

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

Overview

Key Conclusions

Introduction

Methods

Occupational Burden of Asthma Incidence

Occupational Burden of COPD and Chronic Bronchitis

Occupational Burden of IPF

Occupational Burden of PAP and Other Interstitial Lung Diseases

Occupational Burden of HP (Extrinsic Allergic Alveolitis) and Other

Granulomatous Lung Diseases, Including Sarcoidosis

Occupational Burden of TB and CAP Conclusions

ORCID IDs: 0000-0001-9043-175X (P.D.B.); 0000-0002-6340-9300 (I.A.-M.); 0000-0002-2246-7002 (J.R.B.); 0000-0002-5422-9199 (K.J.C.); 0000-0001-5941-090X (D.F.); 0000-0002-4846-7828 (D.M.); 0000-0001-8180-1018 (N.M.); 0000-0002-2318-4004 (R.N.N.); 0000-0002-7415-258X (C.J.R.); 0000-0002-2043-7571 (T.S.); 0000-0001-8509-7603 (K.T.); 0000-0003-0991-6237 (D.V.); 0000-0001-6486-6725 (C.A.R.).

®You may print one copy of this document at no charge. However, if you require more than one copy, you must place a reprint order. Domestic reprint orders: amy.schrivier@sheridan.com; international reprint orders: louisa.mott@springer.com.

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.

Correspondence and requests for reprints should be addressed to Paul D. Blanc, M.D., M.S.P.H., University of California, 350 Parnassus Avenue, Suite 609, San Francisco, CA 94143. E-mail: paul.blanc@ucsf.edu.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 199, Iss 11, pp 1312–1334, Jun 1, 2019

Copyright © 2019 by the American Thoracic Society

DOI: 10.1164/rccm.201904-0717ST

Internet address: www.atsjournals.org

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) 286 females (6,253)	Exposure to high-risk substances by JEM	14 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.

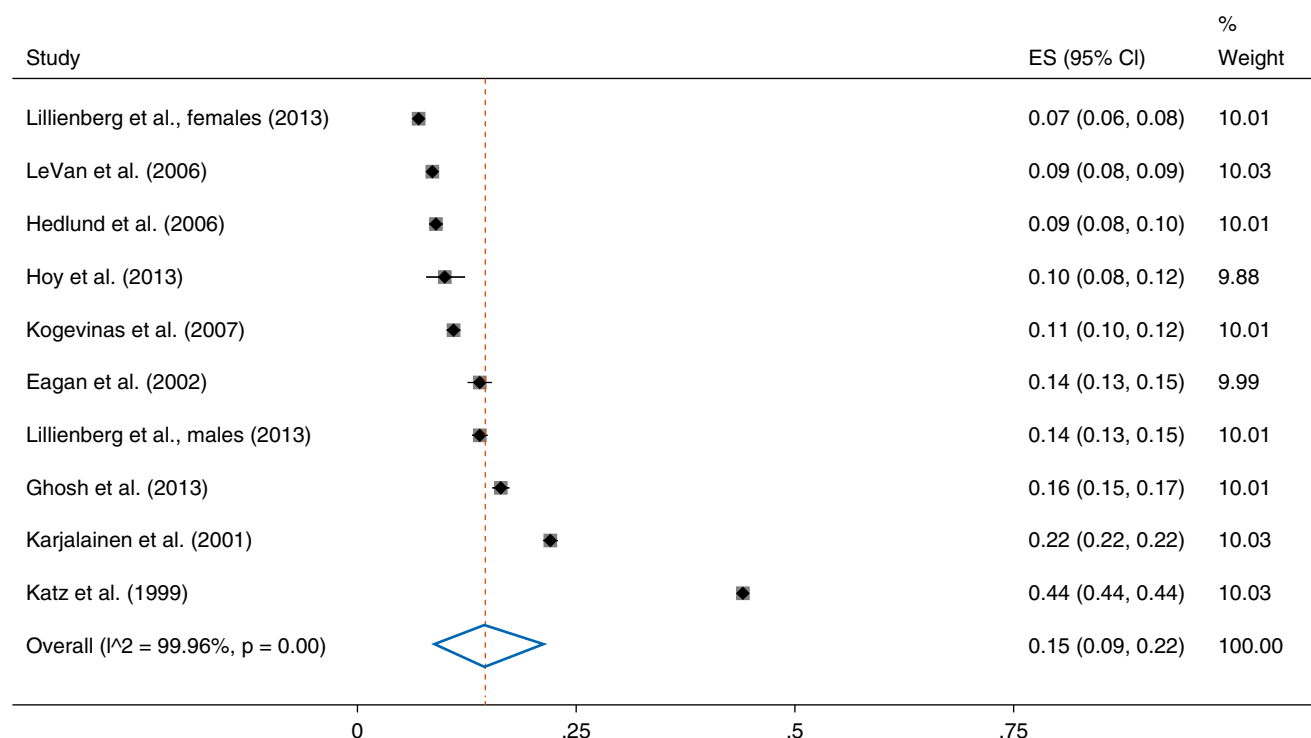


Figure 1. Asthma: population attributable fraction (PAF). Forest plot of studies relevant to estimating the occupational contribution to asthma. The estimated PAF, confidence interval (CI), and weighted contribution for each study, as well as the calculated pooled estimate (red dashed line) and 95% CI, 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 FEV₁ 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 (M)	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 (Vlaagtwedde-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
Würtl, 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
Toren, 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.

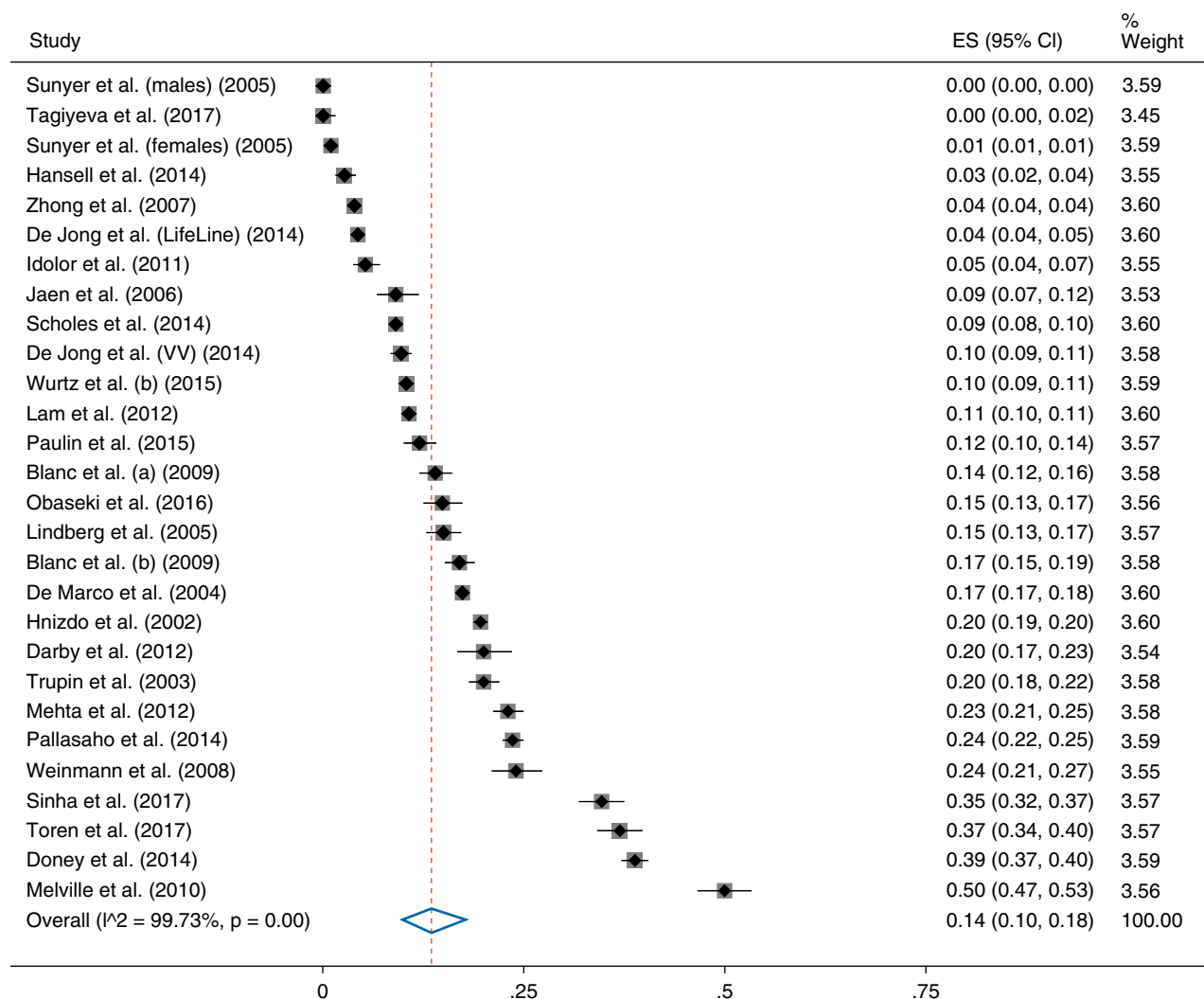


Figure 2. Chronic obstructive pulmonary disease (COPD): population attributable fraction (PAF). Forest plot of studies relevant to estimating the occupational contribution to COPD. The estimated PAF, confidence interval (CI), and weighted contribution for each study are shown, as well as the calculated 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 (%)
Montnémy, 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

