The role of occupational exposures in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Introduction: Occupational exposures are considered to be one of the newer and important risk factors for Chronic Obstructive Pulmonary Disease (COPD) besides tobacco smoking. However, the evidence mostly comes from smaller and cross-sectional studies and important questions remain unanswered, such as which specific exposures are responsible, the magnitude of the risk involved, and how the risk varies between men and women and between smokers and nonsmokers. The aim of this thesis was to examine the association between objectively assessed occupational exposures and changes in COPD-related outcomes over two decades in the European Community Respiratory Health Survey (ECRHS), a large multicentre population-based longitudinal study.

Methods: General population samples aged 20-44 years were randomly enrolled in the ECRHS between 1991 and 1993, and twice followed up over the course of 20 years. Complete job histories during this follow-up were linked to the ALOHA(+) Job-Exposure Matrix, generating occupational exposures to 12 categories of agents. Spirometries were performed at each study visit. The outcomes of interest were: lung function decline, chronic bronchitis incidence and post-bronchodilator COPD incidence.

Results: Exposure to biological dust, gases & fumes and pesticides was associated with higher COPD incidence, with 21% of all COPD cases attributable to these three agents. Pesticides were associated with higher incidence of chronic phlegm but only in women, and gases & fumes and solvents also with chronic phlegm but only in men. Mineral dust exposure was associated with higher chronic phlegm incidence and metals exposure with hicher chronic bronchitis incidence, in both sexes. All studied exposures except solvents were associated with accelerated decline in the FEV1/FVC ratio, particularly in male smokers. Women exposed to biological dust also tended to have higher declines in FVC, as did men exposed to pesticides.

Conclusions: A substantial proportion of the total COPD burden is attributable to occupational exposures. The effect of occupation on COPD-related outcomes is complex, and depends on exposure type, sex and smoking status. Further research is warranted to provide more details about the observed associations.

RESUM

Introducció: Les exposicions ocupacionals es consideren un dels factors de risc importants per a la malaltia pulmonar obstructiva crònica (MPOC) juntament amb tabaquisme. No obstant això, l'evidència prové principalment d'estudis de mida petita i transversals i preguntes importants segueixen sense resposta, per exemple quines exposicions específiques són responsables, la magnitud del risc involucrat i com el risc varia entre homes i dones o entre fumadors i no fumadors. L'objectiu d'aquesta tesi és examinar l'associació entre exposicions ocupacionals objectivament avaluades i els canvis en els resultats relacionats amb la MPOC durant dues dècades en l'Enquesta de Salut Respiratòria de la Comunitat Europea (ECRHS), un gran estudi longitudinal multicèntric poblacional.

Mètodes: La mostra de la població general amb edats compreses entre 20 i 44 anys es va seleccionar aleatòriament a l'ECRHS entre 1991 i 1993, i a els participants se'ls hi va fer seguiment dues vegades en el transcurs de 20 anys. L'historial complet de treballs durant el període de seguiment es va vincular amb la Matriu d'Ocupació-Exposició ALOHA (+), generant estimacions d'exposicions ocupacionals a 12 categories d'agents. Les espirometries es van realitzar en cada visita d'estudi. Els resultats d'interès van ser: disminució de la funció pulmonar, incidència de bronquitis crònica i incidència de MPOC després de broncodilatació.

Resultats: L'exposició a pols, gasos i fums biològics i pesticides es va associar amb una major incidència de MPOC, amb un 21% de tots els casos de MPOC atribuïbles a aquests tres agents. Els pesticides es van associar amb una major incidència d'expectoració crònica, però només en les dones, i gasos i fums i dissolvents també amb expectoració crònica, però només en els homes. L'exposició a la pols mineral es va associar amb una major incidència d'expectoració crònica i l'exposició a metalls amb incidència de bronquitis crònica, en ambdós sexes. Totes les exposicions estudiades, excepte els dissolvents, es van associar amb una disminució accelerada de la relació FEV1 / CVF, (VEMS/CVF) particularment en fumadors homes. Les dones exposades a la pols d'origen biològic també van tenir majors disminucions en la capacitat vital forçada (CVF), igual que els homes exposats als pesticides.

