Occupational exposures and incidence of chronic bronchitis and related symptoms over two decades: the European Community Respiratory Health Survey

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Key messages

1. *What is already known about this subject?*

   Chronic bronchitis is an important COPD-related outcome, and certain occupational exposures have been previously associated with its prevalence.

2. *What are the new findings?*

   This study provides strong prospective evidence for an association between occupational exposures, particularly metals and mineral dust exposure, and chronic bronchitis incidence.

3. *How might this impact on policy or clinical practice in the foreseeable future?*

   Occupation may be associated not just with COPD, but also with particular COPD phenotypes. Occupation needs to be taken into account in the clinical evaluation of COPD patients.

Abstract

Objectives: Chronic bronchitis (CB) is an important COPD related phenotype, with distinct clinical features and prognostic implications. Occupational exposures have been previously associated with increased risk of CB but few studies have examined this association prospectively using objective exposure assessment. We examined the effect of occupational exposures on CB incidence in the European Community Respiratory Health Survey (ECRHS).

Methods: Population samples aged 20-44 were randomly selected in 1991-1993, and followed up twice over 20 years. Participants without chronic cough or phlegm at baseline were analyzed. Coded job histories during follow-up were linked to the ALOHA Job-Exposure Matrix, generating occupational exposure estimates to twelve categories of chemical agents. Their association with CB incidence over both follow-ups was examined with Poisson models using Generalized Estimating Equations.

Results: 8,794 participants fulfilled the inclusion criteria, contributing 13,185 observations. Only participants exposed to metals had a higher incidence of CB (RR=1.70, 95% CI: 1.16 – 2.50) compared to non-exposed to metals. Mineral dust exposure increased the incidence of chronic phlegm (RR=1.72, 95% CI: 1.43 – 2.06). Incidence of chronic phlegm was increased in men exposed to gases/fumes and to solvents and in women exposed to pesticides.

Conclusions: Occupational exposures are associated with chronic phlegm and chronic bronchitis, and the evidence is strongest for metals and mineral dust exposure. The observed differences between men and women warrant further investigation.

Introduction

Chronic Bronchitis (CB) has been defined as the presence of cough and sputum production for at least three months in two consecutive years. CB is common in patients with Chronic Obstructive Pulmonary Disease (COPD) [1]. COPD is a leading cause of mortality and morbidity worldwide [2], and is characterized by largely persistent airflow limitation, respiratory symptoms and frequent symptom exacerbations [3]. Tobacco smoking is the primary risk factor for COPD, although a number of other environmental factors have been identified [4], including occupational exposures [5]. CB is one of the validated COPD related clinical phenotypes with distinct clinical features [6].

CB is also seen in persons without airflow limitation, especially among smokers [7]. Besides its detrimental impact on quality of life [8], CB is important because it has been associated with more frequent exacerbations, accelerated lung function decline, increased incidence of COPD and increased all-cause mortality [7,9–11], even among those without airflow limitation [12].

Although occupation is currently considered an established risk factor for COPD [13], few studies have specifically examined the association between CB and certain occupational exposures [14], particularly dusts and fumes, and most such studies have been cross-sectional [5]. The European Community Respiratory Health Survey (ECRHS) is a large multicentre population-based longitudinal study that includes detailed information on occupation and respiratory outcomes, and can therefore provide strong prospective evidence. An earlier analysis in this cohort, which enrolled adults of fairly young age, did not show an association of occupational exposures with the incidence of CB, but only with chronic phlegm for mineral dust and gases/fumes exposure [15]. Now the ECRHS has accumulated 20 years of follow-up, allowing a relative aging of the study population. Furthermore, we recently demonstrated an association between occupational exposures (biological dust, gases/fumes and pesticides) and COPD incidence within a subset of the ECRHS cohort [16]. Following up from that analysis, our objective was to examine the effect of a variety of occupational exposures on CB incidence in the ECRHS.

Methods

ECRHS study overview

The aims and methods of the ECRHS have been described before [17]. In brief, the study began in 1991–1993 and enrolled random general population samples aged 20 to 44 years in 55 centres from 23 countries. A first follow-up visit was performed between 1998 and 2002 (ECRHS II) and a second between 2010 and 2012 (ECRHS III). At baseline and at both follow-ups participants completed a detailed questionnaire via face-to-face interview and underwent a clinical examination, spirometry and other measurements. Ethical approval for each centre was obtained from their respective competent bodies, and written informed consent was obtained from all participants.