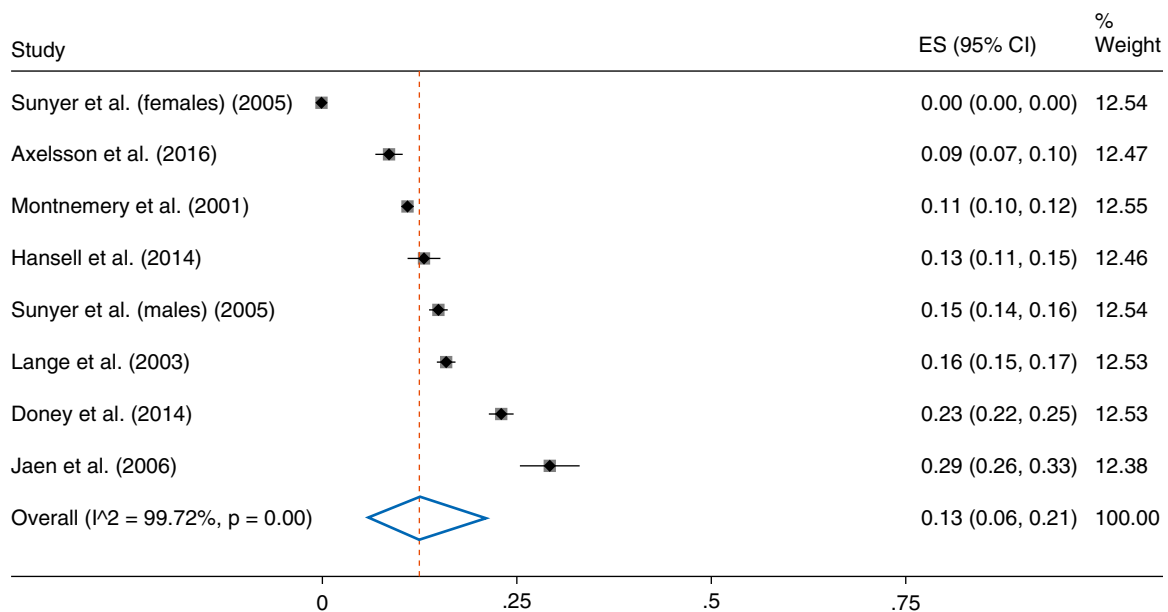


Figure 3. Chronic bronchitis: population attributable fraction (PAF). Forest plot of studies relevant to estimating the occupational contribution to chronic bronchitis. The estimated PAF, confidence interval (CI), and weighted contribution for each study are shown, as well as the calculated pooled estimate (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) Hubbard, 1996, UK (79)	40 218	Clinical, CXR, PFT Clinical, CXR, CT, PFT	1.3 (0.8–2.0) NA	11.0 (2.3–52.4) 1.7 (1.1–2.7)	2.9 (0.9–9.9) 1.7 (1.0–2.9)	10.9 (1.2–96) NA	1.6 (0.5–4.8) NA	17 NA	12 10	10 6	12 NA	5 NA
	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
Paolucci, 2013, Italy (92)	65	Clinical, CT	NA	2.8 (1.1–7.2)	1.1 (0.4–3.3) (soft wood) 0.9 (0.3–2.8) (hard wood)	NA	2.0 (0.9–4.4)	NA	9	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 Paolucci 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

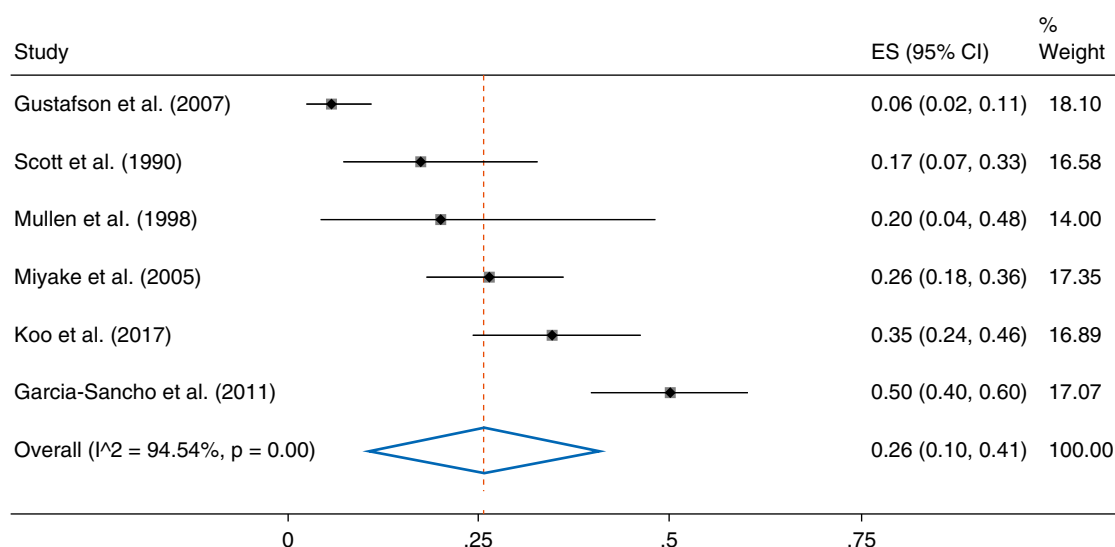


Figure 4. Idiopathic pulmonary fibrosis (IPF): population attributable fraction (PAF) from vapors, gas, dust, or fumes (VGDF). Forest plot of studies relevant to estimating the occupational contribution to IPF of VGDF (combined categories of exposure considered in the studies included). The estimated 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.

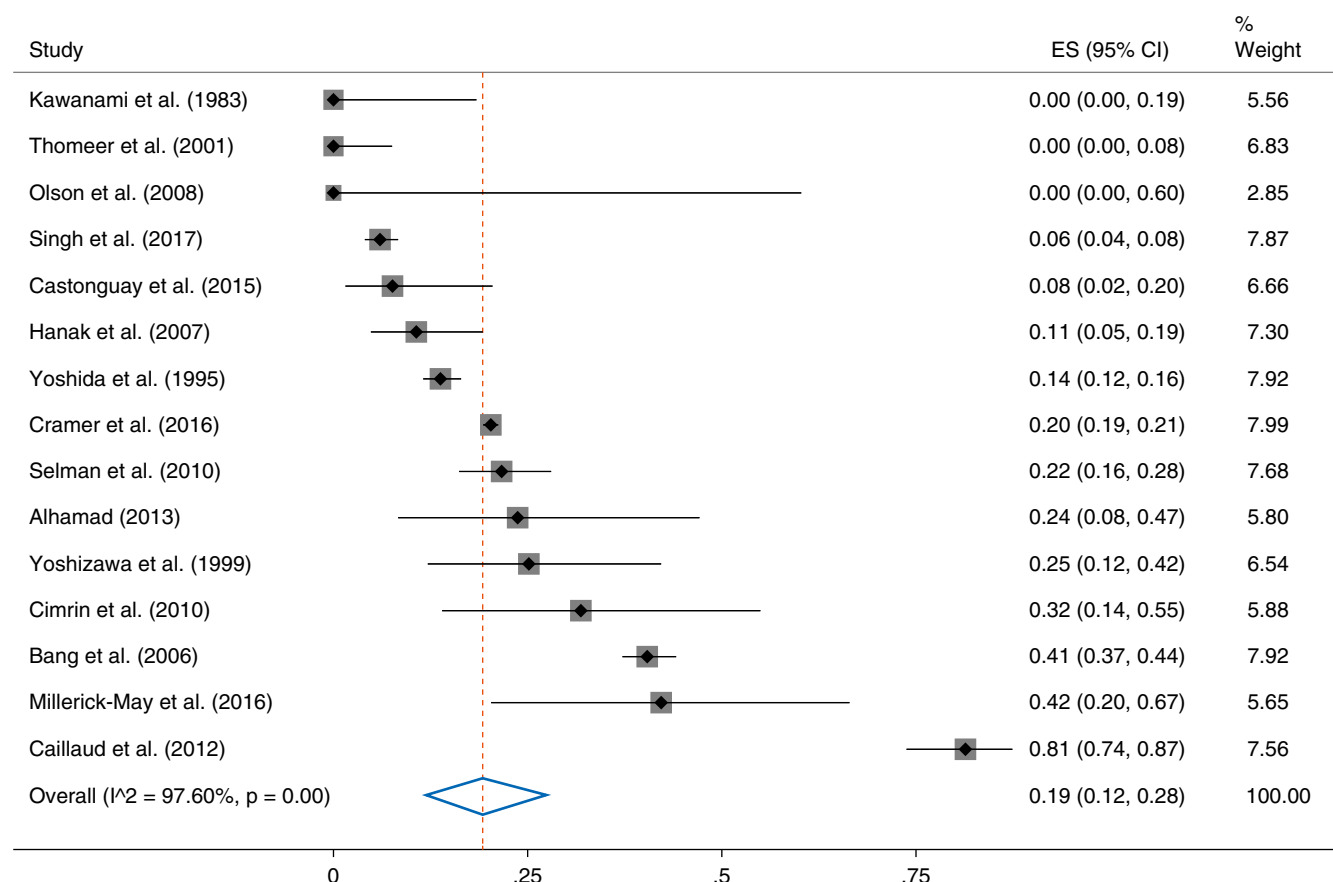


Figure 5. Hypersensitivity pneumonitis (HP): occupational burden. Forest plot of studies relevant to estimating the contribution of work exposures to HP. The occupational prevalence of HP, confidence interval (CI), and weighted contribution for each study are shown, as well as the calculated pooled estimate (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 metaprevalence 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
Fijolek, 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
Cimrin, 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 _{intermediate} : 1.1 (0.8–1.5) OR _{high} : 1.3 (1.1–1.5)	Intermediate: 0.2 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) OR _{high} : 1.6 (1.5–1.8) OR _{super high} : 2.5 (1.7–3.7)	Medium: 3.04 High: 3.4 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 findings	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) 1,472 TB/8,414 (mine B)	IRR, 3.1 (mine A) IRR, 2.5 (mine B)	Mine A: 1.1 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
Jiamjarasrangi, 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; <i>Mycoplasma</i> 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 Relative risk for all and lobar pneumonias Inorganic dusts All pneumonia, 1.87 Lobar pneumonia, 3.37 Metal fumes All pneumonia, 2.31 Lobar pneumonia, 3.67	47 70 57 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”.

