Reference) | Study Type and Population | Total (*N*) | Cases (*n*) | Exposure | PAF (%) |
|---|---|---|---|---|---|
| Montnémery, 2001, Sweden (61) | Population based | 8,469 | 390 | Self-reported | 11.0 |
| Lange, 2003, Denmark (62) | Population based | 3,736 | 602 | Self-reported | 16.0 |
| Sunyer, 2005, international (39) | Population based (longitudinal), males | 3,951 | 273 | VGDF by JEM | 15.0 |
| Sunyer, 2005, international (39) | Population based (longitudinal), females | 4,312 | 250 | VGDF by JEM | 0.0 |
| Jaén, 2006, Spain (40) | Population based | 576 | 69 | Self-reported | 29.4 |
| Doney, 2014, USA (51) | Population based | 3,508 | 280 | Self-reported (severe exposure) | 23.1 |
| Hansell, 2014, New Zealand (50) | Population based | 1,017 | 86 | JEM (high exposure) | 13.1 |
| Axelsson, 2016, Sweden (63) | Population based | 1,172 | 84 | Self-reported | 8.6 |

*Definition of abbreviations*: JEM = job exposure matrix; PAF = population attributable fraction; USA = United States; VGDF = vapors, gas, dust, or fumes. The pooled PAF for the occupational contribution to chronic bronchitis was 13% (95% confidence interval, 6–21%).

## Occupational Burden of PAP and Other Interstitial Lung Diseases

PAP has been categorized as primary (idiopathic), secondary, or congenital (94, 95). Primary PAP involves autoantibodies to granulocyte–macrophage colony–stimulating factor (94); secondary PAP is attributed to a variety of occupational exposures, most notably silica (96–108). Cases of autoimmune PAP have been reported in occupationally exposed persons (98, 99, 109–111).

We included 29 relevant publications since 1958 subsuming 1,539 PAP cases (with a range of 10–241 cases per series) (112–140), excluding overlapping reports (141–144). The reported occupational exposure prevalence ranged from 0% to 67%, with a pooled prevalence of 29% (95% CI, 21–37%) (Table 6). A range of exposures was reported, including vapors or gases (cleaning fluids, gasoline, hairspray, paint, and pesticides), inorganic dusts (asbestos, cement, chalk, coal, glass fiber, and silica), organic dusts (cotton, flour, wood, and wool), and metal dusts or fumes (aluminum, copper, indium, iron, and zirconium). Among 19 publications that specifically reported on silica (786 PAP cases), the exposure prevalence ranged from 0% to 22%, with pooled prevalence of 5% (95% CI, 2–8%) (112, 114–120, 124–127, 129, 133, 135–137, 139, 140). Among the five publications describing 345 autoimmune PAP cases, occupational exposure prevalence ranged from 26% to 55% (121, 132, 133, 139, 141).

Although PAP has a more robust literature relevant to the occupational burden of disease, there are a number of other respiratory syndromes in which occupational associations have been observed in disease outbreaks, in certain work settings, or after suspect exposures (142, 145–161). Table E2 provides selected examples of these reported associations, which include bronchiolitis and the

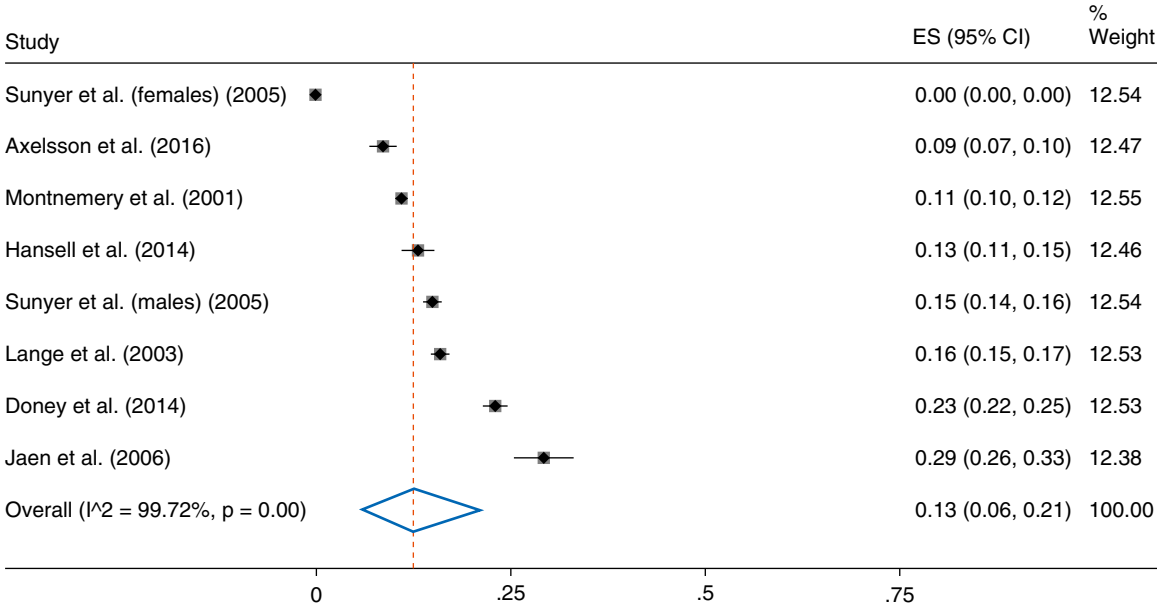


**Figure 3.** Chronic bronchitis: population attributable fraction (PAF). Forest plot of studies relevant to estimating the occupational contribution to chronic bronchitis. The estimated PAF, confidence interval (CI), and weighted contribution for each study are shown, as well as the calculated pooled estimate (red dashed line) and 95% CI. For chronic bronchitis, the pooled PAF for work exposures is 13% (95% CI, 6–21%). ES = effect size.

