Ever and cumulative occupational exposure and lung function decline in longitudinal population-based studies: a systematic review and meta-analysis

Golam Rabbani [1], Naima Nimmi,[2] Geza P Benke,[3] Shyamali C Dharmage,[4] Dinh Bui,[4] Malcolm R Sim [3], Michael J Abramson,[3] Sheikh M Alif [3,4]

ABSTRACT

Objectives Adverse occupational exposures can accelerate age-related lung function decline. Some longitudinal population-based studies have investigated this association. This study aims to examine this association using findings reported by longitudinal population-based studies.

Methods Ovid Medline, PubMed, Embase, and Web of Science were searched using keywords and text words related to occupational exposures and lung function and 12 longitudinal population-based studies were identified using predefined inclusion criteria. The quality of the studies was assessed using the Newcastle-Ottawa Scale. Lung function decline was defined as annual loss of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) or the ratio (FEV_1/FVC). Fixed and random-effects meta-analyses were conducted to calculate pooled estimates for ever and cumulative exposures. Heterogeneity was assessed using the I^2 test, and publication bias was evaluated using funnel plots.

Results Ever exposures to gases/fumes, vapours, gases, dusts, fumes (VGDF) and aromatic solvents were significantly associated with FEV_1 decline in meta-analyses. Cumulative exposures for these three occupational agents observed a similar trend of FEV_1 decline. Ever exposures to fungicides and cumulative exposures to biological dust, fungicides and insecticides were associated with FEV_1 decline in fixed-effect models only. No statistically significant association was observed between mineral dust, herbicides and metals and FEV_1 decline in meta-analyses.

Conclusion Pooled estimates from the longitudinal population-based studies have provided evidence that occupational exposures are associated with FEV_1 decline. Specific exposure control and respiratory health surveillance are required to protect the lung health of the workers.

INTRODUCTION

Lung function decline is a normal feature of ageing in adults, but excessive decline can result in lung function deficits imposing substantial public health burden.[1] A lower level of lung function and decline in forced expiratory volume in 1 s (FEV_1) as a predictor of lung function is associated with the development of chronic 0bstructive pulmonary disease (COPD),[2] which is now the world's fourth leading cause of death and projected to be the third leading cause by 2030.[3] Accelerated decline in FEV_1 or FEV_1/forced vital capacity (FVC) is

---

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Epidemiological studies suggest that some occupational exposures are associated with the decline in forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) or FEV_1/FVC. However, the findings from general population-based studies are inconclusive and not systematically synthesised.

WHAT THIS STUDY ADDS

⇒ We found exposures to gases/fumes, vapours, gases, dusts, fumes (VGDF), aromatic solvents, biological dust, fungicides and insecticides were associated with FEV_1 decline. Other exposures such as herbicides, mineral dust and metals did not show statistically significant associations in the pooled analysis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Periodic workplace health surveillance and lung function testing in exposed occupations will help to identify respiratory disease at an early stage to control the exposure and to protect against further disease progression.

---

also associated with increased risks of cardiovascular morbidity and mortality as well as all-cause mortality.[3]

There is some evidence that occupational exposures can be a risk factor for lung impairment. The relationships between occupational exposures and lung function status and decline have been investigated in workplace-based studies, specifically in farmers, bakers, timber, cotton textile, manufacturing and construction workers.[4–7] Several cross-sectional studies have also shown that occupational exposures to vapours, gases, dusts, fumes (VGDF) were associated with poor lung function in the general population.[8–10] Given these links, it is important to investigate the lung function decline using longitudinal studies, where people have different work histories throughout their careers, and the outcomes may vary between follow-ups.[11] There are a limited number of longitudinal population-based studies that investigated this association, and their findings are contradictory and inconclusive.

Previous systematic reviews have been conducted to synthesise the evidence for the relationship
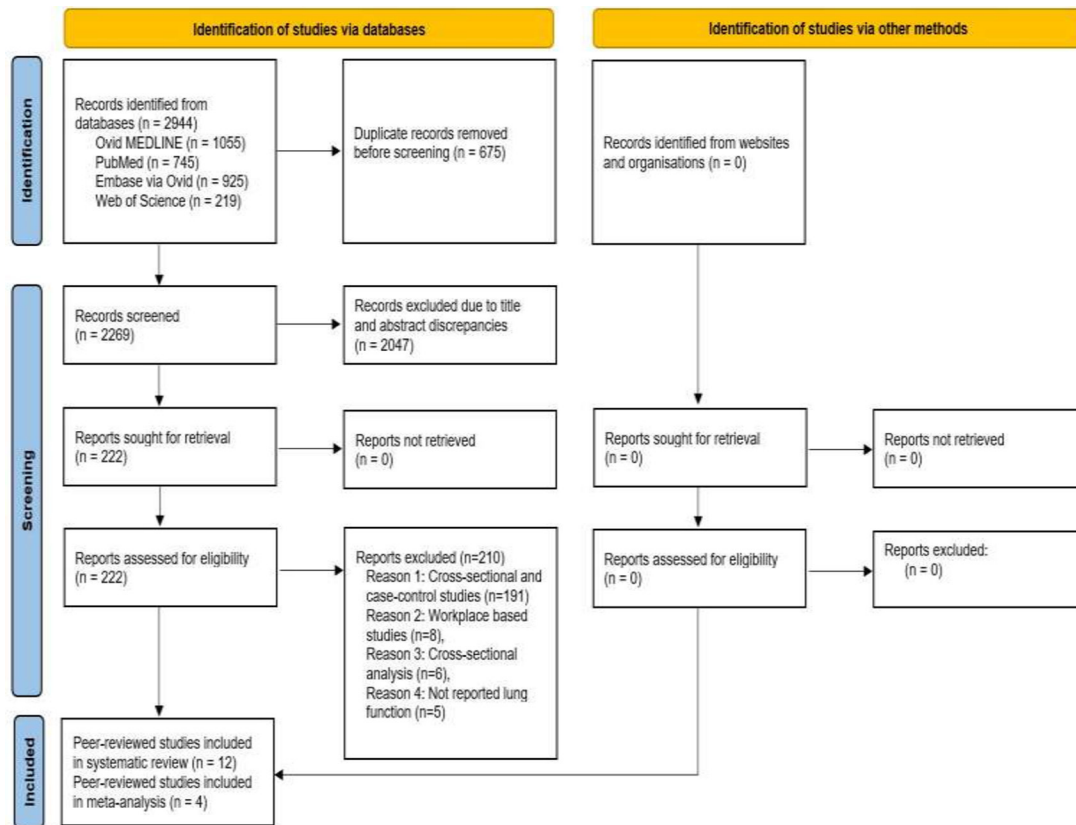
BMJ

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Mata-Analysis) 2020 flowchart of peer-reviewed study selection process.

between occupational exposures and lung function, but they were limited to a few specific occupational exposures and risk of airflow obstruction and only included cross-sectional studies.[11–13] A recent systematic review and meta-analysis reported an association between exposure to organic dust and lung function decline using data from workplace-based studies.[12] While other studies identified the association between exposre to biological dusts, mineral dusts, respirable quartz dust, gases/fumes and pesticides and the risk of COPD,[14] they did not investigate lung function decline.[11 13 15] Given there was no systematic review or meta-analysis synthesising the relationship between occupational exposures (ever and cumulative) and lung function decline in longitudinal population-based studies, we aimed to examine this association using findings reported by longitudinal population-based studies.