Outcome definition, study population and spirometry

At each study visit participants were asked “Do you usually cough during the day, or at night, in the winter?” followed by “Do you cough like this on most days for as much as three months each year?”; a positive response to both questions was defined as chronic cough. Participants were also asked “Do you usually bring up any phlegm from your chest during the day, or at night, in the winter?” followed by “Do you bring up phlegm like this on most days for as much as three months each year?”; a positive response to both questions was defined as chronic phlegm. CB was defined as the presence of both chronic cough and chronic phlegm, i.e. a positive response to all four questions above.

CB was the main outcome of the study, but chronic cough and chronic phlegm were also separately examined as secondary outcomes. Chronic phlegm (which implies coughing up the sputum) can be regarded as a more sensitive outcome that is still related to CB. Chronic cough (without phlegm), on the other hand, is much less specific and can be also indicative of other respiratory disorders, such as asthma or interstitial lung disease. The study population included all participants who had neither chronic cough nor chronic phlegm at baseline (ECRHS I) and were followed at least once, i.e. at ECRHS II and/or ECRHS III.

Forced spirometry testing during follow-up was performed according to the ATS/ERS standards for reproducibility, keeping the maximum Forced Volume Capacity (FVC) and Forced Expiratory Volume in 1 second (FEV1) per participant. No bronchodilator was administered. For each participant, the presence of airflow limitation was defined as an FEV1/FVC ratio under the Lower Limit of Normal (LLN) for age, height and gender according to the GLI-2012 equations [18]. Furthermore, the severity of airflow limitation was graded according to the GOLD classification categories, as follows: Normal (FEV1/FVC ≥ LLN), Stage I (FEV1/FVC < LLN, FEV1 ≥ 80% predicted), Stage II (FEV1/FVC < LLN, 50% ≤ FEV1 < 80% predicted), Stage III-IV (FEV1/FVC < LLN, FEV1 < 50% predicted).

Occupational exposure assessment

At both follow-up interviews, participants were asked to provide a detailed list of their occupations and industries from jobs held since the previous study visit. Jobs performed for at least 8 hours a week for at least three months were included. Each such employment was recorded in free text and subsequently coded in the International Classification of Occupations-88 (ISCO-88) by trained local coders in each country. Occupational exposures were assessed by linking the ISCO-88 occupational codes to the semi-quantitative ALOHA(+) Job-Exposure Matrix (JEM), a general-purpose JEM that has been used in many similar occupational epidemiology studies [19,20]. For every job code, the ALOHA(+) JEM assigns three levels of exposure (none, low, high) to ten categories of agents (biological dusts, mineral dusts, gases/fumes, herbicides, insecticides, fungicides, aromatic solvents, chlorinated solvents, other solvents, and metals) and two composites of the above (All pesticides and Vapors/Gases/Dusts/Fumes – VGDF).

Data analysis

Associations between the three outcomes (CB, chronic cough, chronic phlegm) and occupational exposures were examined in Poisson regression models fitted using Generalized Estimating Equations (GEE) with an exchangeable working correlation matrix [21]. Such GEE models provide population-averaged Relative Risk

(RR) effect estimates over the follow-up visits of a longitudinal study, accounting for the correlation between multiple observations from the same study participant [22]. In addition, GEE implicitly accounts for the nested clustering structure by study centre and by country. All models were adjusted for age, sex, lifetime smoking pack-years, current smoking, Socioeconomic Status (SES), current asthma and severity of airflow limitation at follow-up. We also included quadratic terms for age and lifetime smoking pack-years, in order to account for potential nonlinear relationships between these important covariates and CB incidence [23]. SES was defined according to the participants' age of completion of formal education, and classified into three categories: high (>19 years), middle (16-19 years), low (<16 years). Current asthma was defined as a positive response to either of the following three questions: “have you had an attack of asthma in the last 12 months?”, “are you currently taking any medicines for asthma?” and “have you been woken by an attack of shortness of breath at any time in the last 12 months?”.

For each of the 12 ALOHA(+) exposures one model was fit, comparing any exposure (to the respective agent) to no exposure (to that agent). Stratified effects by sex and by smoking status (ever smokers vs never smokers) were obtained by including appropriate interaction terms in the models, and dose-response was examined by including separate terms for only low and for ever high exposure (to each agent). Four sensitivity analyses were performed; one without adjustment for severity of airflow limitation, one excluding all incident asthma cases, another both excluding incident asthma cases and without adjustment for severity of airflow limitation, and another without adjustment for SES. Comparisons between models were performed using the Quasi-likelihood Information Criterion (QIC) statistic [24]; between two models fitted on the same dataset, the one with the lower QIC is the best supported by the data. To address missingness with respect to covariates, we used multiple imputation with chained equations [25]; 50 imputed datasets were created, with models fit on each one and the results pooled. For details on the multiple imputation procedure and comparison with the corresponding complete case analyses, see the online supplement. All analyses were performed with the R statistical environment, version 3.4.2 [26], using packages “geepack”, “mice” and “QICpack”.