**Table 4.** Case-Referent Studies of Occupational Risk Factors for Idiopathic Pulmonary Fibrosis

| First Author, Year, Location (Reference) | Cases (*N*) | IPF Case Definition Criteria | OR (95% CI) | | | | | PAF (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | VGDF | Metal | Wood | Ag | Silica | VGDF | Metal | Wood | Ag | Silica |
| Scott, 1990, UK (77) | 40 | Clinical, CXR, PFT | 1.3 (0.8–2.0) | 11.0 (2.3–52.4) | 2.9 (0.9–9.9) | 10.9 (1.2–96) | 1.6 (0.5–4.8) | 17 | 12 | 10 | 12 | 5 |
| Hubbard, 1996, UK (79) | 218 | Clinical, CXR, CT, PFT | NA | 1.7 (1.1–2.7) | 1.7 (1.0–2.9) | NA | NA | NA | 10 | 6 | NA | NA |
| Mullen, 1998, USA (80) | 15 | Clinical, lung biopsy, CT | 2.4 (0.7–8.4) | NA | 3.3 (0.4–25.8) | NA | 11.0 (1.1–115) | 20 | NA | 7 | NA | 20 |
| Baumgartner, 2000, USA (81) | 248 | Clinical, biopsy, CT | NA | 2.0 (1.0–4.0) | 1.6 (0.8–3.3) | 1.6 (1.0–2.5) | 3.9 (1.2–12.7) | NA | 5 | 3 | 7 | 2 |
| Hubbard, 2000, UK (82) | 22 | Death certificate | NA | 1.1 (0.4–2.7) | NA | NA | NA | NA | 5 | NA | NA | NA |
| Miyake, 2005, Japan (83) | 102 | Lung biopsy, BAL, CT | 5.6 (2.1–17.9) | 9.6 (1.7–181.1) | 6 (0.3–112.4) | NA | 1.8 (0.5–7.0) | 26 | 11 | 4 | NA | 5 |
| Gustafson, 2007, Sweden (84) | 140 | Pulmonary fibrosis requiring tissue | 1.1 (0.7–1.7) | 0.9 (0.5–1.6) | 1.2 (0.7–2.2) | NA | 1.4 (0.7–2.7) | 6 | NA | 3 | NA | 3 |
| García-Sancho, 2011, Mexico (87) | 100 | Clinical, CT, lung biopsy | 2.8 (1.5–5.5) | NA | NA | NA | NA | 50 | NA | NA | NA | NA |
| Awadalla, 2012, Egypt (Men) (88) | 95 | Clinical, CT, PFT | NA | 1.6 (0.7–3.6) | 2.7 (1.1–6.8) | 1.0 (0.4–2.3) | 1.1 (0.5–2.7) | NA | 6 | 9 | NA | 1 |
| Awadalla, 2012, Egypt (Women) (88) | 106 | Clinical, CT, PFT | NA | NA | 4.3 (0.8–22.1) | 3.3 (1.2–10.1) | NA | NA | NA | 6 | 14 | NA |
| Paolocci, 2013, Italy (92) | 65 | Clinical, CT | NA | 2.8 (1.1–7.2) | 1.1 (0.4–3.3) (soft wood)<br>0.9 (0.3–2.8) (hard wood) | NA | 2.0 (0.9–4.4) | NA | 9 | 0<br>0 | NA | 11 |
| Koo, 2017, Korea (91) | 78 | Clinical, CT | 2.7 (0.7–10.9) | 5.0 (1.4–18.2) | 2.5 (0.5–12.4) | NA | 1.2 (0.4–3.8) | 35 | 22 | 5 | NA | 5 |

*Definition of abbreviations*: Ag = agricultural dusts; CI = confidence interval; CT = computed tomography; CXR = chest radiograph; IPF = idiopathic pulmonary fibrosis; NA = not applicable; OR = odds ratio; PAF = population attributable fraction; PFT = pulmonary function test; UK = United Kingdom; USA = United States; VGDF = vapors, gas, dust, or fumes, which represent all the exposure categories shown combined and, in selected studies, additional exposures as well.

All studies had case–control designs, with most by interview-based self-reported exposure assessment (Hubbard exposure by job category). Awadalla and colleagues stratified their study sample by male ($n = 95$) and female ($n = 106$). The study by Paolocci and colleagues, which estimated risk with two separate wood variables, later appeared as a full publication (89).

**Table 5.** Pooled Population Attributable Fraction Estimates for Occupation and Idiopathic Pulmonary Fibrosis

| Exposure | Risk Estimates (*N*) | Pooled OR (95% CI) | Pooled PAF (%) (95% CI) |
|---|---|---|---|
| VGDF | 6 | 2.0 (1.2–3.2) | 26 (10–41) |
| Metal dusts | 9 | 2.0 (1.3–3.0) | 8 (4–13) |
| Wood dusts | 11 | 1.7 (1.3–2.2) | 4 (2–6) |
| Agricultural dusts | 5 | 1.6 (0.8–3.0) | 4 (0–12) |
| Silica | 8 | 1.7 (1.2–2.4) | 3 (2–5) |

*Definition of abbreviations*: CI = confidence interval; OR = odds ratio; PAF = population attributable fraction; VGDF = vapors, gas, dust, or fumes, which represent all the other exposure categories shown combined and, in selected studies, additional exposures as well.

flavoring chemical diacetyl; cryptogenic organizing pneumonia and textile dye ("Ardystil syndrome"); and diffuse pulmonary hemorrhage and trimellitic anhydride (142, 145–161).

## Occupational Burden of HP (Extrinsic Allergic Alveolitis) and Other Granulomatous Lung Diseases, Including Sarcoidosis

We synthesized data from 15 relevant publications for HP, the earliest paper dating from 1983 (*see* Table 7). We excluded case series limited to a single avocation or occupation (e.g., bird fanciers or machinists) (162, 163), if there were insufficient data to determine the proportion due to an occupational exposure (164), or if there were overlapping cases (165) that were included in another publication (166). The studies included (166–180) were all case series (or registries), except for one case–control design (167), but used variable criteria for diagnosing HP and assessing causation. For the case series, we considered the work-related cases within a larger series to represent the occupational burden of disease. The estimated occupational burden of disease (Figure 5) ranged from 0% to 81.3%, with a weighted metaproportion of 19% (95% CI, 12–28%).

In addition to HP, we also considered the occupational burden of other noninfectious granulomatous lung diseases. Inhalation of beryllium can cause granulomatous lung disease that mimics sarcoidosis; other metals have also been associated with granulomatous responses; and sarcoidosis prevalence has been reported to be elevated among various occupational groups, including firefighters, navy recruits, workers in the lumber industry, rock or glass wool workers, salespeople, and World Trade Center disaster emergency responders (181, 182). Several large case-referent studies of patients with sarcoidosis who were not beryllium sensitized have found that occupational exposures to organic dusts, bioaerosols, and metals increased risk of sarcoidosis (183–185). A study of sarcoidosis prevalence in Switzerland found higher frequencies in regions with metal industry and intense agriculture (186). In a large U.S. study using national death certificate data, sarcoidosis mortality risk was significantly elevated in association with metalworking, health care, teaching, sales, banking, and administration (181). Mortality data also suggest that occupational exposures may increase risk for a more severe sarcoidosis phenotype (187).