METHODS
Search strategy and selection criteria
This systematic review and meta-analysis was performed according to the updated version of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guideline (figure 1).[16] The study was registered in PROSPERO (International Prospective Register of Systematic Reviews) in 2020 (CRD42020154227). The detailed prespecified protocol is available on request.

An extensive search strategy was developed to retrieve all articles published up to September 2021 in Ovid Medline, PubMed, Embase and Web of Science. We combined three sets of Medical Subject Headings (MeSH) keywords and text words to identify articles (online supplemental material 1). Additional searches were undertaken in the reference lists from retrieved articles in

order to identify studies that may have been missed from the initial search. We followed the Population, Exposure, Comparator group and Outcome (PECO) criteria defined by Morgana et al.[17] We defined cohorts as the population, the occupationally exposed group as exposure, the non-exposed group (to particular agent) as comparator and lung function decline as the outcome of interest.

Search results were compiled using the bibliographic software Endnote X9.3. Two independent researchers (GR and NN) screened retrieved articles. The same investigators independently assessed full texts of records deemed eligible for inclusion. Any discrepancies were resolved by discussion and consensus with a third investigator (SMA).

Inclusion and exclusion criteria
We included English language peer-reviewed studies that reported associations between occupational exposures of interest including biological dust, mineral dust, VGDF, fungicides, herbicides, insecticides, aromatic solvents, chlorinated solvents, metals, fibres or mists and lung function decline. We included longitudinal population-based studies with at least 1 year of follow-up that reported an association between occupational exposures and lung function decline. We excluded studies that did not report lung function decline with repeated lung function measurements. We also excluded cross-sectional, case-control, case-series, reviews, editorials, letters and correspondence.

Exposure definitions
The exposures were subdivided into not exposed (to particular agent, not against any occupational exposures), ever exposed,

less likely to be exposed or low exposed, and highly exposed according to the exposure assessment methods such as expert assessment, Job Exposure Matrices (JEMs) or self-reported exposure. Cumulative duration of exposure and lung function decline were also extracted from the selected studies. All the studies defined the non-exposed group as those not exposed to particular occupational exposures as defined by the JEM.

Outcome definitions

The primary outcome considered in our review was annual loss (decline rate) of pre-bronchodilator or post-bronchodilator (1) FEV_1, (2) FVC, or (3) the ratio of FEV_1/FVC.

Quality assessment of included studies

We assessed risk of bias of included studies using the nine items of the Newcastle-Ottawa Scale (NOS) for cohort studies.[18] The quality of the included studies was established by evaluating the study settings, completeness and duration of the follow-up, validity and completeness of exposure and outcomes ascertainment, generalisability of the study findings and adjustment for the known confounding variables using NOS (more details are given in the online supplemental material 1). The scale granted a maximum of nine points for each cohort, studies were assessed as good quality if they scored at least six items, moderate quality if they scored in four or five items, and low quality if they scored for three or fewer items.[19] All the included studies scored six or more in quality assessment.

Data extraction and statistical analysis

The following information was extracted: first author, study location, sample size, study design, duration of follow-up, age at inception, occupational exposures assessment methods, measurement of lung function decline and confounders adjusted. FEV_1 and FVC or ratios of FEV_1/FVC were extracted with corresponding coefficient (β) and 95% confidence intervals (CIs) for the 11 exposures from the studies included. Studies with similar type of exposures and uniform pattern of outcomes assessment were combined for meta-analysis. Although there was variation in the study results, methodology and location, we included four studies for ever exposures and three studies for cumulative exposures out of 12 in meta-analysis (one study was added twice because it reported two cohort results separately in the same article). Sub-group analysis was conducted for FEV_1 of nine exposures with similar exposure assessment (ALOHA plus JEM). As the heterogeneity between the studies varied, we performed both fixed and random effects meta-analysis and the pooled estimates were displayed using forest plots, and the publication bias was assessed using the funnel plot[20] and Egger's test (p<0.05 considered representative of statistical significance).[21] The heterogeneity between studies was assessed using Higgins I^2 statistic.[22] We used Stata version 16.1 (Stata Corporation, College Station, Texas, USA) to perform the statistical analyses and pooled estimates were calculated by using the 'metan' package.

RESULTS
Study selection

In total, 2944 records were identified through the initial database searches. Following the removal of 675 duplicates, the titles and abstracts of 2269 records were screened to identify papers eligible for full-text assessment. This left 222 articles where the full texts were reviewed. Studies were also included for full-text assessment if it was not clear from the title and/or abstract

whether the article included data on occupational exposures and lung function decline. Twelve relevant articles were finally included in this systematic review, and four articles included in the meta-analysis of ever exposures and three articles for cumulative exposures (figure 1).

The summary characteristics of the 12 population-based cohort studies[1 2 23–32] are presented in table 1 and the data on lung function decline are presented in online supplemental material table S1. The duration of follow-up in the studies ranged from 4.5 to 25 years, sample sizes ranged from 237 to 17 833, and the mean age at baseline ranged from 33.9 to 60.6 years. Eleven studies included both male and female participants, and one study included only male participants.[26] The methodological quality of all the studies included in the systematic review ranged from six to eight out of a scale of nine (table 2). This parameter indicated a good overall quality, so sensitivity analysis was not conducted by excluding any papers.

The studies used different exposure assessment methods. Most of the studies used JEMs to assess exposures,[1 2 23 24 28–32] however only three studies were based on self-report.[25–27] Exposure metrics (eg, ever/never, low/high, cumulative) were assigned by lifetime work history calendars,[1 2 29 30 32] current job titles[2 24 28 31] and any jobs at baseline or follow-up.[25–27] All studies reported FEV_1 and six studies[1 23 24 28 30 32] also reported FVC as indices of lung function. The units for lung function decline were presented as either ml/year or %predicted/year.

Ten studies followed American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines to perform spirometry,[1 2 23–26 29–32] but two studies did not mention any spirometry guidelines.[27 28] Eight studies presented outcomes using pre-bronchodilator (BD) spirometry,[1 2 24 26–28 30 31] two studies used post-BD spirometry,[25 32] one study used both pre-BD and post-BD,[23] and one study perform spirometry without BD.[29] One study included early COPD and current smokers at the baseline of the cohort,[25] whereas the other cohorts did not have this criterion. All studies adjusted the associations for age, sex and smoking status except for one,[23] which adjusted only for sex and socioeconomic status as this study developed a directed acyclic graph model for potential confounders and found smoking did not confound the association. Another three studies additionally adjusted for asthma, previous respiratory infection or lung diseases, co-exposures, among other factors.[1 2 29]

Occupational exposures (ever and cumulative) and lung function decline

Of the 12 studies, six reported associations between biological dust and decline in FEV_1, FVC or ratio of FEV_1/FVC as lung function outcomes (online supplemental material table S1).[1 2 24 30–32] Two studies reported a significant decline in FEV_1 for ever exposures to biological dust compared with never exposures.[24 32] The pooled estimates from both fixed and random effect meta-analysis found little evidence of heterogeneity (I^2=0%) and 1.42 mL/year decline in FEV_1 was observed with ever exposures to biological dust (figure 2). However, a meta-analysis of cumulative exposures provided evidence of an association for biological dust in the fixed effect model (table 3, online supplemental material figure S1). Publication bias was assessed by funnel plot (online supplemental material figure S3A and online supplemental material S4A) and an Egger's test for small-study effects showed no publication bias (p=0.001).