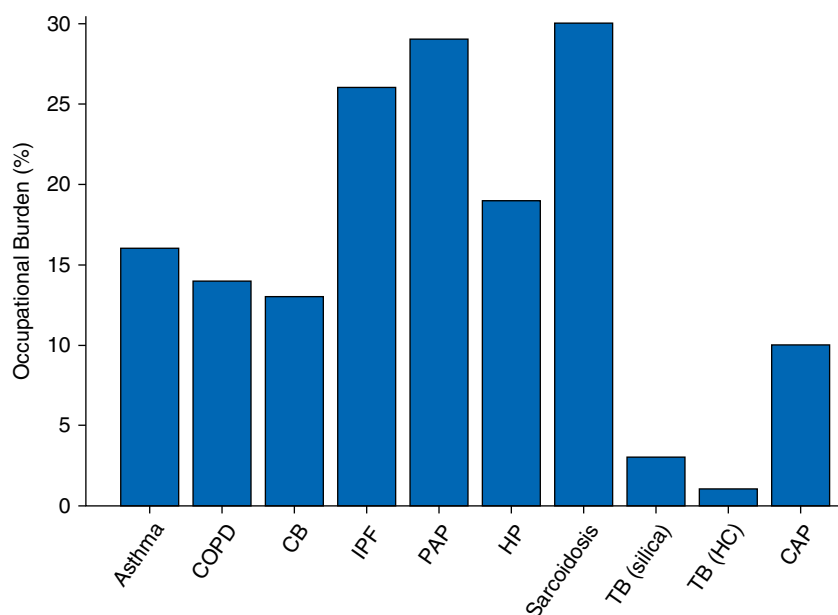


Figure 6. Summary of the occupational burden of nonmalignant respiratory disease, by condition: the estimated contribution of work exposures to the burden of disease across multiple nonmalignant respiratory conditions. The occupational population attributable fractions for asthma (16%), chronic obstructive 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. ■

This official statement was prepared by an *ad hoc* task force representing the American Thoracic Society and the European Respiratory Society.

Members of the task force are as follows:

PAUL D. BLANC, M.D., M.S.P.H. (*Co-Chair*)¹
 CARRIE A. REDLICH, M.D., M.P.H. (*Co-Chair*)²
 ISABELLA ANNESI-MAESANO, M.D., Ph.D.³
 JOHN R. BALMES, M.D.¹
 KRISTIN J. CUMMINGS, M.D., M.P.H.⁴
 DAVID FISHWICK, M.D.⁵
 DAVID MIEDINGER, M.D., Ph.D.⁶
 NICOLA MURGIA, M.D., Ph.D.⁷
 RAJEN N. NAIDOO, M.D., Ph.D.⁸
 CARL J. REYNOLDS, M.D.⁹
 TORBEN SIGSGAARD, M.D., Ph.D.¹⁰
 KJELL TORÉN, M.D., Ph.D.¹¹
 DENIS VINNIKOV, M.D., Ph.D.^{12,13}

¹University of California San Francisco, San Francisco, California; ²Yale University, New Haven, Connecticut; ³Paris, France; ⁴National Institute for Occupational Safety and Health, Morgantown, West Virginia; ⁵Centre for Workplace Health, Health and Safety Laboratory, Buxton, United Kingdom; ⁶University of Basel, Basel, Switzerland; ⁷University of Perugia, Perugia, Italy; ⁸University of KwaZulu-Natal, Durban, South Africa; ⁹Imperial College School of Medicine, London, United Kingdom; ¹⁰Aarhus University, Aarhus, Denmark; ¹¹University of Gothenburg, Gothenburg, Sweden; ¹²Al-Farabi Kazakh National University, Almaty, Kazakhstan; and

¹³National Research Tomsk State University, Tomsk, Russian Federation

Author Disclosures: J.R.B. was a physician member of the California Air Resources Board. D.M. serves as Chief Occupational Health Officer and owns shares and stock options for F. Hoffmann-La Roche Ltd. N.M. received nonfinancial support from AlkAbello, GlaxoSmithKline, and Teva. P.D.B., C.A.R., I.A.-M., K.J.C., D.F., R.N.N., C.J.R., T.S., K.T., and D.V. reported no relationships with relevant commercial interests.

References

1. Driscoll T, Nelson DI, Steenland K, Leigh J, Concha-Barrientos M, Fingerhut M, *et al.* The global burden of non-malignant respiratory disease due to occupational airborne exposures. *Am J Ind Med* 2005;48:432–445.
2. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, *et al.*; Environmental and Occupational Health Assembly, American Thoracic Society. American Thoracic Society statement: occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003;167:787–797.
3. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, *et al.*; Committee on Nonsmoking COPD, Environmental and Occupational Health Assembly. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;182:693–718.
4. Henneberger PK, Redlich CA, Callahan DB, Harber P, Lemièrre C, Martin J, *et al.*; ATS Ad Hoc Committee on Work-Exacerbated Asthma. An official American Thoracic Society statement: work-exacerbated asthma. *Am J Respir Crit Care Med* 2011;184:368–378.
5. Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? *Proc Am Thorac Soc* 2006;3:293–298.
6. Reynolds CJ, Blanc P. Organising pneumonia and other uncommon interstitial disorders. In: Taylor AN, Cullinan P, Blanc P, Pickering A, editors. *Parkes' occupational lung disorders*, 4th ed. Boca Raton, FL: CRC Press; 2017. pp. 317–330.
7. Quirce S, Vandenplas O, Campo P, Cruz MJ, de Blay F, Koschel D, *et al.* Occupational hypersensitivity pneumonitis: an EAACI position paper. *Allergy* 2016;71:765–779.
8. Balmes JR, Abraham JL, Dweik RA, Fireman E, Fontenot AP, Maier LA, *et al.*; ATS Ad Hoc Committee on Beryllium Sensitivity and Chronic Beryllium Disease. An official American Thoracic Society statement: diagnosis and management of beryllium sensitivity and chronic beryllium disease. *Am J Respir Crit Care Med* 2014;190:e34–e59.
9. Ling D, Menzies D. Occupation-related respiratory infections revisited. *Infect Dis Clin North Am* 2010;24:655–680.
10. Driscoll T, Nelson DI, Steenland K, Leigh J, Concha-Barrientos M, Fingerhut M, *et al.* The global burden of disease due to occupational carcinogens. *Am J Ind Med* 2005;48:419–431.
11. De Matteis S, Consonni D, Bertazzi PA. Exposure to occupational carcinogens and lung cancer risk: evolution of epidemiological estimates of attributable fraction. *Acta Biomed* 2008;79:34–42.
12. Hutchings S, Rushton L. Estimating the burden of occupational cancer: assessing bias and uncertainty. *Occup Environ Med* 2017;74:604–611.
13. Mazitova NN. Occupational factors and chronic obstructive pulmonary disease: a meta-analysis [in Russian]. *Fundam Res* 2011;9:588–592.
14. Omland O, Würtz ET, Aasen TB, Blanc P, Brisman JB, Miller MR, *et al.* Occupational chronic obstructive pulmonary disease: a systematic literature review. *Scand J Work Environ Health* 2014;40:19–35.
15. Blanc PD, Torén K. Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update. *Int J Tuberc Lung Dis* 2007;11:251–257.
16. Alif SM, Dharmage SC, Bowatte G, Karahalios A, Benke G, Dennekamp M, *et al.* Occupational exposure and risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Expert Rev Respir Med* 2016;10:861–872.
17. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, *et al.*; GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017;5:691–706.
18. Ryu JY, Sunwoo YE, Lee SY, Lee CK, Kim JH, Lee JT, *et al.* Chronic obstructive pulmonary disease (COPD) and vapors, gases, dusts, or fumes (VGDF): a meta-analysis. *COPD* 2015;12:374–380.
19. Fishwick D, Sen D, Barber C, Bradshaw L, Robinson E, Sumner J; COPD Standard Collaboration Group. Occupational chronic obstructive pulmonary disease: a standard of care. *Occup Med (Lond)* 2015;65:270–282.
20. Torén K, Blanc PD. Asthma caused by occupational exposures is common: a systematic analysis of estimates of the population-attributable fraction. *BMC Pulm Med* 2009;9:7.
21. World Health Organization (WHO). WHO global health workforce statistics [accessed 2018 Nov 9]. Available from: <http://www.who.int/hrh/statistics/hwfstats/en/>.
22. World Health Organization (WHO). Tuberculosis data [accessed 2018 Nov 9]. Available from: <http://www.who.int/tb/data/en/>.
23. World Bank. DataBank: world development indicators [accessed 2018 Nov 9]. Available from: <http://databank.worldbank.org/data/reports.aspx?source=2&series=SH.TBS.INCD&country=ZAF>.
24. Baur X, Sigsgaard T, Aasen TB, Burge PS, Heederik D, Henneberger P, *et al.*; ERS Task Force on the Management of Work-related Asthma. Guidelines for the management of work-related asthma. *Eur Respir J* 2012;39:529–545.
25. Eagan TM, Gulsvik A, Eide GE, Bakke PS. Occupational airborne exposure and the incidence of respiratory symptoms and asthma. *Am J Respir Crit Care Med* 2002;166:933–938.
26. Hoy RF, Burgess JA, Benke G, Matheson M, Morrison S, Gurrin L, *et al.* Occupational exposures and the development of new-onset asthma: a population-based cohort study from the ages of 13 to 44 years. *J Occup Environ Med* 2013;55:235–239.
27. LeVan TD, Koh WP, Lee HP, Koh D, Yu MC, London SJ. Vapor, dust, and smoke exposure in relation to adult-onset asthma and chronic respiratory symptoms: the Singapore Chinese Health Study. *Am J Epidemiol* 2006;163:1118–1128.
28. Lillienberg L, Andersson E, Janson C, Dahlman-Höglund A, Forsberg B, Holm M, *et al.* Occupational exposure and new-onset asthma in a population-based study in Northern Europe (RHINE). *Ann Occup Hyg* 2013;57:482–492.
29. Ghosh RE, Cullinan P, Fishwick D, Hoyle J, Warburton CJ, Strachan DP, *et al.* Asthma and occupation in the 1958 birth cohort. *Thorax* 2013;68:365–371.
30. Katz I, Moshe S, Sosna J, Baum GL, Fink G, Shemer J. The occurrence, recrudescence, and worsening of asthma in a population of young adults: impact of varying types of occupation. *Chest* 1999;116:614–618.
31. Karjalainen A, Kurppa K, Martikainen R, Klaukka T, Karjalainen J. Work is related to a substantial portion of adult-onset asthma incidence in the Finnish population. *Am J Respir Crit Care Med* 2001;164:565–568.
32. Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lillienberg L, Plana E, *et al.* Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet* 2007;370:336–341.
33. Hedlund U, Eriksson K, Rönmark E. Socio-economic status is related to incidence of asthma and respiratory symptoms in adults. *Eur Respir J* 2006;28:303–310.
34. Lillienberg L, Dahlman-Höglund A, Schiöler L, Torén K, Andersson E. Exposures and asthma outcomes using two different job exposure matrices in a general population study in northern Europe. *Ann Occup Hyg* 2014;58:469–481.
35. Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2002;156:738–746.
36. Trupin L, Earnest G, San Pedro M, Balmes JR, Eisner MD, Yelin E, *et al.* The occupational burden of chronic obstructive pulmonary disease. *Eur Respir J* 2003;22:462–469.
37. de Marco R, Accordini S, Cerveri I, Corsico A, Sunyer J, Neukirch F, *et al.*; European Community Respiratory Health Survey Study Group. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. *Thorax* 2004;59:120–125.
38. Lindberg A, Jonsson AC, Rönmark E, Lundgren R, Larsson LG, Lundbäck B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. *Chest* 2005;127:1544–1552.