Epidemiological evidence on the proportion of chronic beryllium disease misdiagnosed as sarcoidosis is limited to a few case series (188–192) and one case-referent study (193). Combining beryllium-focused studies of sarcoidosis

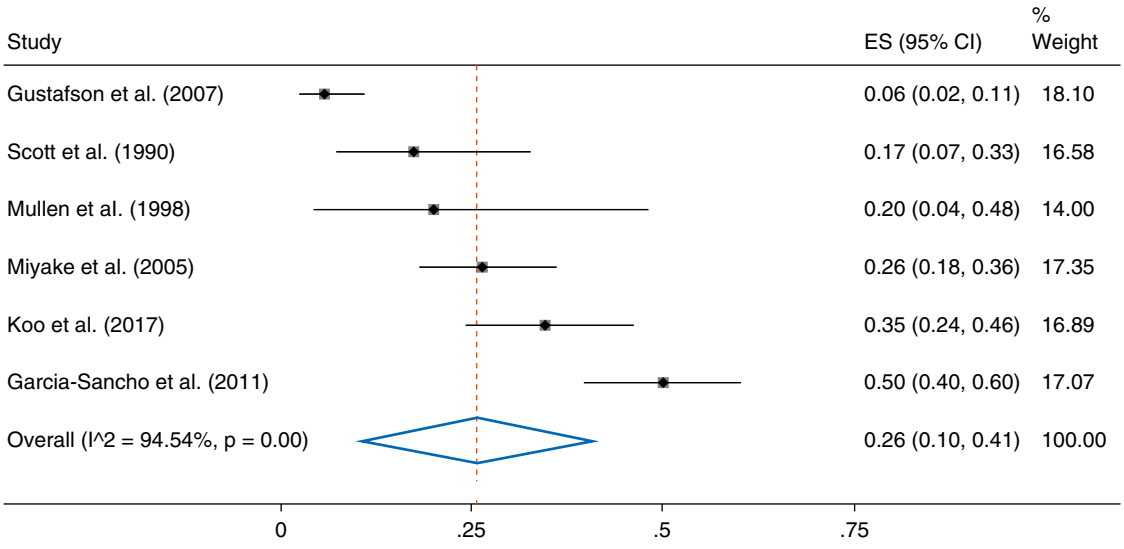


**Figure 4.** Idiopathic pulmonary fibrosis (IPF): population attributable fraction (PAF) from vapors, gas, dust, or fumes (VGDF). Forest plot of studies relevant to estimating the occupational contribution to IPF of VGDF (combined categories of exposure considered in the studies included). The estimated PAF, confidence interval (CI), and weighted contribution for each study are shown, as well as the calculated pooled estimate (red dashed line) and 95% CI. For IPF, the pooled PAF for VGDF is 26% (95% CI, 10–41%). ES = effect size.

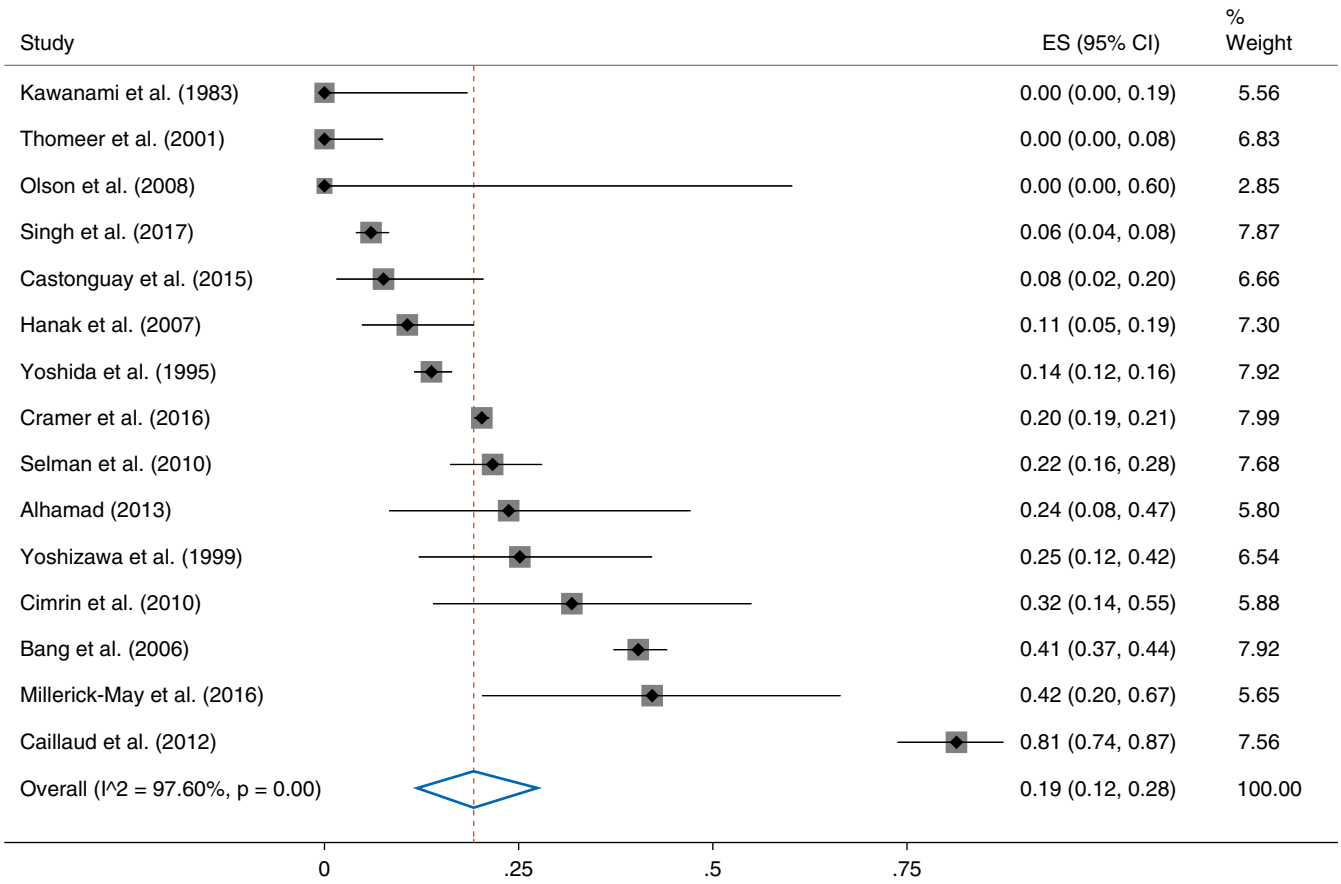


**Figure 5.** Hypersensitivity pneumonitis (HP): occupational burden. Forest plot of studies relevant to estimating the contribution of work exposures to HP. The occupational prevalence of HP, confidence interval (CI), and weighted contribution for each study are shown, as well as the calculated pooled estimate (red dashed line) and 95% CI. The pooled proportion of occupational HP among all HP cases is 19% (95% CI, 12–28%). ES = effect size.

with other studies that estimated occupational risk, we identified seven studies to use to estimate the occupational burden of sarcoidosis (Table 8) (181, 183, 184, 188–190, 193). The pooled estimated occupational proportion of sarcoidosis ranged from 0% to 54%, with a weighted metaproportion of 30% (95% CI, 17–45%).