Results

Figure 1 illustrates the flow of ECRHS participants into our final study sample; in total 8794 participants fulfilled the selection criteria and were included in the analysis, originating from 30 study centres in 15 countries (Australia, Belgium, Denmark, Estonia, France, Germany, Iceland, Italy, Norway, Spain, Sweden, Switzerland, UK, UK and the USA). Median age at baseline was 34.3 years. Of those participants, 4515 participated in both follow-up visits, 3361 only in ECRHS II and 918 only in ECRHS III. The descriptive characteristics of the study population are summarized on Table 1. 116 participants (1.5%) had CB at the ECRHS II, and the percentage increased to 2.1% at the ECRHS III (p=0.014). Approximately half of all participants were ever smokers, and across both follow-ups smokers were more likely to report CB (129/5845, 2.2%) than never smokers (63/5266, 1.2%, p<0.001). The proportion of participants with any occupational exposure since baseline (ECRHS I) ranged from 1.5% (to herbicides at ECRHS II) up to 40.5%

(to gases/fumes at ECRHS III). Substantial correlations between individual exposures were noted, particularly within the pesticides and solvents categories (Figure 2). A number of participants had missing covariate information, especially as regards spirometry and smoking status information, particularly at ECRHS III (Table 1). Therefore multiple imputation was performed; pooled results are presented below, unless otherwise noted.

Table 2 summarizes the results from the main, fully-adjusted GEE model, for the three outcomes of interest (CB, chronic cough and chronic phlegm). Any exposure to metals, as compared to no metals exposure, resulted in an increased incidence of CB (RR=1.70, 95% CI: 1.16 – 2.50); less pronounced increased risks were also observed for exposure to mineral dust (RR=1.35, 95% CI: 0.99 – 1.83) and chlorinated solvents (RR=1.21, 95% CI: 0.81 – 1.81). To put this in perspective, these effects are similar or greater than the adjusted effects of 10 pack-years of smoking (Table 2). Neither exclusion of incident asthma cases from the analysis, omitting adjustment for severity of airway obstruction, nor omitting adjustment for SES did meaningfully impact these results (Supplementary Table 1). In the models with separate terms for only low and ever high exposure, there was no strong evidence (on the basis of a lower QIC compared to the main models) for a dose-response effect of any exposure on CB incidence (Supplementary Table 2). Similarly, no significant differences were found by gender or by smoking status (Supplementary Table 3), although metal exposure appeared to have a stronger effect on CB incidence among never smokers (RR=2.45, 95% CI: 1.23 – 4.91) than among ever smokers (RR=1.51, 95% CI: 0.97 – 2.36).

Associations were generally weaker for chronic cough (Table 2) and only exposure to metals showed an effect on incidence (RR=1.29, 95% CI: 1.02 – 1.64), which was not substantially modified by intensity of exposure, gender or by smoking status, and was similar in all three sensitivity analyses.

With respect to chronic phlegm we observed increased incidence for exposure to metals, aromatic and chlorinated solvents, mineral dust, gases and fumes and VGDF (Table 2). Exclusion of incident asthma cases or omitting adjustment for airway obstruction did not materially change the results (Supplementary Table 1). Moreover, there was evidence (lower QIC) for effect modification by gender (Table 3); a significant effect on chronic phlegm incidence was observed only in men for gases and fumes (RR=1.51, 95% CI: 1.20 – 1.91), VGDF (RR=1.63, 95% CI: 1.29 – 2.06), and also for other solvents (RR=1.27, 95% CI: 1.00 – 1.62). On the other hand, women exposed to insecticides and fungicides had higher incidence of chronic phlegm (RR=2.10, 95% CI: 1.10 – 4.01 and RR=2.03, 95% CI: 1.03 – 4.02 respectively), which was not the case for men. No effect modification was observed by smoking status for any of the 12 ALOHA(+) exposures. However, we observed evidence of an exposure-response relationship between VGDF exposure and chronic phlegm; any high exposure to VGDF resulted in an RR of 1.55 (95% CI: 1.25 – 1.91) compared to no exposure, while only low exposure to VGDF showed a lower risk (RR=1.20, 95% CI: 1.02 – 1.41).

Discussion

This is the first study to use CB as outcome, and estimate incidence rather than its prevalence, in a

prospective fashion. Several important associations were found for CB and chronic phlegm, and, to a lesser extent, for chronic cough.