Seven studies reported the association between ever exposures to mineral dust and decline in FEV_1, FVC or ratio of FEV_1/FVC.[1 2 24 26 30–32] None of the studies reported the statistically

Table 1 Summary characteristics of the 12 longitudinal population-based studies included in the systematic review that examined the association between occupational exposures (ever and cumulative) and lung function decline

First author (year)	Location and study name	Sample size	Duration of follow-up (year)	Age at inception (years, mean±SD)	Method of exposure assessment	Summary of the studies	Confounders adjusted
Studies used pre-bronchodilator							
Skaaby et al.[30] (2021)	Denmark; Copenhagen City Heart Study	8202	9	48±7	ACE JEM and lifetime work history	No associations were observed between exposure to biological dust, mineral dust, gases/fumes and VGDF and lung function decline	Sex, smoking height, education, weights and baseline FEV_1
Skaaby et al.[30] (2021)	Denmark; Copenhagen General Population Study	7942	9	47±5	ACE JEM and lifetime work history	Men and smokers are at higher risk of having a lower lung function than women and non-smokers	Age, sex, smoking, pack-years, height, education, monthly income
Faruque et al.[24] (2020)	Netherlands; Lifelines Cohort Study	13759	4.5	44±12	ALOHA plus JEM and current or last held job	Aromatic solvents, gases/fumes and metals were associated with lung function decline in middle age	Sex, smoking, pack-years; height, socioeconomic status; childhood asthma, current asthma and co-exposures
Alif et al.[1] (2019)	Australia; TAHS Study	767	6 (2004–2010)	44.8±0.8	ALOHA plus JEM and lifetime work history	Dust exposure related to the loss of FEV_1, but not FEV_1/FVC ratio	Sex, age, smoking, pack-years, height
Liao et al.[28] (2015)	USA; Framingham Heart Study	1332	17	47.4±10.6	JEM (modified from UCSF COPD JEM) and current job	Pesticide exposure was associated with annual decline in lung function	Sex, age, pack-years, level of lung function and co-exposures
de Jong et al.[2] (2014)	Netherlands; Vlagtwedde-Vlaardingen Study	2527	25 (1965–1990)	35 (median)	ALOHA plus JEM and current job	Exposed to dust, gases and fumes were not related to change in lung function in a population of relatively young participants	Age, smoking, number of cigarettes, height, body mass index, change in body mass index, length of follow-up
Sunyer et al.[31] (2005)	ECRHS study	8263	9 (1991/93–1998/02)	Male 34.01, female 33.94 (mean)	JEM and current job	Exposures to gases and metals were associated with decline in FEV_1	Age, smoking, height
Humerfelt et al.[26] (1993)	Norway, population registry of Bergen	951 (only male)	23 (1965/70–1988/90)	38±8.8	Self-reported jobs at follow-up	Exposed to dust in men increased the decline in FEV_1	Age, smoking, height
Krzyzanowski et al.[27] (1985)	Poland, Krakow study	1864	13 (1968–1981)	19–70 (range)	Self-reported at baseline and follow-up		
Studies used post-bronchodilator							
Tagiyeva et al.[32] (2017)	UK; WHEASE cohort	237	25 (1989–2014)	60.6±1.5	ACE JEM and lifetime work history	Exposed to biological dust and vapours increased the risk of reduced lung function over 50 years in people who did not have childhood wheezing	Sex, age, pack-years of smoking, educational status
Harber et al.[25] (2007)	USA, Canada; multicentre lung health study	5724	5 (1986–1991)	Male 48.4, female 48.5 (mean)	Self-reported jobs at baseline and follow-up	Exposure to fumes was associated with the rate of decline in lung function in men with early COPD	Age, smoking status (cigarettes per day, yes/no), height, race
Studies used both pre-bronchodilator and post-bronchodilator							
Bui et al.[23] (2019)	Australia; TAHS study	857	8 (2008–2016)	53.1±0.7	ALOHA plus JEM and lifetime work history	Exposure to VGDF was associated with lung function decline	Sex and socioeconomic status
Study used without bronchodilator							
Lytras et al.[29] (2020)	ECRHS and SAPALDIA	17833	16.3 (1991/93–2010/12 and 1991–2001/11)	56.9 (mean)	ALOHA plus JEM and lifetime work history	Long-term occupational exposures to biological dust, mineral dust and metals were associated with an accelerated decline in FEV_1, and the FEV_1/FVC ratio	Age, sex, height, current asthma, smoking status (current, lifetime, pack-year), socioeconomic status, asthma (maternal, paternal, childhood)

ACE JEM, Airborne Chemical Exposure Job Exposure Matrix; ALOHA, A Lot of Occupational Hygiene Assumptions; ECRHS, European Community Respiratory Health Survey Study; FEV_1, Forced Expiratory Volume in 1 sec; FVC, Forced Vital Capacity; GPJEM, General Population Job Exposure Matrix; JEM, Job Exposure Matrix; SAPALDIA, Swiss Cohort Study on Air Pollution and Lung Disease in Adults; TAHS, Tasmanian Longitudinal Health Study; VGDF, Vapours, Dust, Gases and Fumes; VGDFFIM, Vapours, Dust, Gases, Fumes, Fibers and Mists; WHEASE, What Happens Eventually to Asthmatic children: Sociologically and Epidemiologically.

Table 2 Methodological quality score of 12 studies included in the systematic review based on Newcastle-Ottawa quality assessment score

Author (year)	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	(Out of 9)
Skaaby et al[30] (2021)	1	1	0	1	1	1	1	0	6
Lytras et al[29]	1	1	0	1	2	1	1	1	8
Faruque et al[24] (2020)	1	1	0	1	1	1	1	1	7
Alif et al[1] (2019)	1	1	0	1	2	1	1	1	8
Bui et al[23] (2019)	1	1	0	1	0	1	1	1	6
Tagjyeva et al[32] (2017)	1	1	0	1	1	1	1	1	7
Liao et al[28] (2015)	1	1	0	1	1	1	1	0	6
de Jong et al[2] (2014)	1	1	0	1	1	1	1	0	6
Harber et al[25]	1	1	0	1	1	1	1	1	7
Sunyer et al[31] (2005)	1	1	0	1	1	1	1	1	7
Humerfelt et al[26] (1993)	1	1	0	1	1	1	1	1	7
Krzyzanowski et al[27] (1985)	1	1	0	1	1	1	1	1	7

significant association for decline in FEV_1, however Sunyer *et al* reported that women had a greater decline in FEV_1 but the association was not significant for men.[31] One study by Faruque *et al* reported a significant decline in FVC with exposure to mineral dust compared with never exposures (online supplemental material table S1).[24] Meta-analysis for both ever and cumulative exposures did not show significant decline in FEV_1 compared with never exposures (figure 2, table 3). No publication bias was found by visualising the funnel plot (online supplemental material figure S3A, S4A), and Egger's test for small-study effects also showed no sign of publication bias (p=0.001).