## Occupational Burden of TB and CAP

Certain occupational groups are at increased risk for TB infection or bacterial CAP. The occupational burden of these infectious diseases, however, has been infrequently quantified (194–197). Searching back to 1990, we identified 9 silica-related and 17 healthcare worker (HCW)-related relevant studies for inclusion in this analysis (198–222) (Tables 9 and 10). We excluded studies that dealt exclusively with latent TB, did not use diagnostic criteria for TB, or were reviewed in previous analyses (and thus were not included in our estimates) (195, 223).

We considered TB in two distinct occupational risk groups: those exposed occupationally to silica and those exposed as HCWs. For TB among the silica exposed, three U.S. studies and six South African studies allowed estimation of an occupation-associated burden of disease (209–217). For the U.S. studies, the estimated burden ranged from 3.2% to 4.9%. For the South African studies using gold miner cohorts, the occupational burden was estimated by deriving an IRR for miners relative to national rates of disease; the median silica-associated burden was 2.3% (range, 0.8–7.9%) (Table 9). One other estimate of the occupational burden from an Iranian study, strikingly higher than all other studies (36%), was omitted because selection bias may have been present (224).

As shown in Table 10, we found little consistency in estimates of the occupational burden of TB in HCWs. In five studies, the incidence rate among HCWs was lower than that of the general population (200, 202, 203, 218, 219), yielding an estimated burden of zero. Among those with an appreciable burden (IRR $\geq$ 1), the occupational burden ranged from 0.1% (198) to 8.9% (198). In one of these studies (221), even though there was an increased TB IRR overall, this was accounted for by foreign-born HCWs, and work-acquired infection was confirmed in only a handful of cases. Based on all 17 HCW studies, the overall median estimate was 1.0% (range, 0–8.9%) (Table 10). A previous review of TB among HCWs (195) reported similar occupational burdens of disease among low– and high–TB incidence countries.

We identified 15 publications relevant to the occupational burden of CAP. Six were population-based case–control studies estimating CAP risk (225–230). Of these, the earlier of two overlapping publications from the same Spanish research group was

**Table 6.** Occupational Exposures in Pulmonary Alveolar Proteinosis

| First Author, Year, Location (Reference) | Exposure Measure | Cases (*N*) | Occupational Burden (%) |
|---|---|---|---|
| Davidson,1969, international (112) | Reported history | 139 | 50 |
| McEuen, 1978, USA (113) | Lung tissue particles | 37 | 35 |
| Rubin, 1980, Canada (114) | Reported history | 13 | 15 |
| Kariman, 1984, USA (115) | Reported history | 23 | 0 |
| Prakash, 1987, USA (116) | Reported history | 34 | 9 |
| Asamoto, 1995, Japan (117) | Reported history | 68 | 15 |
| Goldstein, 1998, USA (118) | Reported history | 24 | 50 |
| Kim, 1999, Korea (119) | Reported history | 10 | 40 |
| Briens, 2002, France, Belgium (120) | Questionnaire | 41 | 39 |
| Inoue, 2008, Japan (121) | Questionnaire | 199 | 26 |
| Fang, 2009, China (122) | Reported history | 11 | 18 |
| Xu, 2009, China (123) | Reported history | 241 | 8 |
| Byun, 2010, Korea (124) | Reported history | 38 | 0 |
| Bonella, 2011, Germany (125) | Questionnaire | 70 | 51 |
| Fang, 2012, China (126) | Reported history | 25 | 36 |
| Campo, 2013, Italy (127) | Reported history | 73 | 36 |
| Zhao, 2013, China (128) | Reported history | 30 | 67 |
| Fijołek, 2014, Poland (129) | Reported history | 17 | 24 |
| Ilkovich, 2014, Russia (130) | Reported history | 68 | 59 |
| Yang, 2014, China (131) | Reported history | 10 | 20 |
| Akasaka, 2015, Japan (132) | Reported history | 31 | 26 |
| Xiao, 2015, China (133) | Questionnaire | 45 | 38 |
| Bai, 2016, China (134) | Questionnaire | 101 | 50 |
| Deleanu, 2016, Romania (135) | Reported history | 20 | 20 |
| Hadda, 2016, India (136) | Reported history | 35 | 14 |
| Huang, 2016, China (137) | Reported history | 17 | 29 |
| Mo, 2016, China (138) | Reported history | 11 | 18 |
| Guo, 2017, China (139) | Reported history | 37 | 49 |
| Hwang, 2017, Korea (140) | Reported history | 71 | 48 |

*Definition of abbreviation*: USA = United States.
All studies are case series except four case–control studies (113, 126, 133, 158) and one national registry (121). "Reported history" refers to occupational or exposure history from the clinical record. Occupational burden is based on the prevalence among cases of occupations likely to involve inhalational exposures or inhalational exposures likely to be occupational. The pooled occupational burden was 29% (95% confidence interval, 21–37%).

excluded (225), as well as the earlier of two related publications from Canada (226). The four remaining case-referent studies (Table 11) yielded a median PAF of 10% (range, 3–45%) for the occupational burden of pneumonia.

We identified nine cohort studies focusing on specific exposures or a single industry (231–239). Seven estimated risk of pneumonia in welders or in individuals with metal fume exposure (231, 232, 235–239); two also estimated risk for inorganic dusts (231, 232). For metal fume/welding exposures, the median AF was 52.5% (range, 38–73%). Four studies considered risk associated with inorganic dust (231–234). The AF estimates from these studies varied widely (Table 11).