Our study is the first large prospective population-based study to clearly show that occupational exposure to metals increases the incidence of CB. Only one smaller population-based study has recently associated exposure to metals with fixed airflow obstruction [27], and an industry-based study linked metals to deterioriation in lung function [28]. Occupations involving exposure to metals in our study cohort included jobs such as motor vehicle mechanics, other machinery engineers and technicians, plumbers and pipe fitters. The mechanisms via which metals exposure may be associated with CB symptoms are not clear. Metals are a heterogenous category of exposures, that have been linked with various forms of pulmonary toxicity [29]. For one metal in particular, vanadium (present in steel and in fossil fuels), there is both occupational epidemiologic and experimental evidence of an association with bronchitis [30,31].

Many workers in these occupations were also exposed to mineral dust, which also showed a trend towards increased CB incidence, especially with incident asthma cases omitted from analysis. Other frequent jobs with mineral dust exposure but without metals exposure included truck and lorry drivers (low probability and high intensity), and helpers/cleaners in offices, hotels and other establishments (high probability and low intensity), the latter jobs frequently performed by women. A number of population-based studies have associated dusts exposure in general with CB symptoms [5], but only one cross-sectional study has done so specifically for mineral dust, showing an even higher risk in ever smokers [32]. Our study adds substantially to the evidence base for this association. In addition, we did not find an interaction of mineral dust exposure (or any other exposure) with smoking, nor with sex, for the outcome of CB symptoms.

We also examined chronic cough and chronic phlegm separately, two outcomes that are less specific than CB; this particularly applies to chronic cough, for which no association was found in this study with occupational exposures other than metals. However, we found many interesting associations with chronic phlegm as outcome, which were very similar to those observed in a recent cross-sectional study from the Netherlands that used the same job-exposure matrix to assign exposure and the same outcome definitions as our study [33]. Moreover, we found that the effects were different for men and women; although mineral dust exposure increased the incidence of chronic phlegm in both men and women, metals, gases/fumes and solvents had this effect only among men. In addition we found increased chronic phlegm incidence only among women exposed to insecticides and fungicides; although the numbers of exposed cases were small, this finding deserves further attention as pesticides have recently been associated with accelerated lung function decline [20] and airway obstruction [34]. Chronic phlegm is the key presenting symptom of chronic bronchitis and there is an active interest in its exact role in the pathogenesis and progression of COPD [35]. There is recent evidence that chronic phlegm may represent an early developmental phase of COPD particularly among smokers [10], for some COPD cases [36]. As a result, the association of occupational exposures with this outcome is important and may represent a pathway through which occupation mediates its effects on COPD risk.

It is of particular interest to compare these findings about CB with our recently published analysis on

occupational exposures and spirometry-defined COPD incidence in the ECRHS [16]. That analysis used a narrower subset of the cohort (3,343 participants with complete follow-up between ECRHS I and III) and found an association with COPD incidence for biological dust, gases/fumes and pesticides, but not for metals or mineral dust exposure. In contrast, we found here no association with CB or chronic phlegm for biological dust, and associations with chronic phlegm only for gases/fumes and pesticides (the latter only among women). These differences may indicate that the effects of occupational exposures are complex, and mediated by different pathogenetic mechanisms that are currently poorly understood [37], resulting in variable effects on COPD and CB incidence. It is also a reminder that these are associated but distinct entities; an individual can have COPD without ever having CB, and not all patients will CB will end up with COPD [37].

The prevalence of chronic respiratory symptoms, including chronic bronchitis, is higher among patients with COPD [38]. The severity of airflow limitation may be associated, if only weakly, with CB symptoms [38,39]. Therefore we decided in advance to adjust our analyses for the severity of airflow limitation; however it was found to not substantially affect the relationship between CB and occupational exposures. Exclusion of incident asthma cases resulted in slightly higher effect estimates for both mineral dust and metals exposure, particularly with CB as outcome. Exclusion of participants with asthma essentially increases the specificity of the study questions for the ascertainment of CB, thereby reducing non-differential misclassification of outcome which might bias estimates toward the null.

The strengths of the current study include the prospective design, long follow-up of 20 years (one of the longest to date) and large population size. Job histories were collected for the entire follow-up period, which for many participants represented most of their working life to date; therefore occupational exposures could be assessed for a variety of agents, and in an objective way using a JEM rather than self-reported, which could be more vulnerable to recall and/or reporting bias. We were able to control for multiple important confounders for CB, including not just smoking but also lifetime smoking pack-years, and also socioeconomic status and current asthma. We also accounted for nonlinear relationships of CB with age and smoking pack-years, in order to reduce residual confounding as far as possible. Multiple imputation was employed to effectively handle missing covariates, which can be a problem in any large population-based study. In addition, the multi-centre and multi-country design increases the generalizability of our findings.