Exposures to gases/fumes have been reported in seven studies.[1 24–26 30–32] The meta-analysis found a statistically significant decline in FEV_1 for ever and cumulative exposures to gases/fumes compared with never exposures (figure 2, table 3, online supplemental material figure S1). There was a moderate amount of heterogeneity for ever exposures ($I^2=45.7\%$) but cumulative exposures showed little evidence of heterogeneity ($I^2=0\%$) between the studies. Funnel plot (online supplemental material figure S3A and online supplemental material S4A) and Egger's test for small-study effects showed no publication bias in the analysis (p=0.001).

Combined exposures to VGDF and decline in FEV_1 were reported in five studies (online supplemental material table S1).[1 2 23 30 32] The meta-analysis of both fixed and random-effects models found a statistically significant decline in FEV_1 (1.77 mL/year and 3.31 mL/year) for ever exposures to VGDF compared with never exposures (figure 2). The trend was consistent for cumulative exposures to VGDF and decline in FEV_1 (table 3, online supplemental material figure S1). There was a large amount of heterogeneity for ever exposures ($I^2=71.7\%$) and no evidence of heterogeneity ($I^2=0\%$) for cumulative exposures between the studies was found. Funnel plot (online supplemental material figure S3A, S4A) and Egger's test for small-study effects showed no publication bias in the analysis (p=0.001).

The meta-analysis of ever and cumulative exposures to fungicides, herbicides and insecticides and the decline in FEV_1 found consistent results in both models. Ever exposures to fungicides were found to be associated with a 3.11 mL/year decline in FEV_1 (figure 3) in the fixed-effect model and a similar trend was observed for cumulative exposures (table 3). However, the association was not statistically significant in the random-effects models for both ever and cumulative exposures. No statistically significant association was found for ever and cumulative exposures to herbicides and insecticides and a decline in FEV_1 was found. The heterogeneity between the studies showed small to moderate heterogeneity (figure 3, online supplemental material S2). The funnel plot (nd online supplemental material figure S3B, S4B) and Egger's test for small-study effects showed no publication bias in the analysis (p=0.18 and p=0.00, respectively).

The decline in FEV_1 was significantly associated with the ever and cumulative exposures to aromatic solvents. The pooled estimates of ever exposures to aromatic solvents was found to be associated with a greater decline in FEV_1 for both models (6.16 mL/year and 7.35 mL/year, respectively) compared with never exposures (figure 4). Cumulative exposures to aromatic solvents also exhibited a statistically significant decline in FEV_1 (0.60 mL/intensity-year) compared with never exposures (table 3, online supplemental material figure S2). No association was found between metals and decline in FEV_1. There was a moderate amount of heterogeneity for ever exposures ($I^2=57.4\%$) and no evidence of heterogeneity ($I^2=0\%$) for cumulative exposures between the studies was found. The funnel plot (online supplemental material figure S3B, S4B) and Egger's
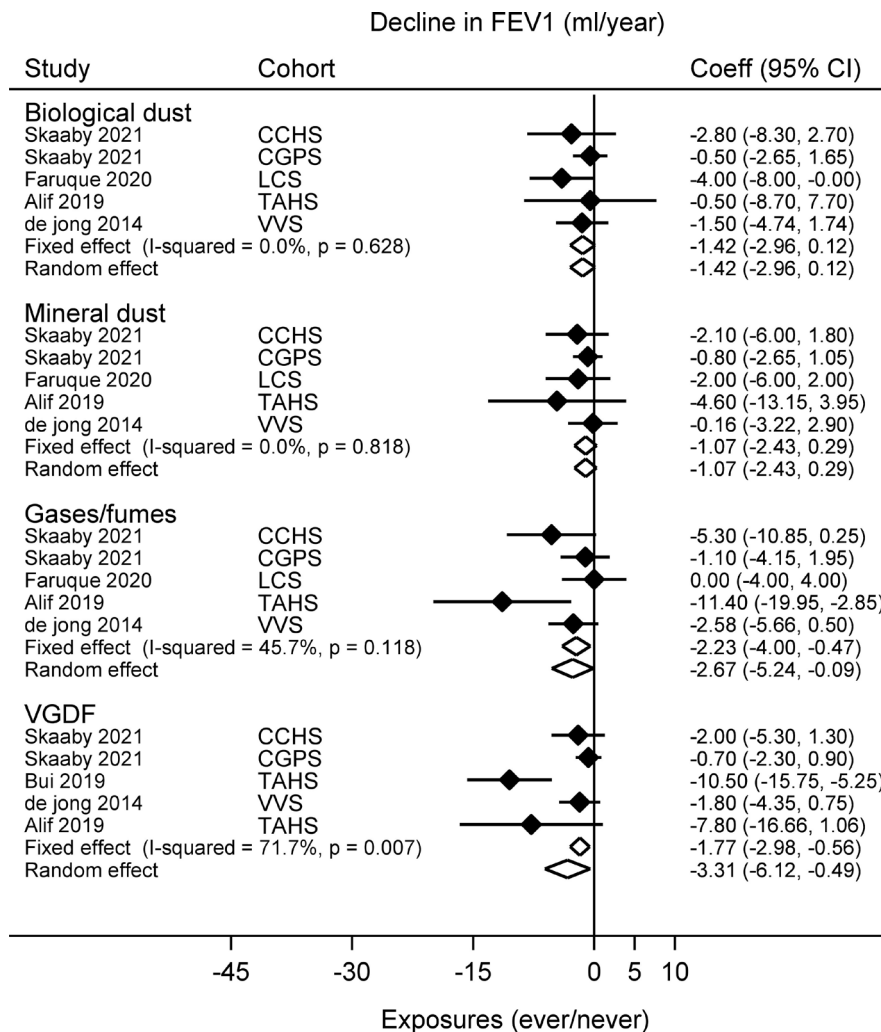
Decline in FEV1 (ml/year)

Figure 2 Forest plot showing the association between exposures to biological dust, mineral dust, gases/fumes and vapours, dust, gases and fumes (VGDF) and forced expiratory volume in 1 s (FEV$_1$) decline. CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; LCS, Lifelines Cohort Study; TAHS, Tasmanian Longitudinal Health Study; VVS, Vlagtwedde-Vlaardingen Study.

test for small-study effects showed no publication bias in the analysis (p=0.25 and p=0.0, respectively).