Conclusions: Una proporció important dels casos de MPOC és atribuïble a exposicions ocupacionals. L'efecte de l'ocupació en els resultats relacionats amb la MPOC és complex i depèn del tipus d'exposició, el sexe i el tabaquisme. Es requereix més investigació per proporcionar més infromació sobre les associacions observades.

RESUMEN

Introducción: Las exposiciones ocupacionales se consideran uno de los factores de riesgo importantes para la enfermedad pulmonar obstructiva crónica (EPOC) junto con tabaquismo. Sin embargo, la evidencia proviene principalmente de estudios de pequeño tamaño y transversales y preguntas importantes siguen sin respuesta, por ejemplo qué exposiciones específicas son responsables, la magnitud del riesgo involucrado y cómo el riesgo varía entre hombres y mujeres o entre fumadores y no fumadores. El objetivo de esta tesis es examinar la asociación entre exposiciones ocupacionales objetivamente evaluadas y los cambios en los resultados relacionados con la EPOC durante dos décadas en la Encuesta de Salud Respiratoria de la Comunidad Europea (ECRHS), un gran estudio longitudinal multicéntrico poblacional.

Métodos: La muestra de la población general con edades comprendidas entre 20 y 44 años se seleccionó aleatoriamente en el ECRHS entre 1991 y 1993, y a los participantes se les hizo seguimiento dos veces en el transcurso de 20 años. El historial completo de trabajos durante el periodo de seguimiento se vinculó con la Matriz de Ocupación-Exposición ALOHA (+), generando estimaciones de exposiciones ocupacionales a 12 categorías de agentes. Las espirometrías se realizaron en cada visita de estudio. Los resultados de interés fueron: disminución de la función pulmonar, incidencia de bronquitis crónica e incidencia de EPOC después del broncodilatador.

Resultados: La exposición a polvo, gases y humos biológicos y pesticidas se asoció con una mayor incidencia de EPOC, con un 21% de todos los casos de EPOC atribuibles a estos tres agentes. Los pesticidas se asociaron con una mayor incidencia de expectoración crónica, pero solo en las mujeres, y gases y humos y disolventes también con expectoración crónica, pero solo en los hombres. La exposición al polvo mineral se asoció con una mayor incidencia de expectoración crónica y exposición a metales con incidencia de bronquitis crónica, en ambos sexos. Todas las exposiciones estudiadas, excepto los disolventes, se asociaron con una disminución acelerada de la relación FEV1/CVF (VEMS/CVF), particularmente en fumadores varones. Las mujeres expuestas al polvo de origen biológico también tenían mayor disminución en la Capacidad Vital Forzada (CVF), al igual que los hombres expuestos a los pesticidas.

Conclusiones: Una proporción importante de los casos de EPOC es atribuible a exposiciones ocupacionales. El efecto de la ocupación en los resultados relacionados con la EPOC es complejo y depende del tipo de exposición, el sexo y el tabaquismo. Se requiere más investigación para proporcionar más infromación sobre las asociaciones observadas.

PREFACE

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of morbidity in the world, whose impact is increasing as the population ages. Tobacco smoking is the primary cause of COPD, but other environmental risk factors have been recognized, including occupational exposures. Occupation is a defining feature in every adult person's life, and current economic trends mean that people are working longer and switch jobs more frequently. As such, and with smoking gradually on the decline, occupation plays an increasingly important role in respiratory health.

The evidence linking occupational exposures to COPD has been numerous, but mostly comes from smaller and lower quality studies. Many questions remain unanswered, regarding the kind of exposures, the magnitude of the effects, and differences by smoking status or between men and women. This thesis aims to provide some high-quality evidence on the role of occupation in COPD, and begin to answer some of these questions. The data come from the European Community Respiratory Health Survey (ECRHS), an international prospective population-based study with an accumulated follow-up of 20 years. The study has collected a wealth of individual information, including full job histories allowing comprehensive exposure assessment. As a result it is possible to do very detailed analyses and get good estimates of the effects of occupational exposures on multiple COPD-related outcomes.