## Conclusions

This comprehensive literature review and analysis of nonmalignant respiratory disease demonstrates a substantial occupational burden for multiple respiratory conditions not typically considered potentially work related (Figure 6). The findings for asthma, COPD, and chronic bronchitis build on prior estimates and reinforce the validity of an occupational PAF in the 15–20% range. The occupational contribution to the burden of cases diagnosed as IPF, other interstitial lung diseases, HP and other noninfectious granulomatous diseases (including sarcoidosis), and selected respiratory infections has not been estimated previously using an in-depth literature review and data synthesis approach.

One limitation of this review is that we censored study eligibility for the purposes of data synthesis after December 2017. To address this potential shortcoming, after completing the main analyses, we performed a supplemental literature review covering January through September 2018, identifying three additional publications that would have met criteria for inclusion to estimate occupational burden, one each relevant to COPD, chronic bronchitis, and HP (240–242). All three studies' results were consistent with our original findings. A 20-year longitudinal follow-up study of 3,343 participants of the population-based European Community Respiratory Survey found that work exposures, assessed by JEM, increased the risk of developing COPD (240). The PAF for VGDF yielded by the data from this study was 14.1%, consistent with our estimate. A cross-sectional study of 5,539 Colombians reported increased risk of chronic bronchitis associated with self-reported VGDF exposure, yielding a PAF of 16.1% (242), also consistent with our findings. The final recent publication, a U.S. retrospective health claim–based study that estimated the incidence and prevalence of HP, found that 17.0% of HP cases had occupational exposure–associated International Classification of Diseases codes, also consistent with our findings (241).

Several other limitations of this in-depth literature review and data synthesis should be noted. The literature we identified was extremely heterogeneous and not amenable to a formal systematic review that could apply all of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria. Thus, we have avoided applying the label "systematic review" to this analysis. In particular, we made no attempt to formally grade publication quality, to apply methodologic restrictions on acceptability (beyond limiting the asthma analysis to prospective studies), or to weight results (beyond taking into account study size in pooled estimates). Study heterogeneity necessitated using differing approaches (e.g., PAF and prevalence) to estimate the occupational contribution to the burden of the various respiratory conditions.

Study heterogeneity also likely contributed to the wide range in the observed values for the estimated occupational burdens within the conditions we studied. To better assess this potential limitation, we also estimated all of the pooled burdens, excluding the highest and lowest values, as well as calculating the median rather than the pooled value. Reanalyses after excluding

**Table 7.** Occupational Associations with Hypersensitivity Pneumonitis

| First Author, Year, Location (Reference) | Study Type | Cases (*N*) | Disease Definition | Exposure/Job Information | Comments | Occupational Burden (%) |
|---|---|---|---|---|---|---|
| Kawanami, 1983, USA (168) | Case series | 18 | Clinical, radiographic, physiologic, and laboratory data | History, clinical data, and serologic testing in 13 patients | 72.2% environmental; 27.7% unknown cause | 0 |
| Yoshida, 1995, Japan (169) | Case series | 835 | Criteria of the Japan Research Committee on Diffuse Pulmonary Disease for Hypersensitivity Pneumonitis | History, clinical data, and serologic testing | 79.4% environmental; 6.8% unknown cause | 13.8 |
| Yoshizawa, 1999, Japan (170) | Case series | 36 | Clinical and imaging criteria | History, clinical data, and serologic testing | 61.4% environmental; 13.9% unknown cause, series limited to chronic HP | 25.3 |
| Thomeer, 2001, Belgium (171) | Multicenter disease registry | 47 | A set of clinical and imaging criteria; data from the nationwide electronic register | Not clearly stated | 76.6% environmental; 23.4% unknown cause | 0 |
| Bang, 2006, USA (172) | Death certificate date | 814 | Death certificate coding | Occupationally related ICD codes for causes>100% due to multiple coded causes of HP | 38.4% occupational; 55.6% unknown cause | 40.5 |
| Hanak, 2007, USA (173) | Case series from a single center | 85 | Clinical and imaging criteria from the Mayo Clinic database | History, clinical data, and serologic testing | 64.7% environmental; 24.7% unknown cause | 10.6 |
| Olson, 2008, USA (174) | Case series from a single center | 4 | Retrospective case review; only cases with acute exacerbation of fibrotic HP | History, clinical data, and serologic testing; biopsy confirmation | 50% environmental; 50% unknown cause | 0 |
| Selman, 2010, multicountry (166) | Prospective multicenter cohort study | 199 | Clinical and imaging data, supported by the experts' opinion | History, clinical data, and serologic testing | 76.9% environmental; 1.5% unknown cause | 21.6 |
| Cımrın, 2010, Turkey (175) | Review of published cases | 22 | Based on cases as defined in publications reviewed | Heterogeneous | 66.6% environmental; none of unknown cause | 33.3 |
| Caillaud, 2012, France (176) | Case series, multicenter | 139 | Clinical and imaging criteria | History, clinical data, and serologic testing | 18.7% environmental; none of unknown cause | 81.3 |
| Alhamad, 2013, Saudi Arabia (177) | Case series | 21 | A set of clinical and imaging criteria followed by expert review | Questionnaire | 42.9% environmental; 33.3% unknown cause | 23.8 |
| Castonguay, 2015, USA (178) | Case series | 40 | Clinical and imaging criteria | History, clinical data, and serologic testing; case overlap with Hanak *et al.*, 2007 (173) | 55% environmental; 37.5% unknown cause | 7.5 |
| Millerick-May, 2016, USA (179) | Case series | 19 | ATS guidelines for the diagnosis of ILD | History, clinical data, and serologic testing | 51.9% environmental; none of unknown cause | 42.1 |
| Singh, 2017, India (180) | Prospective registry | 513 | Diagnostic criteria, expert review | Questionnaire | 69.4% environmental; 24.8% unknown cause | 5.8 |
| Cramer, 2016 Denmark (167) | Retrospective cohort study | 6,920 | Cases identified from records in Danish National Patient Register | Data on occupation were provided by Statistics Denmark | OR, 1.55 (95% CI, 1.40–1.72); cases exposed = 46% | 20.2 |

*Definition of abbreviations*: ATS = American Thoracic Society; CI = confidence interval; HP = hypersensitivity pneumonitis; ICD = International Classification of Diseases; ILD = interstitial lung disease; OR = odds ratio; USA = United States.

Occupational burden is derived from the proportion of occupationally attributed cases in the series or, in the case of Cramer and colleagues (167), derived from the OR and proportion of exposed cases. The overall burden of occupationally attributed HP is 19% (95% CI, 12–28%).