39. Sunyer J, Zock JP, Kromhout H, Garcia-Esteban R, Radon K, Jarvis D, *et al.*; Occupational Group of the European Community Respiratory Health Survey. Lung function decline, chronic bronchitis, and occupational exposures in young adults. *Am J Respir Crit Care Med* 2005;172:1139–1145.
40. Jaén A, Zock JP, Kogevinas M, Ferrer A, Marín A. Occupation, smoking, and chronic obstructive respiratory disorders: a cross sectional study in an industrial area of Catalonia, Spain. *Environ Health* 2006;5:2.
41. Zhong N, Wang C, Yao W, Chen P, Kang J, Huang S, *et al.* Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. *Am J Respir Crit Care Med* 2007;176:753–760.
42. Weinmann S, Vollmer WM, Breen V, Heumann M, Hnizdo E, Villavej J, *et al.* COPD and occupational exposures: a case-control study. *J Occup Environ Med* 2008;50:561–569.
43. Blanc PD, Menezes AMB, Plana E, Mannino DM, Hallal PC, Toren K, *et al.* Occupational exposures and COPD: an ecological analysis of international data. *Eur Respir J* 2009;33:298–304.
44. Blanc PD, Eisner MD, Earnest G, Trupin L, Balmes JR, Yelin EH, *et al.* Further exploration of the links between occupational exposure and chronic obstructive pulmonary disease. *J Occup Environ Med* 2009;51:804–810.
45. Melville AM, Pless-Mullooli T, Afolabi OA, Stenton SC. COPD prevalence and its association with occupational exposures in a general population. *Eur Respir J* 2010;36:488–493.
46. Idolor LF, DE Guia TS, Francisco NA, Roa CC, Ayuyao FG, Tady CZ, *et al.* Burden of obstructive lung disease in a rural setting in the Philippines. *Respirology* 2011;16:1111–1118.
47. Mehta AJ, Miedinger D, Keidel D, Bettschart R, Bircher A, Bridevaux PO, *et al.*; SAPALDIA Team. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss Cohort Study on air pollution and lung and heart diseases in adults. *Am J Respir Crit Care Med* 2012;185:1292–1300.
48. Lam KBH, Yin P, Jiang CQ, Zhang WS, Adab P, Miller MR, *et al.* Past dust and GAS/FUME exposure and COPD in Chinese: the Guangzhou Biobank Cohort Study. *Respir Med* 2012;106:1421–1428.
49. Darby AC, Waterhouse JC, Stevens V, Billings CG, Billings CG, Burton CM, *et al.* Chronic obstructive pulmonary disease among residents of an historically industrialised area. *Thorax* 2012;67:901–907.
50. Hansell A, Ghosh RE, Poole S, Zock JP, Weatherall M, Vermeulen R, *et al.* Occupational risk factors for chronic respiratory disease in a New Zealand population using lifetime occupational history. *J Occup Environ Med* 2014;56:270–280.
51. Doney B, Hnizdo E, Graziani M, Kullman G, Burchfiel C, Baron S, *et al.* Occupational risk factors for COPD phenotypes in the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. *COPD* 2014;11:368–380.
52. de Jong K, Boezen HM, Kromhout H, Vermeulen R, Postma DS, Vonk JM; LifeLines Cohort study. Pesticides and other occupational exposures are associated with airway obstruction: the LifeLines cohort study. *Occup Environ Med* 2014;71:88–96.
53. Pallasaho P, Kainu A, Sovijärvi A, Lindqvist A, Piirilä PL. Combined effect of smoking and occupational exposure to dusts, gases or fumes on the incidence of COPD. *COPD* 2014;11:88–95.
54. Scholes S, Moody A, Mindell JS. Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40–95 years in England and Wales. *BMJ Open* 2014;4:e005685.
55. Paulin LM, Diette GB, Blanc PD, Putcha N, Eisner MD, Kanner RE, *et al.*; SPIROMICS Research Group. Occupational exposures are associated with worse morbidity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015;191:557–565.
56. Würtz ET, Schlünssen V, Mallng TH, Hansen JG, Omland Ø. Occupational chronic obstructive pulmonary disease in a Danish population-based study. *COPD* 2015;12:435–443.
57. Obaseki DO, Erhabor GE, Gnatiu L, Adewole OO, Buist SA, Burney PG. Chronic airflow obstruction in a black African population: results of BOLD study, Ile-Ife, Nigeria. *COPD* 2016;13:42–49.
58. Tagiyeva N, Sadhra S, Mohammed N, Fielding S, Devereux G, Teo E, *et al.* Occupational airborne exposure in relation to chronic obstructive pulmonary disease (COPD) and lung function in individuals without childhood wheezing illness: a 50-year cohort study. *Environ Res* 2017;153:126–134.
59. Sinha B, Vibha, Singla R, Chowdhury R. An epidemiological profile of chronic obstructive pulmonary disease: a community-based study in Delhi. *J Postgrad Med* 2017;63:29–35.
60. Torén K, Vikgren J, Olin AC, Rosengren A, Bergström G, Brandberg J. Occupational exposure to vapor, gas, dust, or fumes and chronic airflow limitation, COPD, and emphysema: the Swedish CArdioPulmonary BioImage Study (SCAPIS pilot). *Int J Chron Obstruct Pulmon Dis* 2017;12:3407–3413.
61. Montnémy P, Bengtsson P, Elliot A, Lindholm LH, Nyberg P, Löfdahl CG. Prevalence of obstructive lung diseases and respiratory symptoms in relation to living environment and socio-economic group. *Respir Med* 2001;95:744–752.
62. Lange P, Parner J, Prescott E, Vestbo J. Chronic bronchitis in an elderly population. *Age Ageing* 2003;32:636–642.
63. Axelsson M, Ekerljung L, Eriksson J, Hagstad S, Rönmark E, Lötvall J, *et al.* Chronic bronchitis in West Sweden: a matter of smoking and social class. *Eur Clin Respir J* 2016;3:30319.
64. Mak GK, Gould MK, Kuschner WG. Occupational inhalant exposure and respiratory disorders among never-smokers referred to a hospital pulmonary function laboratory. *Am J Med Sci* 2001;322:121–126.
65. Lee SJ, Kim SW, Kong KA, Ryu YJ, Lee JH, Chang JH. Risk factors for chronic obstructive pulmonary disease among never-smokers in Korea. *Int J Chron Obstruct Pulmon Dis* 2015;10:497–506.
66. Würtz ET, Schlünssen V, Mallng TH, Hansen JG, Omland Ø. Occupational COPD among Danish never-smokers: a population-based study. *Occup Environ Med* 2015;72:456–459.
67. Zock JP, Sunyer J, Kogevinas M, Kromhout H, Burney P, Antó JM. Occupation, chronic bronchitis, and lung function in young adults: an international study. *Am J Respir Crit Care Med* 2001;163:1572–1577.
68. Harber P, Tashkin DP, Simmons M, Crawford L, Hnizdo E, Connett J; Lung Health Study Group. Effect of occupational exposures on decline of lung function in early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;176:994–1000.
69. Bang KM, Syamlal G, Mazurek JM. Prevalence of chronic obstructive pulmonary disease in the U.S. working population: an analysis of data from the 1997–2004 National Health Interview Survey. *COPD* 2009;6:380–387.
70. Bang KM, Syamlal G, Mazurek JM, Wassell JT. Chronic obstructive pulmonary disease prevalence among nonsmokers by occupation in the United States. *J Occup Environ Med* 2013;55:1021–1026.
71. Bergdahl IA, Torén K, Eriksson K, Hedlund U, Nilsson T, Flodin R, *et al.* Increased mortality in COPD among construction workers exposed to inorganic dust. *Eur Respir J* 2004;23:402–406.
72. Torén K, Järholm B. Effect of occupational exposure to vapors, gases, dusts, and fumes on COPD mortality risk among Swedish construction workers: a longitudinal cohort study. *Chest* 2014;145:992–997.
73. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, *et al.*; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013;188:733–748.
74. Turner-Warwick M. In search of a cause of cryptogenic fibrosing alveolitis (CFA): one initiating factor or many? *Thorax* 1998;53(Suppl 2):S3–S9.
75. Hubbard R. Occupational dust exposure and the aetiology of cryptogenic fibrosing alveolitis. *Eur Respir J* 2001;18(32 Suppl):119s–121s.
76. Gulati M, Redlich CA. Asbestosis and environmental causes of usual interstitial pneumonia. *Curr Opin Pulm Med* 2015;21:193–200.
77. Scott J, Johnston I, Britton J. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. *BMJ* 1990;301:1015–1017.

78. Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis: epidemiologic approaches to occupational exposure. *Am J Respir Crit Care Med* 1994;150:670–675.
79. Hubbard R, Johnston I, Coultas DB, Britton J. Mortality rates from cryptogenic fibrosing alveolitis in seven countries. *Thorax* 1996;51:711–716.
80. Mullen J, Hodgson MJ, DeGraff CA, Godar T. Case-control study of idiopathic pulmonary fibrosis and environmental exposures. *J Occup Environ Med* 1998;40:363–367.
81. Baumgartner KB, Samet JM, Coultas DB, Stidley CA, Hunt WC, Colby TV, et al.; Collaborating Centers. Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case-control study. *Am J Epidemiol* 2000;152:307–315.
82. Hubbard R, Cooper M, Antoniaki M, Venn A, Khan S, Johnston I, et al. Risk of cryptogenic fibrosing alveolitis in metal workers. *Lancet* 2000;355:466–467.
83. Miyake Y, Sasaki S, Yokoyama T, Chida K, Azuma A, Suda T, et al. Occupational and environmental factors and idiopathic pulmonary fibrosis in Japan. *Ann Occup Hyg* 2005;49:259–265.
84. Gustafson T, Dahlman-Höglund A, Nilsson K, Ström K, Tornling G, Torén K. Occupational exposure and severe pulmonary fibrosis. *Respir Med* 2007;101:2207–2212.
85. Pinheiro GA, Antao VC, Wood JM, Wassell JT. Occupational risks for idiopathic pulmonary fibrosis mortality in the United States. *Int J Occup Environ Health* 2008;14:117–123.
86. García-Sancho Figueroa MC, Carrillo G, Pérez-Padilla R, Fernández-Plata MR, Buendía-Roldán I, Vargas MH, et al. Risk factors for idiopathic pulmonary fibrosis in a Mexican population: a case-control study. *Respir Med* 2010;104:305–309.
87. García-Sancho C, Buendía-Roldán I, Fernández-Plata MR, Navarro C, Pérez-Padilla R, Vargas MH, et al. Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis. *Respir Med* 2011;105:1902–1907.
88. Awadalla NJ, Hegazy A, Elmetwally RA, Wahby I. Occupational and environmental risk factors for idiopathic pulmonary fibrosis in Egypt: a multicenter case-control study. *Int J Occup Environ Med* 2012;3:107–116.
89. Paolucci G, Folletti I, Torén K, Ekström M, Dell'Omo M, Muzi G, et al. Occupational risk factors for idiopathic pulmonary fibrosis in Southern Europe: a case-control study. *BMC Pulm Med* 2018;18:75.
90. Ekström M, Gustafson T, Boman K, Nilsson K, Tornling G, Murgia N, et al. Effects of smoking, gender and occupational exposure on the risk of severe pulmonary fibrosis: a population-based case-control study. *BMJ Open* 2014;4:e004018.
91. Koo JW, Myong JP, Yoon HK, Rhee CK, Kim Y, Kim JS, et al. Occupational exposure and idiopathic pulmonary fibrosis: a multicenter case-control study in Korea. *Int J Tuberc Lung Dis* 2017;21:107–112.
92. Paolucci G, Nicolici V, Folletti I, Torén K, Gambelunghe A, dell'Omo M, et al. Risk factors for idiopathic pulmonary fibrosis in Southern Europe: a case-control study [abstract]. *Eur Respir J* 2013;42(Suppl 57):P1912.
93. Lee SH, Kim DS, Kim YW, Chung MP, Uh ST, Park CS, et al. Association between occupational dust exposure and prognosis of idiopathic pulmonary fibrosis: a Korean national survey. *Chest* 2015;147:465–474.
94. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. *N Engl J Med* 2003;349:2527–2539.
95. Ioachimescu OC, Kavuru MS. Pulmonary alveolar proteinosis. *Chron Respir Dis* 2006;3:149–159.
96. Alper F, Akgun M, Onbas O, Araz O. CT findings in silicosis due to denim sandblasting. *Eur Radiol* 2008;18:2739–2744.
97. Blanc PD. “Acute” silicosis at the 1930 Johannesburg Conference on silicosis and in its aftermath: controversies over a distinct entity later recognized as silicoproteinosis. *Am J Ind Med* 2015;58(Suppl 1):S39–S47.
98. Chew R, Nigam S, Sivakumaran P. Alveolar proteinosis associated with aluminium dust inhalation. *Occup Med (Lond)* 2016;66:492–494.
99. Cummings KJ, Donat WE, Ettensohn DB, Roggli VL, Ingram P, Kreiss K. Pulmonary alveolar proteinosis in workers at an indium processing facility. *Am J Respir Crit Care Med* 2010;181:458–464.
100. Dawkins SA, Gerhard H, Nevin M. Pulmonary alveolar proteinosis: a possible sequel of NO₂ exposure. *J Occup Med* 1991;33:638–641.
101. Grubstein A, Shtraichman O, Fireman E, Bachar GN, Noach-Ophir N, Kramer MR. Radiological evaluation of artificial stone silicosis outbreak: emphasizing findings in lung transplant recipients. *J Comput Assist Tomogr* 2016;40:923–927.
102. Keller CA, Frost A, Cagle PT, Abraham JL. Pulmonary alveolar proteinosis in a painter with elevated pulmonary concentrations of titanium. *Chest* 1995;108:277–280.
103. McCunney RJ, Godefroi R. Pulmonary alveolar proteinosis and cement dust: a case report. *J Occup Med* 1989;31:233–237.
104. Miller RR, Churg AM, Hutcheon M, Lom S. Pulmonary alveolar proteinosis and aluminum dust exposure. *Am Rev Respir Dis* 1984;130:312–315.
105. Owens MW, Kinasewitz GT, Gonzalez E. Sandblaster’s lung with mycobacterial infection. *Am J Med Sci* 1988;295:554–557.
106. Ray RL, Salm R. A fatal case of pulmonary alveolar proteinosis. *Thorax* 1962;17:257–266.
107. Suratt PM, Winn WC Jr, Brody AR, Bolton WK, Giles RD. Acute silicosis in tombstone sandblasters. *Am Rev Respir Dis* 1977;115:521–529.
108. Xipell JM, Ham KN, Price CG, Thomas DP. Acute silicoproteinosis. *Thorax* 1977;32:104–111.
109. Hosokawa T, Yamaguchi E, Shirai S, Fuke S, Takaoka K, Kojima J, et al. A case of idiopathic pulmonary alveolar proteinosis accompanied by T-cell receptor gene rearrangement in bronchoalveolar lavage fluid cells. *Respirology* 2004;9:286–288.
110. Shaughnessy GF, Lee AS. Pulmonary alveolar proteinosis, barbecue smoke, and granulocyte-macrophage colony-stimulating factor therapy. *Am J Med* 2016;129:e7–e8.
111. Uzmezoglu B, Simsek C, Gulgozteren S, Gebesoglu BE. Does dust-associated pulmonary alveolar proteinosis represent an autoimmune disorder? *Am J Ind Med* 2017;60:591–597.
112. Davidson JM, Macleod WM. Pulmonary alveolar proteinosis. *Br J Dis Chest* 1969;63:13–28.
113. McEuen DD, Abraham JL. Particulate concentrations in pulmonary alveolar proteinosis. *Environ Res* 1978;17:334–339.
114. Rubin E, Weisbrod GL, Sanders DE. Pulmonary alveolar proteinosis: relationship to silicosis and pulmonary infection. *Radiology* 1980;135:35–41.
115. Kariman K, Kylstra JA, Spock A. Pulmonary alveolar proteinosis: prospective clinical experience in 23 patients for 15 years. *Lung* 1984;162:223–231.
116. Prakash UB, Barham SS, Carpenter HA, Dines DE, Marsh HM. Pulmonary alveolar phospholipoproteinosis: experience with 34 cases and a review. *Mayo Clin Proc* 1987;62:499–518.
117. Asamoto H, Kitaichi M, Nishimura K, Itoh H, Izumi T. Primary pulmonary alveolar proteinosis: clinical observation of 68 patients in Japan [in Japanese]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1995;33:835–845.
118. Goldstein LS, Kavuru MS, Curtis-McCarthy P, Christie HA, Farver C, Stoller JK. Pulmonary alveolar proteinosis: clinical features and outcomes. *Chest* 1998;114:1357–1362.
119. Kim G, Lee SJ, Lee HP, Yoo CG, Han SK, Shim YS, et al. The clinical characteristics of pulmonary alveolar proteinosis: experience at Seoul National University Hospital, and review of the literature. *J Korean Med Sci* 1999;14:159–164.
120. Briens E, Delaval P, Mairesse MP, Valeyre D, Wallaert B, Lazor R, et al.; Groupe D’études Et de Recherche Sur Les Maladies Orphelines Pulmonaires (GERM O P). Pulmonary alveolar proteinosis [in French]. *Rev Mal Respir* 2002;19:166–182.
121. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N, et al.; Japanese Center of the Rare Lung Diseases Consortium. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. *Am J Respir Crit Care Med* 2008;177:752–762.
122. Fang XQ. Eleven cases analysis of pulmonary alveolar proteinosis. *J Clin Intern Med* 2009;26:623–625.
123. Xu Z, Jing J, Wang H, Xu F, Wang J. Pulmonary alveolar proteinosis in China: a systematic review of 241 cases. *Respirology* 2009;14:761–766.