DISCUSSION

Our systematic review and meta-analysis assesses the evidence on the association between ever and cumulative occupational exposures and lung function decline in longitudinal population-based studies. Ever and cumulative exposures to gases/fumes, VGDF and aromatic solvents were significantly associated with FEV$_1$ decline. Associations between ever exposures to fungicides and cumulative exposures to biological dust, fungicides and insecticides and decline in FEV$_1$ were also observed in fixed-effect models. Exposures to mineral dust, herbicides and metals and decline in FEV$_1$ were not statistically significant in fixed or random effects models for meta-analysis of both ever and cumulative exposures. However, these occupational exposures appeared to confer a decline in lung function in pooled estimates for both of the models.

The pooled estimates of ever exposures to gases/fumes and decline in FEV$_1$ was observed to be statistically significant compared with never exposures. A meta-analysis of cumulative exposures to gases/fumes also found consistent evidence of the decline in FEV$_1$ for both fixed and random effects models. To

our best knowledge, no previous studies have reviewed or meta-analysed these associations. Our systematic review found inconsistent associations between exposure to gases/fumes and FEV$_1$ in population-based studies (online supplemental material table S1). However, the Vlagtwedde-Vlaardingen Dutch cohort found lower FEV$_1$ and FEV$_1$/FVC ratio with high exposure to gases/fumes and the association was significantly stronger for ever smokers.[8] Sunyer *et al* from ECRHS I and II data reported that women had a 3 mL/year greater decline in FEV$_1$ compared with men for high exposure to gases/fumes.[31] The association was also stronger for ex-smokers and no association was observed for men.[31] In addition, a study from Norway found a greater decline in FEV$_1$ only in men in exposure to sulphur dioxide gases.[26] Another study from the Netherlands found faster decline in FVC in exposure to gases/fumes.[24]

Cross-sectional studies have found that occupational exposure to VGDF was clearly associated with lower level of FEV$_1$ and FEV$_1$/FVC in the general population.[10 33 34] The associations between exposure to VGDF and decline in FEV$_1$ are inconsistent in our systematic review (online supplemental material table S1). However, our pooled results showed a strong association between ever and cumulative exposures to VGDF and decline in FEV$_1$. Australian study data used from the TAHS cohort used

Table 3 Association between cumulative exposures (per intensity-year) and decline in FEV₁ (mL) in three studies included in systematic review and meta-analysis

Occupational exposures	Alif et al.[1] (2019) (TAHS cohort)	de Jong et al.[2] (2014) (VVS)	Lytras et al.[29] (2020) (ECRHS cohort)	Lytras et al.[29] (2020) (SAPALDIA cohort)	Meta-analysis (β-coefficient)	
Biological dust	0.1 (−0.04 to 0.3)	−0.02 (−0.04 to 0.00)	−0.39 (−1.13 to 0.31)	−0.81 (−1.59 to −0.05)*	Fixed	−0.02 (−0.04 to −0.00)*
					Random	−0.09 (−0.24 to 0.06)
Mineral dust	0.1 (−0.1 to 0.2)	−0.01 (−0.04 to 0.01)	−0.39 (−0.96 to 0.20)	−0.5 (−1.22 to 0.21)	Fixed	−0.01 (−0.04 to 0.01)
					Random	−0.06 (−0.17 to 0.05)
Gases/fumes	−0.1 (−0.3 to −0.1)*	−0.02 (−0.05 to 0.01)	−0.10 (−0.62 to 0.43)	−0.23 (−0.89 to 0.42)	Fixed	−0.03 (−0.06 to 0.00)
					Random	−0.03 (−0.06 to 0.00)
VGDF	−0.03 (−0.14 to 0.07)	−0.02 (−0.04 to 0.00)*	−0.10 (−0.51 to 0.32)	−0.38 (-0.87 to 0.12)	Fixed	−0.02 (−0.04 to −0.00)*
					Random	−0.02 (−0.04 to −0.00)*
Fungicides	0.2 (−0.2 to 0.5)	−0.03 (−0.05 to −0.01)*	−1.62 (−3.10 to −0.14)*	0.17 (−1.45 to 1.75)	Fixed	−0.03 (−0.05 to −0.01)*
					Random	−0.14 (−0.43 to 0.14)
Herbicides	0.3 (−0.1 to 0.7)	−0.02 (−0.04 to 0.01)	−2.74 (−4.82 to −0.54)*	0.23 (−1.45 to 1.88)	Fixed	−0.02 (−0.05 to 0.00)
					Random	−0.25 (−0.69 to 0.20)
Insecticides	0.1 (−0.2 to 0.4)	−0.03 (−0.05 to −0.01)*	−1.56 (−3.03 to −0.11)*	0.04 (−1.03 to 1.10)	Fixed	−0.03 (−0.05 to −0.01)*
					Random	−0.08 (−0.28 to 0.12)
Aromatic solvents	−0.6 (−1.0 to −0.3)*	NA	0.57 (−0.56 to 1.70)	−0.59 (−1.97 to 0.78)	Fixed	−0.60 (−0.92 to −0.27)*
					Random	−0.60 (−0.92 to −0.27)*
Chlorinated solvent	−0.1 (−0.3 to 0.1)	NA	−0.48 (−1.34 to 0.37)	−0.50 (−1.50 to 0.50)	Fixed	−0.13 (−−0.32 to 0.06)
					Random	−0.13 (−0.32 to 0.06)
Metals	−0.1 (−0.2 to 0.1)	NA	−0.51 (−1.28 to 0.27)	−0.75 (−1.71 to 0.21)	Fixed	−0.13 (-0.27 to 0.02)
					Random	−0.23 (−0.57 to 0.10)

Data are presented as coefficients (95% confidence intervals).
*Statistically significant associations.
ECRHS, European Community Respiratory Health Survey Study; NA, Not Applicable; SAPALDIA, Swiss Cohort Study on Air Pollution and Lung Disease in Adults; TAHS, Tasmanian Longitudinal Health Study; VGDF, Vapours, Dust, Gases and Fumes ; VVS, Vlagtwedde-Vlaardingen Study.