**Table 8.** Occupational Proportion of Granulomatous Disease Diagnosed as Sarcoidosis

| First Author, Year, Location (Reference) | Study Type | Cases (*N*) | Disease Definition | Exposure/Job Information | Comments | Occupational Burden (%) |
|---|---|---|---|---|---|---|
| Fireman, 2003, Israel (190) | Case series | 47 | Tissue diagnosis with positive beryllium lymphocyte transformation test | Possible occupational exposure to beryllium | Case series from one outpatient clinic | 6.4 |
| Kucera, 2003, USA (185) | Sibling case–control | 303 | Clinicoradiographic presentation consistent with sarcoidosis | Structured occupational history questionnaire | ACCESS questionnaire for occupational history | 37 |
| Barnard, 2005, USA (183) | Case–control | 706 | Tissue diagnosis with negative beryllium lymphocyte proliferation test | Structured occupational history questionnaire | Multicenter study, ACCESS questionnaire for occupational history | 51.6 |
| Müller-Quernheim, 2006, Germany (189) | Case series | 84 | Clinicoradiographic presentation consistent with sarcoidosis and positive beryllium lymphocyte proliferation test | Possible occupational exposure to beryllium, determined by questionnaire | Prospective study over 7 yr | 40.4 |
| Ribeiro, 2011, Canada (188) | Case series | 121 | Clinicoradiographic presentation consistent with sarcoidosis and positive beryllium lymphocyte proliferation test | Possible occupational exposure to beryllium, determined by questionnaire | No positive beryllium lymphocyte proliferation test results | 0 |
| Cherry, 2015, Canada (193) | Case-referent | 63 | Medical record review, cases with diagnosis of sarcoidosis, referents with other chronic lung disease | Patient interview, employment in an industry with possible exposure to beryllium | Chronic beryllium disease diagnosis based on Glu69 status | 46 |
| Liu, 2016, USA (181) | Population-based mortality | 3,393 | Sarcoidosis death based on cause of death listed on death certificate | Usual occupation on death certificate | Large national dataset | 53.8 |

*Definition of abbreviations*: ACCESS = A Case-Control Etiologic Study of Sarcoidosis; USA = United States.
Occupational burden is derived from the proportion of occupationally attributed cases in series or derived from a reported odds ratio and proportion of exposed cases. The overall burden of occupationally attributed sarcoidosis is 30% (95% confidence interval, 17–45%).

**Table 9.** Tuberculosis among Silica-exposed Workers

| First Author, Year, Location (Reference) | Study Type | TB Definition/Diagnosis | Exposure/Job Information | Population Cases (*n*)/Control or Total Population (*N*) | Risk Estimates (95% CI when available) | Occupational Burden (%) |
|---|---|---|---|---|---|---|
| Rosenman, 1996, USA (209) | Case–control | Bacteriological or reporting of treatment | SIC and SOC codes used as proxy for exposures | HIV-positive and foreign-born individuals excluded; 149 cases from New Jersey TB Register, 209 control subjects from previous cancer studies | Adjusted OR for silica industries: 1.6 (0.7–3.8) | 4.9 |
| Chen, 1997, USA (210) | Case–control | Death certificate data from NOMS database | Silica-exposed workers | 8,740 cases: 2% intermediate, 14% high; 83,338 control subjects | $OR_{intermed}$: 1.1 (0.8–1.5)<br>$OR_{high}$: 1.3 (1.1–1.5) | Intermediate: 0.2<br>High: 3.2 |
| Calvert, 2003, USA (211) | Case–control | Death certificate data from NOMS database | Subjects assigned to a qualitative silica exposure category | 6,570 cases: medium (11.7%), high (9.5%), super high (0.6%), 32,843 TB control subjects | $OR_{med}$: 1.3 (1.2–1.5)<br>$OR_{high}$: 1.6 (1.5–1.8)<br>$OR_{super\ high}$: 2.5 (1.7–3.7) | Medium: 3.04<br>High: 3.4<br>Super high: 3.6 |
| Kleinschmidt, 1997, South Africa (212) | Cohort | Bacteriological and clinical diagnosis | Gold miners from a single mine, followed from 1975 to 1996 | 449 cases (total cohort = 4,976 gold miners) | IRR, 2.5 | 2.3 |
| Murray, 1999, South Africa (213) | Cohort | Culture-positive sputum | Gold miners from four mines | 376 cases (total cohort = 28,522 gold miners) | IRR, 4.2 | 4.8 |
| Churchyard, 2000, South Africa (214) | Cohort | Bacteriological and clinical diagnosis | Gold miners at a single mine followed from 1993 to 1997 | 2,893 cases | IRR, 7.5 | 7.9 |
| Sonnenberg, 2005, South Africa (215) | Cohort | Culture-positive "probable TB" = score of radiography, sputum, tuberculin, histology, and trial | Gold miners from four mines followed from 1991 to 1997 | 747 cases (total cohort = 23,874) | IRR, 3.9 | 3.8 |
| Glynn, 2008, South Africa (216) | Cohort | Culture and clinical findings | Gold miners from four mines followed from 1991 to 2004 | 620 new cases among 7,583 participants | IRR, 4.3 | 2.0 |
| van Halsema, 2012, South Africa (217) | Cohort | Culture | Gold miners from two mines followed from 2002 to 2008 | 4,268 TB/19,476 (mine A)<br>1,472 TB/8,414 (mine B) | IRR, 3.1 (mine A)<br>IRR, 2.5 (mine B) | Mine A: 1.1<br>Mine B: 0.8 |

*Definition of abbreviations*: CI = confidence interval; IRR = incidence rate ratio; NOMS = National Occupational Mortality Surveillance; OR = odds ratio; SIC = Standard Industrial Classification; SOC = Standard Occupational Classification; TB = tuberculosis; USA = United States.

Except for publications providing an OR, the occupational burden is estimated from an IRR derived from World Bank and World Health Organization data for the silica-exposed labor force and national TB rates. The median silica-associated burden of TB was 2.3% (range, 0.8–7.9%).