124. Byun MK, Kim DS, Kim YW, Chung MP, Shim JJ, Cha SI, *et al*. Clinical features and outcomes of idiopathic pulmonary alveolar proteinosis in Korean population. *J Korean Med Sci* 2010;25:393–398.
125. Bonella F, Bauer PC, Griesse M, Ohshimo S, Guzman J, Costabel U. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. *Respir Med* 2011;105:1908–1916.
126. Fang CS, Wang YC, Zhang TH, Wu J, Wang W, Wang C, *et al*. Clinical significance of serum lipids in idiopathic pulmonary alveolar proteinosis. *Lipids Health Dis* 2012;11:12.
127. Campo I, Mariani F, Rodi G, Paracchini E, Tsana E, Piloni D, *et al*. Assessment and management of pulmonary alveolar proteinosis in a reference center. *Orphanet J Rare Dis* 2013;8:40.
128. Zhao HC, Zhu QS. Effect of whole lung lavage therapy at the same period on pulmonary alveolar proteinosis disease. *Pract J Clin Med* 2013;11:88–90.
129. Fijolek J, Wiatr E, Radzikowska E, Bestry I, Langfort R, Polubiec-Kownacka M, *et al*. Pulmonary alveolar proteinosis during a 30-year observation: diagnosis and treatment. *Pneumonol Alergol Pol* 2014; 82:206–217.
130. Ilkovich YM, Ariel BM, Novikova LN, Bazhanov AA, Dvorakovskaya IV, Ilkovich MM. Pulmonary alveolar proteinosis: a long way to correct diagnosis. Problems of diagnostics and therapy in routine practice. *Ann Clin Lab Sci* 2014;44:405–409.
131. Yang J, Jiang D, Lu JC. Efficacy of the treatment of 10 cases of pulmonary alveolar proteinosis large capacity whole lung lavage. *Zhejiang Clin Med J* 2014;16:397–398.
132. Akasaka K, Tanaka T, Kitamura N, Ohkouchi S, Tazawa R, Takada T, *et al*. Outcome of corticosteroid administration in autoimmune pulmonary alveolar proteinosis: a retrospective cohort study. *BMC Pulm Med* 2015;15:88.
133. Xiao YL, Xu KF, Li Y, Li Y, Li H, Shi B, *et al*. Occupational inhalational exposure and serum GM-CSF autoantibody in pulmonary alveolar proteinosis. *Occup Environ Med* 2015;72:504–512.
134. Bai J, Xu J, Yang W, Gao B, Cao W, Liang S, *et al*. A new scale to assess the severity and prognosis of pulmonary alveolar proteinosis. *Can Respir J* 2016;2016:3412836.
135. Deleanu OC, Zaharie AM, Șerbescu A, Nițu FM, Mihăițan FD, Arghir OC. Analysis of bronchoalveolar lavage fluid in a first Romanian pulmonary alveolar proteinosis cohort. *Rom J Morphol Embryol* 2016;57(2 Suppl):737–743.
136. Hadda V, Tiwari P, Madan K, Mohan A, Gupta N, Bharti SJ, *et al*. Pulmonary alveolar proteinosis: experience from a tertiary care center and systematic review of Indian literature. *Lung India* 2016; 33:626–634.
137. Huang Z, Yi X, Luo B, Zhu J, Wu Y, Jiang W, *et al*. Induced sputum deposition improves diagnostic yields of pulmonary alveolar proteinosis: a clinicopathological and methodological study of 17 cases. *Ultrastruct Pathol* 2016;40:7–13.
138. Mo Q, Wang B, Dong N, Bao L, Su X, Li Y, *et al*. The clinical clues of pulmonary alveolar proteinosis: a report of 11 cases and literature review. *Can Respir J* 2016;2016:4021928.
139. Guo WL, Zhou ZQ, Chen L, Su ZQ, Zhong CH, Chen Y, *et al*. Serum KL-6 in pulmonary alveolar proteinosis: China compared historically with Germany and Japan. *J Thorac Dis* 2017;9:287–295.
140. Hwang JA, Song JH, Kim JH, Chung MP, Kim DS, Song JW, *et al*. Clinical significance of cigarette smoking and dust exposure in pulmonary alveolar proteinosis: a Korean national survey. *BMC Pulm Med* 2017;17:147.
141. Bonella F, Bauer PC, Griesse M, Wessendorf TE, Guzman J, Costabel U. Wash-out kinetics and efficacy of a modified lavage technique for alveolar proteinosis. *Eur Respir J* 2012;40:1468–1474.
142. Abraham JL, McEuen DD. Inorganic particulates associated with pulmonary alveolar proteinosis: SEM and X-ray microanalysis results. *Appl Pathol* 1986;4:138–146.
143. Rosen SH, Castleman B, Liebow AA, Enzinger FM, Hunt RTN. Pulmonary alveolar proteinosis. *N Engl J Med* 1958;258: 1123–1142.
144. Tazawa R, Trapnell BC, Inoue Y, Arai T, Takada T, Nasuhara Y, *et al*. Inhaled granulocyte/macrophage-colony stimulating factor as therapy for pulmonary alveolar proteinosis. *Am J Respir Crit Care Med* 2010;181:1345–1354.
145. Philit F, Etienne-Mastroianni B, Parrot A, Guérin C, Robert D, Cordier JF. Idiopathic acute eosinophilic pneumonia: a study of 22 patients. *Am J Respir Crit Care Med* 2002;166:1235–1239.
146. Rom WN, Weiden M, Garcia R, Yie TA, Vathesatogkit P, Tse DB, *et al*. Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. *Am J Respir Crit Care Med* 2002;166:797–800.
147. Lowry T, Schuman LM. Silo-filler's disease; a syndrome caused by nitrogen dioxide. *J Am Med Assoc* 1956;162:153–160.
148. Eschenbacher WL, Kreiss K, Loughheed MD, Pransky GS, Day B, Castellan RM. Nylon flock-associated interstitial lung disease. *Am J Respir Crit Care Med* 1999;159:2003–2008.
149. Kreiss K, Gomaa A, Kullman G, Fedan K, Simoes EJ, Enright PL. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N Engl J Med* 2002;347:330–338.
150. Akpınar-Elci M, Travis WD, Lynch DA, Kreiss K. Bronchiolitis obliterans syndrome in popcorn production plant workers. *Eur Respir J* 2004;24:298–302.
151. Ghanei M, Mokhtari M, Mohammad MM, Aslani J. Bronchiolitis obliterans following exposure to sulfur mustard: chest high resolution computed tomography. *Eur J Radiol* 2004;52: 164–169.
152. Cullinan P, McGavin CR, Kreiss K, Nicholson AG, Maher TM, Howell T, *et al*. Obliterative bronchiolitis in fibreglass workers: a new occupational disease? *Occup Environ Med* 2013;70:357–359.
153. Moya C, Antó JM, Taylor AJ; Collaborative Group for the Study of Toxicity in Textile Aerographic Factories. Outbreak of organising pneumonia in textile printing sprayers. *Lancet* 1994;344: 498–502.
154. Romero S, Hernández L, Gil J, Aranda I, Martín C, Sanchez-Payá J. Organizing pneumonia in textile printing workers: a clinical description. *Eur Respir J* 1998;11:265–271.
155. Herbert A, Sterling G, Abraham J, Corrin B. Desquamative interstitial pneumonia in an aluminum welder. *Hum Pathol* 1982;13:694–699.
156. Ahmad D, Morgan WK, Patterson R, Williams T, Zeiss CR. Pulmonary haemorrhage and haemolytic anaemia due to trimellitic anhydride. *Lancet* 1979;2:328–330.
157. Cullen MR, Balmes JR, Robins JM, Smith GJ. Lipoid pneumonia caused by oil mist exposure from a steel rolling tandem mill. *Am J Ind Med* 1981;2:51–58.
158. Han C, Liu L, Du S, Mei J, Huang L, Chen M, *et al*. Investigation of rare chronic lipid pneumonia associated with occupational exposure to paraffin aerosol. *J Occup Health* 2016;58:482–488.
159. Pu CY, Al Rasheed MRH, Sekosan M, Sharma V. Pet groomer's lung: a novel occupation related hypersensitivity pneumonitis related to pyrethrin exposure in a pet groomer. *Am J Ind Med* 2017;60: 141–145.
160. Moon J, du Bois RM, Colby TV, Hansell DM, Nicholson AG. Clinical significance of respiratory bronchiolitis on open lung biopsy and its relationship to smoking related interstitial lung disease. *Thorax* 1999;54:1009–1014.
161. Woo OH, Yong HS, Oh YW, Lee SY, Kim HK, Kang EY. Respiratory bronchiolitis-associated interstitial lung disease in a nonsmoker: radiologic and pathologic findings. *AJR Am J Roentgenol* 2007; 188:W412–W414.
162. Barber CM, Burton CM, Hendrick DJ, Pickering CAC, Robertson AS, Robertson W, *et al*. Hypersensitivity pneumonitis in workers exposed to metalworking fluids. *Am J Ind Med* 2014;57: 872–880.
163. Morell F, Roger A, Reyes L, Cruz MJ, Murio C, Muñoz X. Bird fancier's lung: a series of 86 patients. *Medicine (Baltimore)* 2008;87:110–130.
164. Wang P, Jones KD, Urisman A, Elicker BM, Urbania T, Johansson KA, *et al*. Pathologic findings and prognosis in a large prospective cohort of chronic hypersensitivity pneumonitis. *Chest* 2017;152: 502–509.
165. Lacasse Y, Selman M, Costabel U, Dalphin JC, Ando M, Morell F, *et al*; HP Study Group. Clinical diagnosis of hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2003;168:952–958.
166. Selman M, Lacasse Y, Pardo A, Cormier Y. Hypersensitivity pneumonitis caused by fungi. *Proc Am Thorac Soc* 2010;7: 229–236.