On the other hand, the study has certain limitations. The incidence of CB in our cohort was very low (around 2%) compared to other studies, and lower than the reported prevalence of 3.4%-22% for the general population, thereby diminishing the study power to detect associations; there are multiple possible reasons for this, including the relatively young age of the cohort, the exclusion of participants with cough or phlegm at baseline, and, potentially, the “healthy worker effect” due to both lower recruitment and/or higher dropout among participants with occupationally exposed jobs. The proportion of occupationally exposed women was much lower than men, as in most occupational epidemiology studies, making inference about effects in women more difficult. Future studies need to try and recruit more women, in order to assess potential effect modification by gender. In addition, although the study population was one of the largest to date, it was still

insufficient to do subgroup analyses or to reliably assess heterogeneity across study centres and countries. Finally, the use of a JEM tailored for general population studies cannot prevent a certain degree of exposure misclassification, since not all individuals in the same occupation will have been similarly exposed. As a consequence this might have resulted in somewhat attenuated, but not biased, risk estimates.

In conclusion, this study provides strong prospective evidence about the association of particular occupational exposures (metals, mineral dust, pesticides in women) with chronic bronchitis and chronic phlegm, thus highlighting their potential role in the pathogenesis and clinical presentation of COPD. This should be viewed in the wider context of the enviromental and lifestyle exposures associated with COPD. Future research should investigate the differences observed between men and women. Still, these findings highlight the need to avoid these exposures in the relevant occupations or control them via appropriate protective measures, as well as the need to take occupation into consideration when assessing individual patients for their COPD risk.

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Contributorship statement

Study idea & design: TL, MK, JPZ, HK, JMA, KT, DJ

Data collection: MK, HK, AEC, JMA, HB, JW, JH, DN, IU, JMM, JAG, APV, CRS, IP, PD, BL, SV, TG, OS, MH, BF, DN, AJM, NPH, GB, RJ, KT, TS, VS, MO, PDB, JW, RB, ASB, RV, DJ, JPZ

Data analysis: TL, JPZ

Data interpretation: all authors

Initial manuscript draft: TL, MK, JPZ

Critical revision of the manuscript for important intellectual content: all authors

Final approval of the manuscript for publication: all authors

Competing interests

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Bibliography

1 Kim V, Crapo J, Zhao H, *et al.* Comparison between an alternative and the classic definition of chronic bronchitis in COPDGene. *Ann Am Thorac Soc* 2015;**12**:332–9. doi:10.1513/AnnalsATS.201411-518OC

2 Lozano R, Naghavi M, Foreman K, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2095–128. doi:10.1016/S0140-6736(12)61728-0

3 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2017 report. 2017.

4 Eisner MD, Anthonisen N, Coultas D, *et al.* 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. doi:10.1164/rccm.200811-1757ST

5 Blanc PD, Torén K. Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update. *Int J Tuberc Lung Dis* 2007;**11**:251–7.

6 Kim V, Criner GJ. The chronic bronchitis phenotype in chronic obstructive pulmonary disease: features and implications. *Curr Opin Pulm Med* 2015;**21**:133–41. doi:10.1097/MCP.0000000000000145

7 Guerra S, Sherrill DL, Venker C, *et al.* Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk. *Thorax* 2009;**64**:894–900. doi:10.1136/thx.2008.110619

8 Meek PM, Petersen H, Washko GR, *et al.* Chronic Bronchitis Is Associated With Worse Symptoms and Quality of Life Than Chronic Airflow Obstruction. *Chest* 2015;**148**:408–16. doi:10.1378/chest.14-2240

9 de Marco R, Accordini S, Cerveri I, *et al.* Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. *Am J Respir Crit Care Med* 2007;**175**:32–9. doi:10.1164/rccm.200603-381OC

10 Allinson JP, Hardy R, Donaldson GC, *et al.* The Presence of Chronic Mucus Hypersecretion across Adult Life in Relation to Chronic Obstructive Pulmonary Disease Development. *Am J Respir Crit Care Med* 2016;**193**:662–72. doi:10.1164/rccm.201511-2210OC

11 Kim V, Han MK, Vance GB, *et al.* The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. *Chest* 2011;**140**:626–33. doi:10.1378/chest.10-2948

12 Woodruff PG, Barr RG, Bleecker E, *et al.* Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. *N Engl J Med* 2016;**374**:1811–21. doi:10.1056/NEJMoa1505971

13 Martinez CH, Delclos GL. Occupational exposures and chronic obstructive pulmonary disease. Causality established, time to focus on effect and phenotypes. *Am J Respir Crit Care Med* 2015;**191**:499–501. doi:10.1164/rccm.201501-0106ED