**Table 10.** Tuberculosis among Healthcare Workers

| First Author, Year, Location (Reference) | Study Type | TB Definition/Diagnosis | Exposure/Job Information | Cases (*n*)/Control or Total Population (*N*) | Risk Estimate | Occupational Burden (%) |
|---|---|---|---|---|---|---|
| Rosenman, 1996, USA (209) | Case–control | Bacteriological or treatment reporting | SIC and SOC codes used as proxy for exposures | HIV-positive, foreign-born cases excluded; 149 cases from TB registry; 290 cancer referents | OR, 2.8 (95% CI, 1.4–5.7) | 8.2 |
| Raitio, 2000, Finland (203) | National register review | Bacteriologically, histologically, and/or clinically | All HCWs assessed for occupational TB, extracted from national register | 658 cases between 1966 and 1995 | IRR, 0.67 | 0 |
| Laraqui, 2001, Morocco (218) | Cross-sectional | Case notification | All HCWs notified by health services between 1994 and 1997 | 130 cases among 152,447 HCWs | IRR, 0.72 | 0 |
| Eyob, 2002, Ethiopia (204) | Cohort | Sputum culture or clinical or radiological findings | HCWs at a specialist TB center | 24 cases among 175 HCWs | IRR, 7.2* | 0.4 |
| Jiamjarasrangsi, 2005, Thailand (198) | Cohort | TB diagnoses in medical records database | Thai HCWs observed at a single hospital | 78 cases among 3,894 HCWs | IRR, 3.5 | 0.1 |
| Tam, 2006, Hong Kong (219) | National registry records review | Not stated | Surveillance data of occupational TB reported to the Labor Department | 141 cases among 57,869 HCWs over 5 yr | IRR, 0.5 | 0 |
| de Vries, 2006, Netherlands (200) | Records review | Restriction fragment length polymorphism typing (DNA fingerprinting) | Cases ''working in the healthcare/social-welfare sector'' from a national TB registry | 94 cases among 126,500 HCWs | IRR, 0.8 | 0 |
| Ong, 2006, USA (201) | Cohort study | TB reported to San Francisco Department of Public Health | All cases of TB reported over multiple years | 33 cases among HCWs among 2,510 cases reported | IRR, 1.2 | 1.0 |
| Pazin-Filho, 2008, Brazil (205) | Database review | Clinical, sputum | HCWs at a university hospital | 21 cases among HCWs | IRR, 2.6* nurse technicians | 1.4 |
| Roche, 2008, Australia (199) | Database review | Laboratory, clinical diagnosis of TB | HCWs recorded in National Notifiable Diseases Surveillance System | 65 cases among HCWs reported in 2006 | IRR, 2.1 | 4.0 |
| Costa, 2011, Portugal (206) | Cohort | Clinical, bacteriological, radiological | HCWs at the São João Hospital followed from 2005 to 2010 | 62 cases among 6,112 HCWs | IRR, 3.2 | 4.4 |
| Lambert, 2012, USA (202) | Database review | Review of National TB Surveillance System records | TB cases reported to the CDC | 6,049 cases among HCWs among the 200,774 cases | IRR, 0.8 | 0 |
| Tudor, 2014, South Africa (207) | Retrospective cohort | Based on records captured | HCWs in three hospitals with specialist MDR-TB wards | 112 cases among 1,313 HCW records reviewed | IRR, 2.0* | 1.3 |
| Toms, 2015, Australia (220) | National database review | National Notifiable Diseases Surveillance System | Working in a healthcare setting in the past 12 mo | 24 cases among HCWs in 2013 | IRR, 1.1 | 0.1 |
| Klimuk, 2014, Belarus (208) | Retrospective record review | Sputum smear, culture, drug susceptibility testing | Review of records from TB healthcare facilities | 116 cases among 5,441 HCWs | IRR, 5.4 | 8.9 |
| O'Hara, 2017, South Africa (222) | National database review | Laboratory-confirmed diagnosis | All HCWs in a particular province in South Africa | 2,677 cases of TB among 32,039 HCWs over 11-yr period | IRR, 1.14* | 1.2 |
| Davidson, 2017, UK (221) | National TB surveillance | Notified TB cases from surveillance database | HCW work information extracted from database | 2,320 cases of HCW TB between 2009 and 2013 | IRR, 1.5* | 2.8 |

*Definition of abbreviations*: CI = confidence interval; HCW = healthcare worker; IRR = incidence rate ratio; MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; SIC = Standard Industrial Classification; SOC = Standard Occupational Classification; TB = tuberculosis; UK = United Kingdom; USA = United States.

Except for one publication providing an OR, the occupational burden is estimated from an IRR either reported or derived from World Bank and World Health Organization data for the HCW labor force and national TB rates. The median HCW-associated burden of TB was 1.0% (range, 0.8–9%).

*Author-reported IRR.

**Table 11.** Studies Used to Calculate the Occupational Population Attributable Fraction and Attributable Fraction in Community-acquired Pneumonia

| First Author, Year, Location (Reference) | Type of Study | Population/Cases/Control Subjects | Pneumonia Type/Definition | Exposure Information | PAF or AF (%)* |
|---|---|---|---|---|---|
| Occupational PAF of pneumonia | | | | | |
| Farr, 2000, UK (227) | Case–control | 175 cases from British Thoracic Society study of patients with community-acquired pneumonia; 385 control subjects | Acute respiratory infiltrate; *Mycoplasma* excluded; 70% with streptococcal pneumonia confirmation | Self-reported dusty occupation (OR, 1.71) | 16 |
| Palmer, 2003, UK (228) | Case–control | 525 cases, 1,222 referents aged 20–64 yr; 158 lobar; 142 segmental; 225 bronchopneumonia | New/worse respiratory infection, new chest radiograph opacity, hospital admission | Self-reported metal fumes in prior year; OR, 1.6, all; OR, 1.8, lobar pneumonia | 3, 4 |
| Neupane, 2010, Canada (230) | Case–control | 365 cases of pneumonia; 494 control subjects | Admission to hospital for pneumonia, temperature >38°C, new opacity | Self-reported exposure to VGDF (OR, 5.78) | 45 |
| Almirall, 2015, Spain (229) | Case–control | 1,336 cases of pneumonia; 1,326 control subjects | Acute respiratory illness, new radiographic findings, antibiotics | Self-reported exposure to dust (OR, 1.7) | 3 |
| Occupational AF of pneumonia in specific cohorts | | | | | |
| Beaumont, 1980, USA (235) | Cohort mortality | 8,679 metal trades union; 3,247 welders | All pneumonia | Job classification based on union records | 41 |
| Newhouse, 1985, UK (236) | Cohort mortality | 1,027 welders at a shipyard | All pneumonia | Personnel records from shipyard: job title, tasks; SMR for pneumonia, 269 | 46 |
| Coggon, 1994, UK (237) | Cohort mortality | Male welders England and Wales, 1979–1980 and 1982–1999; 55 pneumonia deaths | Lobar pneumonia | OPCS; welders PMR, 255 | 62 |
| Graham, 2004, USA (233) | Cohort mortality | 5,408 Vermont granite workers; 2,539 deceased, determined by death certificates | All pneumonia, ICD codes | Employment records SMR, <100 | 0 |
| Veiga, 2006, Brazil (234) | Cohort mortality | 2,856 coal miners | All pneumonia | Employment records SMR for pneumonia in miners, 263 | 62 |
| Palmer, 2009, UK (238) | Population mortality | Occupations with exposure to metal fumes, aged 18–64 yr | Lobar pneumonia, ICD-9 codes | OPCS; welders PMR, 242 (166–342) | 59 |
| Wong, 2010 Canada (239) | Retrospective chart review | 1,768 cases of pneumococcal disease; 863 cases aged 18–65 yr; 18 cases in welders | Invasive pneumococcal disease, positive culture results (blood, CSF, other) | Self-reported current occupation OR for welders, 2.7 | 63 |
| Koh, 2011, Korea (231) | Retrospective cohort | Mineral dust– and metal fume–exposed workers: 365 cases (59 in foundry workers); control group (noise-only exposure), 927 cases | All pneumonia (viral, bacterial, fungal), >1-d hospitalization; SAR for pneumonia | National Health Insurance claims, employer, SIC codes; foundry workers SAR, 1.64 (men) | 38 |
| Torén, 2011, Sweden (232) | Prospective cohort of construction workers | 183,194 construction workers aged 20–64 yr; followed for 32 yr; 145 deaths resulting from pneumonia, 62 deaths resulting from lobar pneumonia | Mortality of all infectious pneumonia, lobar pneumonia, pneumococcal pneumonia; viral and fungal pneumonia excluded; Swedish Cause of Death Register | Self-reported job title, JEM<br>Relative risk for all and lobar pneumonias<br>Inorganic dusts<br>All pneumonia, 1.87<br>Lobar pneumonia, 3.37<br>Metal fumes<br>All pneumonia, 2.31<br>Lobar pneumonia, 3.67 | <br><br><br>47<br>70<br><br>57<br>73 |