both pre-BD and post-BD spirometry measurements and found strong associations for high exposure to VGDF and decline in FEV₁ in both measurements (we included pre-BD measurement in our meta-analysis).[23] A Dutch cohort found a lower level of FEV₁ and FEV₁/FVC with high exposure to VGDF and the association was strong for ever smokers (96 mL/year decline).[8] However, a multicentre study by Zock et al did not find a decline in FEV₁ for high exposure to VGDF, but a mean 61 mL/year decline in FEV₁ was observed for current smokers.[34] VGDF exposure was also associated with a decline in FEV₁/FVC ratio
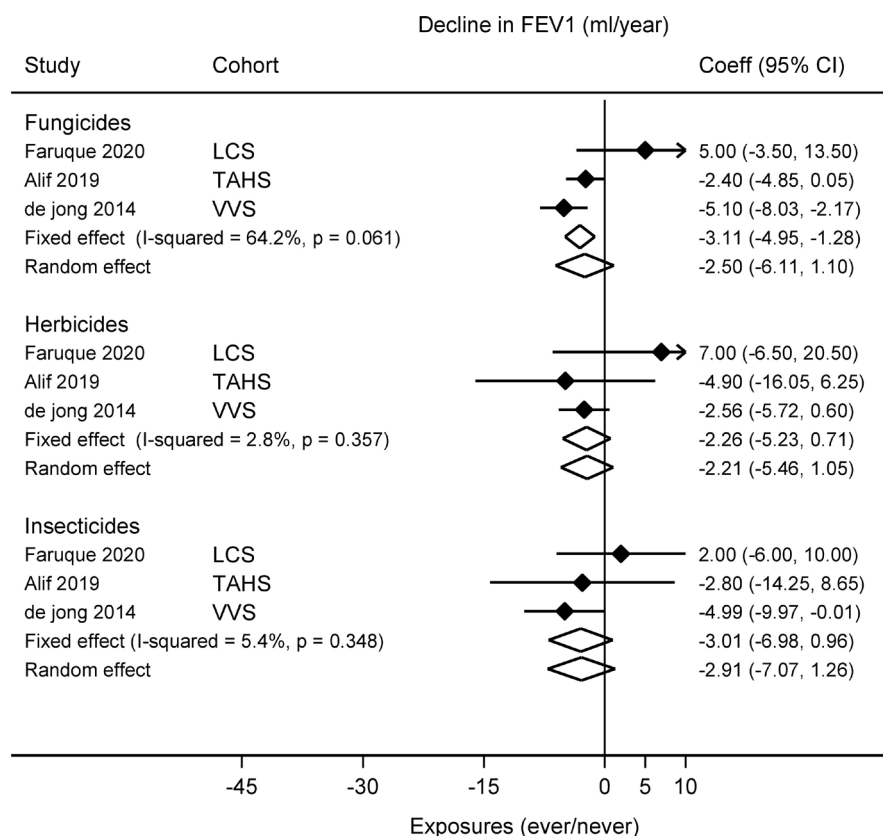
Figure 3 Forest plot showing the association between exposures to fungicides, herbicides and insecticides and forced expiratory volume in 1 s (FEV₁) decline. LCS, Lifelines Cohort Study; TAHS, Tasmanian Longitudinal Health Study; VVS, Vlagtwedde-Vlaardingen Study.
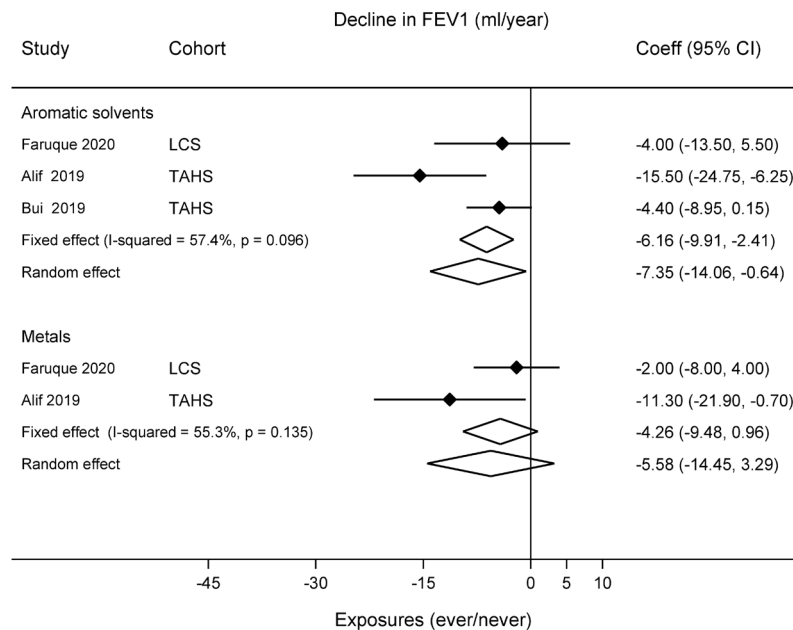
Figure 4 Forest plot showing the association between exposures to aromatic solvents and metals and forced expiratory volume in 1 s (FEV$_1$) decline. LCS, Lifelines Cohort Study; TAHS, Tasmanian Longitudinal Health Study.

reported in two longitudinal population-based studies in our systematic review.[1 23]

The associations between exposure to herbicides, insecticides and fungicides were inconsistent in the systematic review (online supplemental material table S1). The pooled estimates also showed similar trends for ever and cumulative exposures and decline in FEV$_1$. However, ever exposures to fungicides and cumulative exposures to fungicides and insecticides exhibited an association only in fixed-effect models but the association was attenuated in the random effect models. Similar to our meta-analysis, several workplace-based cross-sectional studies also found lower FEV$_1$ and FVC following exposure to fungicides, herbicides and insecticides in farmers or agricultural workers or pesticide applicators,[35–39] whereas a few studies also found no associations.[40 41] A recent systematic review and meta-analysis reported a reduction of FEV$_1$/FVC following pesticide (cholinesterase inhibiting) exposure in the general population.[42] However, a Dutch cohort study reported that high exposures to fungicides, herbicides and insecticides were associated with significantly lower levels of FEV$_1$ and exposure to fungicides are also related to lower levels of FEV$_1$/FVC.[8]

The reason for these inconsistencies could be related to spirometric criteria, where some studies reported pre-BD, but others post-BD measurements. The ATS/ERS guideline recommends using post-BD spirometry to distinguish between reversible (asthma) and irreversible (airflow obstruction) obstruction, particularly in younger adults.[43] However, none of the studies included used post-BD to measure lung function. The previous NHANES III study described that the use of a bronchodilator might vary the association up to 200% due to differences in spirometric criteria between population-based studies.[44]

Results from population-based studies have provided evidence of the association between lung function decline and solvent exposures (online supplemental material table S1), which is consistent with several population-based cross-sectional studies.[8 45–47] We found a significant association between ever and cumulative exposures to aromatic solvents and FEV$_1$ decline in our meta-analysis compared with never exposures. Two studies from the Australian TAHS cohort found a strong association between exposure to aromatic solvents and decline in FEV$_1$ and FVC, when lung function was defined using pre-BD spirometry and adjusted for all possible confounders, including sex, smoking, socioeconomic status and so on.[1 23] However, another study from the same cohort did not find a significant association with post-BD spirometry to define lung function and also did not adjust for smoking in the final model.[23] This also indicates that the difference in spirometry and the use of pre-BD measurements could overestimate the results.

The lung function parameters were not uniform across studies, and therefore it was difficult to include all studies in the meta-analysis for pooled estimates of ever and cumulative exposures and lung function decline. Furthermore, several methods have been used to assess occupational exposures in population-based studies, as direct assessment of exposure is difficult in such studies. Most of the studies reported absolute FEV$_1$ as a measure of lung function decline, while a few reported %predicted or the ratio as a measure of lung function decline. Another concern is that the association between occupational exposures and lung function could be confounded by pre-existing occupational or work-exacerbated asthma and co-exposures. Most of our included studies did not adjust for asthma, except Alif *et al* and Lytras *et al* and only two studies[1 2] included in the meta-analysis were adjusted for co-exposure. To untangle the possible effect of asthma and co-exposure on lung function decline, longitudinal studies should adjust for asthma and co-exposure or use the universal non-exposed group across all exposures in the statistical analysis.