14 Holm M, Kim J-L, Lillienberg L, *et al.* Incidence and prevalence of chronic bronchitis: impact of smoking and welding. The RHINE study. *Int J Tuberc Lung Dis* 2012;**16**:553–7. doi:10.5588/ijtld.11.0288

15 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. doi:10.1164/rccm.200504-648OC

16 Lytras T, Kogevinas M, Kromhout H, *et al.* Occupational exposures and 20-year incidence of COPD: the European Community Respiratory Health Survey. *Thorax* 2018;**73**:1008–15. doi:10.1136/thoraxjnl-

2017-211158

17 Burney PG, Luczynska C, Chinn S, *et al.* The European Community Respiratory Health Survey. *Eur Respir J* 1994;**7**:954–60.

18 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;**40**:1324–43. doi:10.1183/09031936.00080312

19 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. doi:10.1136/thx.2004.035170

20 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. doi:10.1093/aje/kwu053

21 Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;**42**:121–30.

22 Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. *Stat Methods Med Res* 2013;**22**:661–70. doi:10.1177/0962280211427759

23 Castaldi PJ, Demeo DL, Hersh CP, *et al.* Impact of non-linear smoking effects on the identification of gene-by-smoking interactions in COPD genetics studies. *Thorax* 2011;**66**:903–9. doi:10.1136/thx.2010.146118

24 Pan W. Akaike's information criterion in generalized estimating equations. *Biometrics* 2001;**57**:120–5.

25 Sterne JAC, White IR, Carlin JB, *et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;**338**:b2393.

26 R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: : R Foundation for Statistical Computing 2015. http://www.R-project.org/

27 Alif SM, Dharmage SC, Benke G, *et al.* Occupational exposures to solvents and metals are associated with fixed airflow obstruction. *Scand J Work Environ Health* Published Online First: 7 August 2017. doi:10.5271/sjweh.3662

28 Hamzah NA, Mohd Tamrin SB, Ismail NH. Metal dust exposure and lung function deterioration among steel workers: an exposure-response relationship. *Int J Occup Environ Health* 2016;**22**:224–32. doi:10.1080/10773525.2016.1207040

29 Nemery B. Metal toxicity and the respiratory tract. *Eur Respir J* 1990;**3**:202–19.

30 Irsigler GB, Visser PJ, Spangenberg PA. Asthma and chemical bronchitis in vanadium plant workers. *Am J Ind Med* 1999;**35**:366–74.

31 Yu D, Walters DM, Zhu L, *et al.* Vanadium pentoxide (V(2)O(5)) induced mucin production by airway epithelium. *Am J Physiol Lung Cell Mol Physiol* 2011;**301**:L31-39. doi:10.1152/ajplung.00301.2010

32 de Meer G, Kerkhof M, Kromhout H, *et al.* Interaction of atopy and smoking on respiratory effects of occupational dust exposure: a general population-based study. *Environ Health* 2004;**3**:6. doi:10.1186/1476-069X-3-6

33 Dijkstra AE, de Jong K, Boezen HM, *et al.* Risk factors for chronic mucus hypersecretion in individuals with and without COPD: influence of smoking and job exposure on CMH. *Occup Environ Med* 2014;**71**:346–52. doi:10.1136/oemed-2013-101654

34 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. doi:10.1136/oemed-2013-101639

35 Cerveri I, Brusasco V. Revisited role for mucus hypersecretion in the pathogenesis of COPD. *Eur Respir Rev* 2010;**19**:109–12. doi:10.1183/09059180.00002710

36 Lange P, Vestbo J. Chronic Mucus Hypersecretion and the Natural History of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2016;**193**:602–3. doi:10.1164/rccm.201601-0001ED

37 Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;**187**:228–37. doi:10.1164/rccm.201210-1843CI

38 Agusti A, Calverley PMA, Celli B, *et al.* Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010;**11**:122. doi:10.1186/1465-9921-11-122

39 von Hertzen L, Reunanen A, Impivaara O, *et al.* Airway obstruction in relation to symptoms in chronic respiratory disease--a nationally representative population study. *Respir Med* 2000;**94**:356–63. doi:10.1053/rmed.1999.0715

Table 1: Characteristics of the study population, N=8,794 participants without cough or phlegm at baseline (ECRHS I)