*Definition of abbreviations*: AF = attributable fraction; CSF = cerebrospinal fluid; ICD = International Classification of Diseases; JEM = job exposure matrix; OPCS = Office of Population Censuses and Surveys; OR = odds ratio; PAF = population attributable fraction; PMR = proportionate mortality ratio; SAR = standardized admission ratio; SIC = Standard Industrial Classification; SMR = standardized mortality ratio; UK = United Kingdom; USA = United States; VGDF = vapors, gas, dust, or fumes.

The median PAF among four population-based studies (top rows) is 10% (range, 3–45%); the median AF within cohorts is 52.5% (range, 38–73%).

*PAF for "Occupational PAF of pneumonia" and AF for "Occupational AF of pneumonia in specific cohorts".

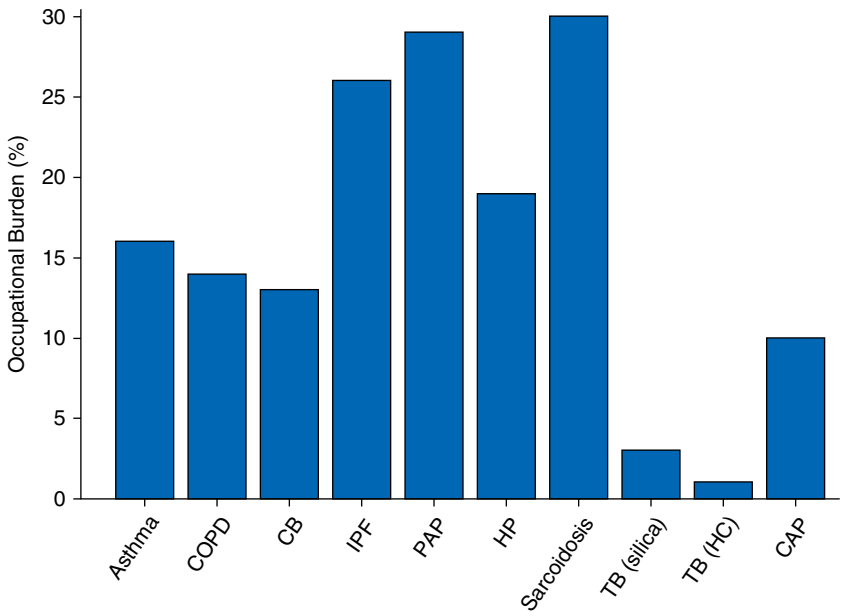


**Figure 6.** Summary of the occupational burden of nonmalignant respiratory disease, by condition: the estimated contribution of work exposures to the burden of disease across multiple nonmalignant respiratory conditions. The occupational population attributable fractions for asthma (16%), chronic obstructive pulmonary disease (COPD) (14%), chronic bronchitis (CB) (13%), idiopathic pulmonary fibrosis (IPF) (26%), and community-acquired pneumonia (CAP) (10%) are shown. The occupational burden estimates for pulmonary alveolar proteinosis (PAP) (29%), hypersensitivity pneumonitis (HP) (19%), sarcoid (30%), silica-associated tuberculosis (TB) (2.3%), and healthcare worker–associated TB (HC) (1.0%) are based on mixed methods.

outlying values yielded point estimates that were similar to the original pooled estimates, as were the median values, neither of which were consistently lower or higher than the initial estimates (data not shown).

Across conditions, a differential in burden estimates is biologically plausible, consistent with differing potencies of risk depending on the nature of the exposure and the pathogenesis of the disease in question. It would be speculative, however, to make causal inferences from these findings, precisely because of the within- and across-condition variability that characterizes this literature.

Yet another limitation of this analysis is that it lacks data that might serve to estimate disability-adjusted life-years lost, a metric that could provide more quantitative assessment of the health impact of different work exposures and comparison across populations. Also of note, this analysis does not include classic pneumoconioses such as silicosis and asbestosis. These are conditions for which the occupational contribution is essentially 100%, obviating the need for an analysis of the estimated burden of those diseases. The pneumoconioses remain important, underrecognized global health problems associated with considerable morbidity and mortality (243–247).

This assessment of the occupational burden of nonmalignant respiratory disease has clinical, research, and ultimately policy implications. There is a pressing need to improve clinical recognition and widen public health awareness of the contribution of occupational factors across a range of nonmalignant respiratory diseases. Greater attention should be given to reducing this occupational disease burden by identifying and implementing effective preventive interventions. In that light, the importance of preventing these diseases needs to be recognized. Policy makers, especially those who set regulatory standards and oversee their enforcement, should reassess current protections for workers around the world who are exposed to recognized hazardous inhalational exposures. ■

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