167. Cramer C, Schlünssen V, Bendstrup E, Stokholm ZA, Vestergaard JM, Frydenberg M, *et al.* Risk of hypersensitivity pneumonitis and interstitial lung diseases among pigeon breeders. *Eur Respir J* 2016;48:818–825.
168. Kawanami O, Basset F, Barrios R, Lacronique JG, Ferrans VJ, Crystal RG. Hypersensitivity pneumonitis in man: light- and electron-microscopic studies of 18 lung biopsies. *Am J Pathol* 1983;110:275–289.
169. Yoshida K, Suga M, Nishiura Y, Arima K, Yoneda R, Tamura M, *et al.* Occupational hypersensitivity pneumonitis in Japan: data on a nationwide epidemiological study. *Occup Environ Med* 1995;52:570–574.
170. Yoshizawa Y, Ohtani Y, Hayakawa H, Sato A, Suga M, Ando M. Chronic hypersensitivity pneumonitis in Japan: a nationwide epidemiologic survey. *J Allergy Clin Immunol* 1999;103:315–320.
171. Thomeer M, Demedts M, Vandeurzen K; VRGT Working Group on Interstitial Lung Diseases. Registration of interstitial lung diseases by 20 centres of respiratory medicine in Flanders. *Acta Clin Belg* 2001;56:163–172.
172. Bang KM, Weissman DN, Pinheiro GA, Antao VC, Wood JM, Syamlal G. Twenty-three years of hypersensitivity pneumonitis mortality surveillance in the United States. *Am J Ind Med* 2006;49:997–1004.
173. Hanak V, Golbin JM, Ryu JH. Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. *Mayo Clin Proc* 2007;82:812–816.
174. Olson AL, Huie TJ, Groshong SD, Cosgrove GP, Janssen WJ, Schwarz MI, *et al.* Acute exacerbations of fibrotic hypersensitivity pneumonitis: a case series. *Chest* 2008;134:844–850.
175. Cimrin AH, Göksel O, Demirel YS. General aspects of hypersensitivity pneumonitis in Turkey. *Tuberk Toraks* 2010;58:242–251.
176. Caillaud DM, Vergnon JM, Madroszyk A, Melloni BM, Murris M, Dalphin JC; French Group of Environmental Immunoallergic Bronchopulmonary Diseases. Bronchoalveolar lavage in hypersensitivity pneumonitis: a series of 139 patients. *Inflamm Allergy Drug Targets* 2012;11:15–19.
177. Alhamad EH. Interstitial lung diseases in Saudi Arabia: a single-center study. *Ann Thorac Med* 2013;8:33–37.
178. Castonguay MC, Ryu JH, Yi ES, Tazelaar HD. Granulomas and giant cells in hypersensitivity pneumonitis. *Hum Pathol* 2015;46:607–613.
179. Millerick-May ML, Mulks MH, Gerlach J, Flaherty KR, Schmidt SL, Martinez FJ, *et al.* Hypersensitivity pneumonitis and antigen identification: an alternate approach. *Respir Med* 2016;112:97–105.
180. Singh S, Collins BF, Sharma BB, Joshi JM, Talwar D, Katiyar S, *et al.* Interstitial lung disease in India: results of a prospective registry. *Am J Respir Crit Care Med* 2017;195:801–813.
181. Liu H, Patel D, Welch AM, Wilson C, Mroz MM, Li L, *et al.* Association between occupational exposures and sarcoidosis: an analysis from death certificates in the United States, 1988–1999. *Chest* 2016;150:289–298.
182. Hena KM, Yip J, Jaber N, Goldfarb D, Fullam K, Cleven K, *et al.*; FDNY Sarcoidosis Clinical Research Group. Clinical course of sarcoidosis in World Trade Center-exposed firefighters. *Chest* 2018;153:114–123.
183. Barnard J, Rose C, Newman L, Canner M, Martyny J, McCammon C, *et al.*; ACCESS Research Group. Job and industry classifications associated with sarcoidosis in a Case-Control Etiologic Study of Sarcoidosis (ACCESS). *J Occup Environ Med* 2005;47:226–234.
184. Newman LS, Rose CS, Bresnitz EA, Rossman MD, Barnard J, Frederick M, *et al.*; ACCESS Research Group. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. *Am J Respir Crit Care Med* 2004;170:1324–1330.
185. Kucera GP, Rybicki BA, Kirkey KL, Coon SW, Major ML, Maliarik MJ, *et al.* Occupational risk factors for sarcoidosis in African-American siblings. *Chest* 2003;123:1527–1535.
186. Deubelbeiss U, Gemperli A, Schindler C, Baty F, Brutsche MH. Prevalence of sarcoidosis in Switzerland is associated with environmental factors. *Eur Respir J* 2010;35:1088–1097.
187. Crouser ED, Amin EN. Severe sarcoidosis phenotypes: an occupational hazard? *Chest* 2016;150:263–265.
188. Ribeiro M, Fritscher LG, Al-Musaed AM, Balter MS, Hoffstein V, Mazer BD, *et al.* Search for chronic beryllium disease among sarcoidosis patients in Ontario, Canada. *Lung* 2011;189:233–241.
189. Müller-Quernheim J, Gaede KI, Fireman E, Zissel G. Diagnoses of chronic beryllium disease within cohorts of sarcoidosis patients. *Eur Respir J* 2006;27:1190–1195.
190. Fireman E, Haimsky E, Noiderfer M, Priel I, Lerman Y. Misdiagnosis of sarcoidosis in patients with chronic beryllium disease. *Sarcoidosis Vasc Diffuse Lung Dis* 2003;20:144–148.
191. Fireman E, Kramer MR, Priel I, Lerman Y. Chronic beryllium disease among dental technicians in Israel. *Sarcoidosis Vasc Diffuse Lung Dis* 2006;23:215–221.
192. Fireman E, Shai AB, Alcalay Y, Ophir N, Kivity S, Stejskal V. Identification of metal sensitization in sarcoid-like metal-exposed patients by the MELISA® lymphocyte proliferation test: a pilot study. *J Occup Med Toxicol* 2016;11:18.
193. Cherry N, Beach J, Burstyn I, Parboosingh J, Schouchen J, Senthilselvan A, *et al.* Genetic susceptibility to beryllium: a case-referent study of men and women of working age with sarcoidosis or other chronic lung disease. *Occup Environ Med* 2015;72:21–27.
194. Sepkowitz KA, Friedman CR, Hafner A, Kwok D, Manoach S, Floris M, *et al.* Tuberculosis among urban health care workers: a study using restriction fragment length polymorphism typing. *Clin Infect Dis* 1995;21:1098–1101.
195. Baussano I, Nunn P, Williams B, Pivetta E, Bugiani M, Scano F. Tuberculosis among health care workers. *Emerg Infect Dis* 2011;17:488–494.
196. Dharmadhikari A, Smith J, Nardell E, Churchyard G, Keshavjee S. Aspiring to zero tuberculosis deaths among southern Africa's miners: is there a way forward? *Int J Health Serv* 2013;43:651–664.
197. Chen W, Liu Y, Wang H, Hnizdo E, Sun Y, Su L, *et al.* Long-term exposure to silica dust and risk of total and cause-specific mortality in Chinese workers: a cohort study. *PLoS Med* 2012;9:e1001206.
198. Jiamjarasrangsri W, Hirunsuthikul N, Kamolratanakul P. Tuberculosis among health care workers at King Chulalongkorn Memorial Hospital, 1988–2002. *Int J Tuberc Lung Dis* 2005;9:1253–1258.
199. Roche PW, Krause V, Konstantinos A, Bastian I, Antic R, Brown L, *et al.*; National Tuberculosis Advisory Committee; Communicable Disease Network Australia. Tuberculosis notifications in Australia, 2006. *Commun Dis Intell Q Rep* 2008;32:1–11.
200. de Vries G, Šebek MM, Lambregts-van Weezenbeek CSB. Healthcare workers with tuberculosis infected during work. *Eur Respir J* 2006;28:1216–1221.
201. Ong A, Rudoy I, Gonzalez LC, Creasman J, Kawamura LM, Daley CL. Tuberculosis in healthcare workers: a molecular epidemiologic study in San Francisco. *Infect Control Hosp Epidemiol* 2006;27:453–458.
202. Lambert LA, Pratt RH, Armstrong LR, Haddad MB. Tuberculosis among healthcare workers, United States, 1995–2007. *Infect Control Hosp Epidemiol* 2012;33:1126–1132.
203. Raitio M, Tala E. Tuberculosis among health care workers during three recent decades. *Eur Respir J* 2000;15:304–307.
204. Eyob G, Gebeyehu M, Goshu S, Girma M, Lemma E, Fontanet A. Increase in tuberculosis incidence among the staff working at the Tuberculosis Demonstration and Training Centre in Addis Ababa, Ethiopia: a retrospective cohort study (1989–1998). *Int J Tuberc Lung Dis* 2002;6:85–88.
205. Pazin-Filho A, Soares CS, da Silva Nascimento Ferrais A, de Tarso Oliveira e Castro P, Bellissimo-Rodrigues F, de Almeida Nogueira J, *et al.* Tuberculosis among health care workers in a Brazilian tertiary hospital emergency unit. *Am J Emerg Med* 2008;26:796–798.
206. Costa JC, Silva R, Ferreira J, Nienhaus A. Active tuberculosis among health care workers in Portugal. *J Bras Pneumol* 2011;37:636–645.
207. Tudor C, Van der Walt M, Margot B, Dorman SE, Pan WK, Yenokyan G, *et al.* Tuberculosis among health care workers in KwaZulu-Natal, South Africa: a retrospective cohort analysis. *BMC Public Health* 2014;14:891.
208. Klimuk D, Hurevich H, Harries AD, Babrukevich A, Kremer K, Van den Bergh R, *et al.* Tuberculosis in health care workers in Belarus. *Public Health Action* 2014;4(Suppl 2):S29–S33.