	ECRHS II	ECRHS III
Number of participants followed up	7819	5366
Median age at follow-up (y), range	43.1 (26.4 – 57.0)	54.4 (38.7 – 67.8)
% male	47.3	47.5
% with chronic bronchitis (cough with phlegm)	1.5	2.1
% with chronic cough	4.6	5.7
% with chronic phlegm	4.0	4.7
% with current asthma	8.7	9.9
% current smokers	26.8	16.7
% ever smokers	52.4	52.9
Median lifetime smoking pack-years (ever smokers only)	13.2	16.2
% with airflow limitation (FEV1/FVC < LLN)	4.8	7.3
Severity (among those with airflow limitation)		
FEV1 >= 80% predicted	60.0	52.7
50% <= FEV1 < 80% predicted	37.1	43.1
FEV1 < 50% predicted	2.9	4.2
Occupational exposures (% with any exposure since baseline)		
Biological dust	26.2	30.5
Mineral Dust	20.3	23.1
Gases & fumes	36.4	40.5
Vapors, Gases, Dusts & Fumes	41.1	45.6
Herbicides	1.5	1.8
Insecticides	2.3	2.9
Fungicides	2.4	3.3
All pesticides	3.2	4.1
Aromatic solvents	12.6	14.5
Chlorinated solvents	10.0	11.9
Other solvents	22.7	26.7
Metals	9.2	10.9
% missing information		
Lifetime smoking pack-years	9.2	30.4
Current smoking	0.9	18.1
Current asthma	1.3	1.5
Socioeconomic status	0.5	3.7
Lung function	16.6	15.1

Table 2: Associations between (a) occupational exposures and 10 pack-years of smoking, and (b) incidence of CB, chronic cough and chronic phlegm. N=8794 participants without cough or phlegm at baseline (ECRHS I) followed-up at ECRHS II and/or III (n=13185 observations)

	Chronic Bronchitis			Chronic cough only			Chronic phlegm only		
	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)
Biological dust	159/9496 (1.7%)	68/3689 (1.8%)	1.00 (0.76 – 1.33)	480/9496 (5.1%)	188/3689 (5.1%)	0.94 (0.80 – 1.10)	385/9496 (4.1%)	179/3689 (4.9%)	1.14 (0.96 – 1.35)
Mineral Dust	164/10359 (1.6%)	63/2826 (2.2%)	1.35 (0.99 – 1.83)	504/10359 (4.9%)	164/2826 (5.8%)	1.11 (0.92 – 1.33)	374/10359 (3.6%)	190/2826 (6.7%)	**1.72 (1.43 – 2.06)**
Gases & fumes	131/8164 (1.6%)	96/5021 (1.9%)	1.14 (0.87 – 1.48)	409/8164 (5.0%)	259/5021 (5.2%)	0.97 (0.83 – 1.13)	299/8164 (3.7%)	265/5021 (5.3%)	**1.33 (1.13 – 1.57)**
Vapors, Gases, Dusts & Fumes	123/7525 (1.6%)	104/5660 (1.8%)	1.09 (0.84 – 1.41)	379/7525 (5.0%)	289/5660 (5.1%)	0.97 (0.83 – 1.13)	270/7525 (3.6%)	294/5660 (5.2%)	**1.36 (1.16 – 1.60)**
Herbicides	223/12974 (1.7%)	4/211 (1.9%)	1.08 (0.39 – 2.96)	655/12974 (5.0%)	13/211 (6.2%)	1.20 (0.71 – 2.05)	551/12974 (4.2%)	13/211 (6.2%)	1.30 (0.75 – 2.24)
Insecticides	222/12852 (1.7%)	5/333 (1.5%)	0.83 (0.34 – 2.02)	650/12852 (5.1%)	18/333 (5.4%)	1.04 (0.66 – 1.63)	546/12852 (4.2%)	18/333 (5.4%)	1.13 (0.72 – 1.80)
Fungicides	222/12823 (1.7%)	5/362 (1.4%)	0.78 (0.32 – 1.92)	649/12823 (5.1%)	19/362 (5.2%)	1.02 (0.65 – 1.60)	544/12823 (4.2%)	20/362 (5.5%)	1.18 (0.76 – 1.83)
All pesticides	220/12716 (1.7%)	7/469 (1.5%)	0.85 (0.40 – 1.82)	644/12716 (5.1%)	24/469 (5.1%)	1.00 (0.67 – 1.49)	541/12716 (4.3%)	23/469 (4.9%)	1.03 (0.68 – 1.56)
Aromatic solvents	195/11419 (1.7%)	32/1766 (1.8%)	1.06 (0.72 – 1.56)	571/11419 (5.0%)	97/1766 (5.5%)	1.09 (0.88 – 1.36)	467/11419 (4.1%)	97/1766 (5.5%)	**1.25 (1.01 – 1.56)**
Chlorinated solvents	198/11769 (1.7%)	29/1416 (2.0%)	1.21 (0.81 – 1.81)	586/11769 (5.0%)	82/1416 (5.8%)	1.14 (0.91 – 1.44)	482/11769 (4.1%)	82/1416 (5.8%)	**1.31 (1.04 – 1.65)**
Other solvents	175/9976 (1.8%)	52/3209 (1.6%)	0.94 (0.69 – 1.28)	518/9976 (5.2%)	150/3209 (4.7%)	0.91 (0.76 – 1.09)	418/9976 (4.2%)	146/3209 (4.5%)	1.09 (0.91 – 1.31)
Metals	194/11878 (1.6%)	33/1307 (2.5%)	**1.70 (1.16 – 2.50)**	588/11878 (5.0%)	80/1307 (6.1%)	**1.29 (1.02 – 1.64)**	483/11878 (4.1%)	81/1307 (6.2%)	**1.43 (1.13 – 1.81)**
Smoking (10 pack-years)			**1.31 (1.13 – 1.52)**			**1.14 (1.04 – 1.25)**			**1.22 (1.10 – 1.35)**