The subjects in most of our included studies had a wide age range, and a few of them included young adults in their thirties.[2 26 31] The decline in FEV$_1$ and FVC may accelerate with age and is also exacerbated by smoking.[19] Several cross-sectional[48 49] and longitudinal studies reported that lung function parameters

such as FEV$_1$ and FVC decline with age.[50 51] Because some factors such as loss of lung elasticity weakened respiratory muscles and decreased surface area for alveolar gas exchange, these were invariably accompanied by ageing.[19] For example, the ECRHS reported that high exposure to VGDF was associated with 61 mL lower FEV$_1$ in current smokers[34] whereas the LifeLines cohort Study from the Netherlands found 96 mL lower FEV$_1$.[8] These differences might related to younger average age of the ECRHS sample (range 20–44 years) compared with the LifeLines cohort (range 18–89 years).[8] Therefore, age is an important factor for change in lung function, as lung function decline is evident above the age of 30,[52] moreover the variability of individual measurements around the median is not uniform across all ages and heights.[53] There was a variation in mean age across the studies which could underestimate the pooled estimate the FEV$_1$ in our meta-analysis. Furthermore, the inclusion of population-based studies reduced the number of exposed people could have further restricted the number of studies to detect an association. Most of our included studies did not present their results stratified by age. Therefore, it was not possible to conduct age specific subgroup analysis in the meta-analysis. Lung function declines with age in normal, asymptomatic adults with higher rates of decline in FEV$_1$ and FVC in men compared with women.[19] Some studies also reported that sex was a modifying factor; however not all studies reported stratified analysis by sex, which prevented us from conducting subgroup analysis.

The strengths of this review are the inclusion of the longitudinal population-based studies with objective measurements of lung function and a minimum of 1 year of follow-up with adjustment for important confounders such as smoking, age and sex. We have attempted to use standardised classification of exposure and outcome definition. We have focused on FEV$_1$ as a parameter of lung function decline, preferably with pre-BD measurement as most of the studies reported it. All studies in the meta-analysis of ever and cumulative exposures used similar spirometry measurements to control the heterogeneity except one study[29] used without BD in the meta-analysis of cumulative exposures. Another important thing is that the consistent exposure-outcome associations existed between ever and cumulative exposures.

Our review used consistent exposure assessment as most of the included studies used ALOHA plus JEM to assess exposures. This is a useful method for occupational exposure assessment because JEM consistently assigns exposures, irrespective of the disease status of an individual, which helps to reduce differential information bias.[11] The advantages of JEM helped to evaluate the possible effect with greater precision. However, a few studies also used less reliable self-reported exposure assessment,[25–27] which was not included in the meta-analysis. Follow-up time is of great importance, and in order to reliably assess lung function decline, several years of follow-up are required to achieve robust estimates, as argued by Burrows et al,[54] and supported by an official statement from the ATS/ERS on spirometry in the workplace.[55] In our systematic review and meta-analysis the follow-up ranged from 4.5 years to 25 years.

There are a few limitations in our study. JEM-based exposure assessment includes crude categories of ever exposures; therefore, we are unable to identify the specific gases, fumes, fungicides, herbicides, insecticides, aromatic solvents, chlorinated solvents, and metals or fibres and the exact duration of exposure responsible for lung function decline in individuals. The number of studies included in the meta-analysis was small due to strict inclusion and exclusion criteria. The inclusion of small numbers of studies in our meta-analysis might restrict statistical power to detect the association in pooled estimates and affect the generalisability of the results. Reporting bias may also be of concern due to the known risk of publication of studies with significant results. We assessed publication bias by visual inspection of funnel plots and did not observe any clear trends of bias. We were also unable to perform any subgroup analysis because the studies did not consistently provide results stratified by factors of interest, for example, age and sex. The response rate in our included studies varied from 11% to 93%, and two studies did not report their response rates.[2 28] As the cut-off at 50% to define a satisfactory response,[12] the loss of follow-up was unlikely to introduce bias in the included studies.

CONCLUSION

In this systematic review and meta-analysis, we found significant evidence that occupational exposures to gases/fumes, VGDF and aromatic solvents were associated with a greater decline in lung function. This trend was also persistent in the meta-analysis of cumulative exposures and lung function decline. In addition, this study also finds the relationship between ever and cumulative exposures to several exposures such as fungicides, insecticides and biological dust and lung function decline. Although, there was a significant decline in lung function parameters for some exposures, there was a high degree of heterogeneity between studies which limits the interpretation in terms of causal association. In addition, due to inconsistent exposure assessment tools and reporting in the individual studies and lack of data in subgroups, we were unable to conduct subgroup analysis, which future studies should focus on.

ORCID iDs
Golam Rabbani http://orcid.org/0000-0002-4172-3438
Malcolm R Sim http://orcid.org/0000-0003-4739-2817
Sheikh M Alif http://orcid.org/0000-0002-0783-8848

REFERENCES

1 Alif SM, Dharmage S, Benke G, et al. Occupational exposure to solvents and lung function decline: a population based study. *Thorax* 2019;74:650–8.

2 de Jong K, Boezen HM, Kromhout H, et al. Association of occupational pesticide exposure with accelerated longitudinal decline in lung function. *Am J Epidemiol* 2014;179:1323–30.

3 Sin DD, Man SFP. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005;2:8–11.

4 Eduard W, Pearce N, Douwes J. Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents. *Chest* 2009;136:716–25.

5 Christiani DC, Wang XR, Pan LD, *et al*. Longitudinal changes in pulmonary function and respiratory symptoms in cotton textile workers. A 15-yr follow-up study. *Am J Respir Crit Care Med* 2001;163:847–53.

6 Nordby K-C, Fell AKM, Notø H, *et al*. Exposure to thoracic dust, airway symptoms and lung function in cement production workers. *Eur Respir J* 2011;38:1278–86.

7 Torén K, Järvholm 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;145:992–7.

8 de Jong K, Boezen HM, Kromhout H, *et al*. Pesticides and other occupational exposures are associated with airway obstruction: the lifelines cohort study. *Occup Environ Med* 2014;71:88–96.

9 Matheson MC, Benke G, Raven J, *et al*. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. *Thorax* 2005;60:645–51.

10 Mehta AJ, Miedinger D, Keidel D, *et al*. 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;185:1292–300.

11 Alif SM, Dharmage SC, Bowatte G, *et al*. Occupational exposure and risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Expert Rev Respir Med* 2016;10:861–72.

12 Bolund AC, Miller MR, Sigsgaard T, *et al*. The effect of organic dust exposure on long-term change in lung function: a systematic review and meta-analysis. *Occup Environ Med* 2017;74:531–42.

13 Pourhassan B, Meysamie A, Alizadeh S, *et al*. Risk of obstructive pulmonary diseases and occupational exposure to pesticides: a systematic review and meta-analysis. *Public Health* 2019;174:31–41.