209. Rosenman KD, Hall N. Occupational risk factors for developing tuberculosis. *Am J Ind Med* 1996;30:148–154.
210. Chen GX, Burnett CA, Cameron LL, Alterman T, Lalich NR, Tanaka S, et al. Tuberculosis mortality and silica exposure: a case-control study based on a national mortality database for the years 1983–1992. *Int J Occup Environ Health* 1997;3:163–170.
211. Calvert GM, Rice FL, Boiano JM, Sheehy JW, Sanderson WT. Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. *Occup Environ Med* 2003;60:122–129.
212. Kleinschmidt I, Churchyard G. Variation in incidences of tuberculosis in subgroups of South African gold miners. *Occup Environ Med* 1997;54:636–641.
213. Murray J, Sonnenberg P, Shearer SC, Godfrey-Faussett P. Human immunodeficiency virus and the outcome of treatment for new and recurrent pulmonary tuberculosis in African patients. *Am J Respir Crit Care Med* 1999;159:733–740.
214. Churchyard GJ, Corbett EL, Kleinschmidt I, Mulder D, De Cock KM. Drug-resistant tuberculosis in South African gold miners: incidence and associated factors. *Int J Tuberc Lung Dis* 2000;4:433–440.
215. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. *J Infect Dis* 2005;191:150–158.
216. Glynn JR, Murray J, Bester A, Nelson G, Shearer S, Sonnenberg P. Effects of duration of HIV infection and secondary tuberculosis transmission on tuberculosis incidence in the South African gold mines. *AIDS* 2008;22:1859–1867.
217. van Halsema CL, Fielding KL, Chihota VN, Lewis JJ, Churchyard GJ, Grant AD. Trends in drug-resistant tuberculosis in a gold-mining workforce in South Africa, 2002–2008. *Int J Tuberc Lung Dis* 2012;16:967–973.
218. Laraqui CH, Ottmani S, Hammou MA, Bencheikh N, Mahjour J. Study of tuberculosis in health care workers in the public sector of Morocco [in French]. *Int J Tuberc Lung Dis* 2001;5:939–945.
219. Tam CM, Leung CC. Occupational tuberculosis: a review of the literature and the local situation. *Hong Kong Med J* 2006;12:448–455.
220. Toms C, Stapledon R, Waring J, Douglas P; National Tuberculosis Advisory Committee, for the Communicable Diseases Network Australia, and the Australian Mycobacterium Reference Laboratory Network. Tuberculosis notifications in Australia, 2012 and 2013. *Commun Dis Intell Q Rep* 2015;39:E217–E235.
221. Davidson JA, Lalor MK, Anderson LF, Tamne S, Abubakar I, Thomas HL. TB in healthcare workers in the UK: a cohort analysis 2009–2013. *Thorax* 2017;72:654–659.
222. O'Hara LM, Yassi A, Zungu M, Malote M, Bryce EA, Barker SJ, et al. The neglected burden of tuberculosis disease among health workers: a decade-long cohort study in South Africa. *BMC Infect Dis* 2017;17:547.
223. Joshi R, Reingold AL, Menzies D, Pai M. Tuberculosis among health-care workers in low- and middle-income countries: a systematic review. *PLoS Med* 2006;3:e494.
224. Yarahmadi A, Zahmatkesh MM, Ghaffari M, Mohammadi S, Labbafinejad Y, Seyedmehdi SM, et al. Correlation between silica exposure and risk of tuberculosis in Lorestan Province of Iran. *Tanaffos* 2013;12:34–40.
225. Almirall J, Bolibar I, Serra-Prat M, Roig J, Hospital I, Carandell E, et al.; Community-Acquired Pneumonia in Catalan Countries (PACAP) Study Group. New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Respir J* 2008;31:1274–1284.
226. Loeb M, Neupane B, Walter SD, Hanning R, Carusone SC, Lewis D, et al. Environmental risk factors for community-acquired pneumonia hospitalization in older adults. *J Am Geriatr Soc* 2009;57:1036–1040.
227. Farr BM, Bartlett CLR, Wadsworth J, Miller DL; British Thoracic Society Pneumonia Study Group. Risk factors for community-acquired pneumonia diagnosed upon hospital admission. *Respir Med* 2000;94:954–963.
228. Palmer KT, Poole J, Ayres JG, Mann J, Burge PS, Coggon D. Exposure to metal fume and infectious pneumonia. *Am J Epidemiol* 2003;157:227–233.
229. Almirall J, Serra-Prat M, Bolibar I, Palomera E, Roig J, Boixeda R, et al. Professions and working conditions associated with community-acquired pneumonia. *Arch Bronchopneumologica* 2015;51:627–631.
230. Neupane B, Jerrett M, Burnett RT, Marrie T, Arain A, Loeb M. Long-term exposure to ambient air pollution and risk of hospitalization with community-acquired pneumonia in older adults. *Am J Respir Crit Care Med* 2010;181:47–53.
231. Koh DH, Moon KT, Kim JY, Choe SW. The risk of hospitalisation for infectious pneumonia in mineral dust exposed industries. *Occup Environ Med* 2011;68:116–119.
232. Torén K, Qvarfordt I, Bergdahl IA, Järholm B. Increased mortality from infectious pneumonia after occupational exposure to inorganic dust, metal fumes and chemicals. *Thorax* 2011;66:992–996.
233. Graham WGB, Costello J, Vacek PM. Vermont granite mortality study: an update with an emphasis on lung cancer. *J Occup Environ Med* 2004;46:459–466.
234. Veiga LH, Amaral EC, Colin D, Koifman S. A retrospective mortality study of workers exposed to radon in a Brazilian underground coal mine. *Radiat Environ Biophys* 2006;45:125–134.
235. Beaumont JJ, Weiss NS. Mortality of welders, shipfitters, and other metal trades workers in boilermakers Local No. 104, AFL-CIO. *Am J Epidemiol* 1980;112:775–786.
236. Newhouse ML, Oakes D, Woolley AJ. Mortality of welders and other craftsmen at a shipyard in NE England. *Br J Ind Med* 1985;42:406–410.
237. Coggon D, Inskip H, Winter P, Pannett B. Lobar pneumonia: an occupational disease in welders. *Lancet* 1994;344:41–43.
238. Palmer KT, Cullinan P, Rice S, Brown T, Coggon D. Mortality from infectious pneumonia in metal workers: a comparison with deaths from asthma in occupations exposed to respiratory sensitizers. *Thorax* 2009;64:983–986.
239. Wong A, Marrie TJ, Garg S, Kellner JD, Tyrrell GJ; SPAT Group. Welders are at increased risk for invasive pneumococcal disease. *Int J Infect Dis* 2010;14:e796–e799.
240. Lytras T, Kogevinas M, Kromhout H, Carsin AE, Antó JM, Bentouhami H, et al. Occupational exposures and 20-year incidence of COPD: the European Community Respiratory Health Survey. *Thorax* 2018;73:1008–1015.
241. Fernández Pérez ER, Kong AM, Raimundo K, Koelsch TL, Kulkarni R, Cole AL. Epidemiology of hypersensitivity pneumonitis among an insured population in the United States: a claims-based cohort analysis. *Ann Am Thorac Soc* 2018;15:460–469.
242. Gonzalez-Garcia M, Caballero A, Jaramillo C, Torres-Duque CA. Chronic bronchitis: high prevalence in never smokers and underdiagnosis. A population-based study in Colombia. *Chron Respir Dis* 2019;16:1479972318769771.
243. Blanc PD, Seaton A. Pneumoconiosis redux: coal workers' pneumoconiosis and silicosis are still a problem. *Am J Respir Crit Care Med* 2016;193:603–605.
244. Cullinan P, Muñoz X, Suojalehto H, Agius R, Jindal S, Sigsgaard T, et al. Occupational lung diseases: from old and novel exposures to effective preventive strategies. *Lancet Respir Med* 2017;5:445–455.
245. Pérez-Alonso A, Córdoba-Doña JA, Millares-Lorenzo JL, Figueroa-Murillo E, García-Vadillo C, Romero-Morillos J. Outbreak of silicosis in Spanish quartz conglomerate workers. *Int J Occup Environ Health* 2014;20:26–32.
246. Harris EC, Palmer KT, Cox V, Darnton A, Osman J, Coggon D. Trends in mortality from occupational hazards among men in England and Wales during 1979–2010. *Occup Environ Med* 2016;73:385–393.
247. Sigsgaard T, Nowak D, Annesi-Maesano I, Nemery B, Torén K, Viegi G, et al.; ERS EOH group 6.2. ERS position paper: work-related respiratory diseases in the EU. *Eur Respir J* 2010;35:234–238.