Pooled results from analysis on 50 multiply imputed datasets. Adjusted for age, sex, lifetime smoking pack-years, current smoking, socioeconomic status (SES), current asthma and severity of airflow limitation. Effect of smoking calculated from the GEE model with metals exposure as covariate.

Table 3: Associations between occupational exposures and incidence of chronic phlegm, stratified by gender. N=8794 participants without cough or phlegm at baseline (ECRHS I) followed-up at ECRHS II and/or III (n=13185 observations)

	Men			Women		
	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)
Biological dust	207/4701 (4.4%)	79/1546 (5.1%)	1.09 (0.85 – 1.41)	178/4795 (3.7%)	100/2143 (4.7%)	1.18 (0.93 – 1.50)
Mineral Dust	150/4267 (3.5%)	136/1980 (6.9%)	**1.76 (1.40 – 2.22)**	224/6092 (3.7%)	54/846 (6.4%)	**1.64 (1.23 – 2.19)**
Gases & fumes*	122/3388 (3.6%)	164/2859 (5.7%)	**1.51 (1.20 – 1.91)**	177/4776 (3.7%)	101/2162 (4.7%)	1.17 (0.92 – 1.48)
Vapors, Gases, Dusts & Fumes*	106/3109 (3.4%)	180/3138 (5.7%)	**1.63 (1.29 – 2.06)**	164/4416 (3.7%)	114/2522 (4.5%)	1.14 (0.91 – 1.44)
Herbicides	278/6098 (4.6%)	8/149 (5.4%)	1.08 (0.55 – 2.14)	273/6876 (4.0%)	5/62 (8.1%)	1.90 (0.79 – 4.55)
Insecticides*	277/6014 (4.6%)	9/233 (3.9%)	0.77 (0.41 – 1.46)	269/6838 (3.9%)	9/100 (9.0%)	**2.10 (1.10 – 4.01)**
Fungicides*	274/5975 (4.6%)	12/272 (4.4%)	0.91 (0.52 – 1.59)	270/6848 (3.9%)	8/90 (8.9%)	**2.03 (1.03 – 4.02)**
All pesticides*	272/5895 (4.6%)	14/352 (4.0%)	0.80 (0.47 – 1.34)	269/6821 (3.9%)	9/117 (7.7%)	1.84 (0.96 – 3.51)
Aromatic solvents	205/4859 (4.2%)	81/1388 (5.8%)	**1.35 (1.05 – 1.73)**	262/6560 (4.0%)	16/378 (4.2%)	0.99 (0.60 – 1.62)
Chlorinated solvents	220/5164 (4.3%)	66/1083 (6.1%)	**1.36 (1.04 – 1.78)**	262/6605 (4.0%)	16/333 (4.8%)	1.17 (0.72 – 1.89)
Other solvents*	196/4554 (4.3%)	90/1693 (5.3%)	**1.27 (1.00 – 1.62)**	222/5422 (4.1%)	56/1516 (3.7%)	0.90 (0.67 – 1.19)
Metals	210/5082 (4.1%)	76/1165 (6.5%)	**1.52 (1.18 – 1.96)**	273/6796 (4.0%)	5/142 (3.5%)	0.86 (0.37 – 2.02)

Pooled results from analysis on 50 multiply imputed datasets. Adjusted for age, sex, lifetime smoking pack-years, current smoking, socioeconomic status (SES), current asthma and severity of airflow limitation.

* Evidence for effect modification by gender (lower QIC for stratified model vs unstratified model)

Figure Legends

Figure 1: Flow chart of ECRHS participants into the study population, and reasons for exclusion

Figure 2: Correlation map (Spearman's rho) between occupational exposures in the study population (n=13185 observations)