14 De Matteis S, Jarvis D, Darnton L, *et al*. Lifetime occupational exposures and chronic obstructive pulmonary disease risk in the UK Biobank cohort. *Thorax* 2022. doi:10.1136/thoraxjnl-2020-216523. [Epub ahead of print: 26 Jan 2022].

15 Brüske I, Thiering E, Heinrich J, *et al*. Respirable quartz dust exposure and airway obstruction: a systematic review and meta-analysis. *Occup Environ Med* 2014;71:583–9.

16 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.

17 Morgan RL, Whaley P, Thayer KA, *et al*. Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environ Int* 2018;121:1027–31.

18 Wells G, Shea B, O'Connell D. *The Newcastle-Ottawa scale (NOS) for assessing the quality of non randomised studies in meta-analyses*. The Ottawa Hospital, 2022. http://www. ohri. ca/ programs/ clinical_epidemiology/ oxford. asp

19 Thomas ET, Guppy M, Straus SE, *et al*. Rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies. *BMJ Open* 2019;9:e028150.

20 Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 2000;53:1119–29.

21 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.

22 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.

23 Bui DS, Perret JL, Walters EH, *et al*. Lifetime risk factors for pre- and post-bronchodilator lung function decline. A population-based study. *Ann Am Thorac Soc* 2020;17:302–12.

24 Faruque MO, Vonk JM, Kromhout H, *et al*. Airborne occupational exposures and lung function in the lifelines cohort study. *Ann Am Thorac Soc* 2021;18:60–7.

25 Harber P, Tashkin DP, Simmons M, *et al*. 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.

26 Humerfelt S, Gulsvik A, Skjaerven R, *et al*. Decline in FEV1 and airflow limitation related to occupational exposures in men of an urban community. *Eur Respir J* 1993;6:1095–103.

27 Krzyzanowski M, Jedrychowski W, Wysocki M. Factors associated with the change in ventilatory function and the development of chronic obstructive pulmonary disease in a 13-year follow-up of the cracow study. risk of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;134:1011–9.

28 Liao S-Y, Lin X, Christiani DC. Occupational exposures and longitudinal lung function decline. *Am J Ind Med* 2015;58:14–20.

29 Lytras T, Beckmeyer-Borowko A, Kogevinas M. Cumulative occupational exposures and lung function decline in two large general population cohorts. *Ann Am Thorac Soc* 2020.

30 Skaaby S, Flachs EM, Lange P, *et al*. Occupational inhalant exposures and longitudinal lung function decline. *Eur Respir J* 2021;58. doi:10.1183/13993003.04341-2020. [Epub ahead of print: 02 12 2021].

31 Sunyer J, Zock JP, Kromhout H, *et al*. Lung function decline, chronic bronchitis, and occupational exposures in young adults. *Am J Respir Crit Care Med* 2005;172:1139–45.

32 Tagiyeva N, Sadhra S, Mohammed N, *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;153:126–34.

33 Blanc PD, Iribarren C, Trupin L, *et al*. Occupational exposures and the risk of COPD: dusty trades revisited. *Thorax* 2009;64:6–12.

34 Zock JP, Sunyer J, Kogevinas M, *et al*. Occupation, chronic bronchitis, and lung function in young adults. an international study. *Am J Respir Crit Care Med* 2001;163:1572–7.

35 Faria NMX, Facchini LA, Fassa AG, *et al*. Pesticides and respiratory symptoms among farmers. *Rev Saude Publica* 2005;39:973–81.

36 Hoppin JA, Valcin M, Henneberger PK, *et al*. Pesticide use and chronic bronchitis among farmers in the agricultural health study. *Am J Ind Med* 2007;50:969–79.

37 Peiris-John RJ, Ruberu DK, Wickremasinghe AR, *et al*. Low-level exposure to organophosphate pesticides leads to restrictive lung dysfunction. *Respir Med* 2005;99:1319–24.

38 Hansen MRH, Jørs E, Sandbæk A, *et al*. Organophosphate and carbamate insecticide exposure is related to lung function change among smallholder farmers: a prospective study. *Thorax* 2021;76:780–9.

39 Cha ES, Lee YK, Moon EK, *et al*. Paraquat application and respiratory health effects among South Korean farmers. *Occup Environ Med* 2012;69:398–403.

40 Fieten KB, Kromhout H, Heederik D, *et al*. Pesticide exposure and respiratory health of Indigenous women in Costa Rica. *Am J Epidemiol* 2009;169:1500–6.

41 Schenker MB, Stoecklin M, Lee K, *et al*. Pulmonary function and exercise-associated changes with chronic low-level paraquat exposure. *Am J Respir Crit Care Med* 2004;170:773–9.

42 Ratanachina J, De Matteis S, Cullinan P, *et al*. Pesticide exposure and lung function: a systematic review and meta-analysis. *Occup Med* 2020;70:14–23.

43 Celli BR, Decramer M, Wedzicha JA, *et al*. An official American thoracic Society/European respiratory Society statement: research questions in COPD. *Eur Respir J* 2015;45:879–905.

44 Celli BR, Halbert RJ, Isonaka S, *et al*. Population impact of different definitions of airway obstruction. *Eur Respir J* 2003;22:268–73.

45 Le Moual N, Orlowski E, Schenker MB, *et al*. Occupational exposures estimated by means of job exposure matrices in relation to lung function in the PAARC survey. *Occup Environ Med* 1995;52:634–43.

46 Heederik D, Pouwels H, Kromhout H, *et al*. Chronic non-specific lung disease and occupational exposures estimated by means of a job exposure matrix: the zutphen study. *Int J Epidemiol* 1989;18:382–9.

47 LeVan TD, Koh W-P, Lee H-P, *et al*. Vapor, dust, and smoke exposure in relation to adult-onset asthma and chronic respiratory symptoms: the Singapore Chinese Health study. *Am J Epidemiol* 2006;163:1118–28.

48 Medbø A, Melbye H. Lung function testing in the elderly--can we still use FEV1/FVC<70% as a criterion of COPD? *Respir Med* 2007;101:1097–105.

49 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–87.

50 Huhti E, Ikkala J. A 10-year follow-up study of respiratory symptoms and ventilatory function in a middle-aged rural population. *Eur J Resp Dis* 1980;61:33–45.

51 Bossé R, Sparrow D, Garvey AJ, *et al*. Cigarette smoking, aging, and decline in pulmonary function: a longitudinal study. *Arch Environ Health* 1980;35:247–52.

52 Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging* 2006;1:253–60.

53 Stanojevic S, Wade A, Stocks J, *et al*. Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med* 2008;177:253–60.

54 Burrows B, Lebowitz MD, Camilli AE, *et al*. Longitudinal changes in forced expiratory volume in one second in adults. methodologic considerations and findings in healthy nonsmokers. *Am Rev Respir Dis* 1986;133:974–80.

55 Redlich CA, Tarlo SM, Hankinson JL, *et al*. Official American thoracic society technical standards: spirometry in the occupational setting. *Am J Respir Crit Care Med* 2014;189:983–93.