This thesis has been written during my affiliation with the Barcelona Institute of Global Health (formerly Centre for Research in Environmental Epidemiology) between 2013 and 2017, and has been supervised by Dr. Jan-Paul Zock and Prof. Manolis Kogevinas. It consists of a compilation of scientific publications in agreement with the regulation of the Doctoral Programme in Biomedicine of the Department of Experimental and Health Sciences at the Pompeu Fabra University. The thesis includes an abstract, an introduction, an overall methods section, the results (in the form of three research publications), and an overall discussion section.

CONTENTS

1.INTRODUCTION

1.1 COPD and chronic bronchitis

Chronic Obstructive Pulmonary Disease (COPD) represents a major public health challenge, and is a leading cause of morbidity and mortality in the world (Lozano *et al.*, 2012; Prince *et al.*, 2015). Globally, it is currently the fourth leading cause of death in the world, but its impact is expected to increase in the following decades as the population ages and exposure to COPD risk factors is continued (Mathers & Loncar, 2006; Herse *et al.*, 2015). COPD causes considerable morbidity due to exacerbations and complications such as pneumonia, leading to increased physician visits and hospitalizations. Chronic conditions and comorbidities such as cardiovascular disease may increase the risk of hospitalization due to COPD.

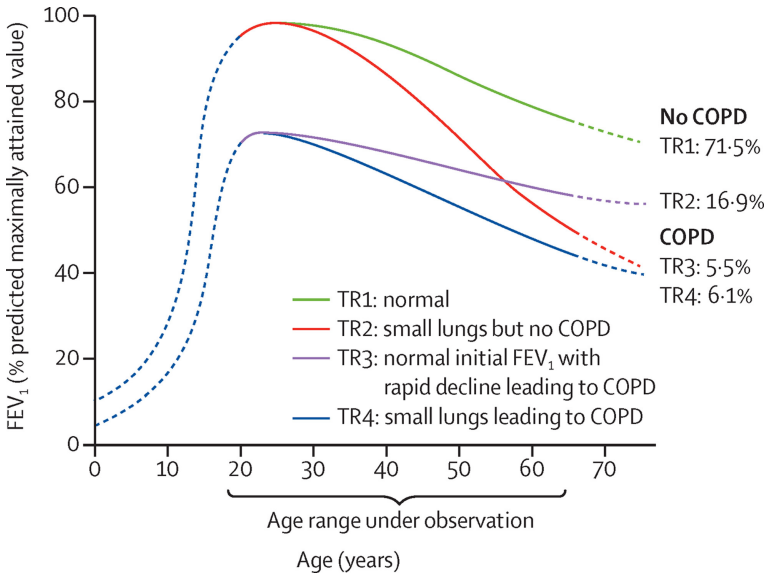
Because of considerable heterogeneity in the criteria and methods used to define COPD in epidemiological studies, there is substantial variability in estimates of COPD prevalence (Halbert *et al.*, 2006). Underreporting of the disease may also affect estimates of its prevalence (Quach *et al.*, 2015). However, it is clear that COPD affects tobacco smokers and ex-smokers much more than non-smokers, as well as men more than women, although the age gap appears to close as smoking becomes more common in women (Landis *et al.*, 2014). The prevalence of COPD is also higher with increasing age (Halbert *et al.*, 2006; Mercado *et al.*, 2015).

COPD has been defined as a common, preventable and treatable disease, characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (Vogelmeier *et al.*, 2017). Chronic inflammation causes structural changes and narrowing of small airways, with airflow limitation and mucociliary dysfunction; additionally there is destruction of lung parenchyma, with reduced elastic recoil of the lungs. These pathophysiologic processes vary from person to person, and have been linked to different clinical presentations; the term “emphysema” refers to parenchymal destruction of the gas-exchanging alveoli in the lung, and in the past has been used as a clinical term, though this has now fallen out of favor. The term “chronic bronchitis” on the other hand, refers to the presence of chronic cough and sputum production for at least three months in two consecutive years, and has both clinical and prognostic value (Kim *et al.*, 2011, 2015).

Tobacco smoking is by far the most important exposure causing COPD (Kohansal *et al.*, 2009), and the prevalence of tobacco smoking strongly correlates with the prevalence of COPD (Laniado-Laborín, 2009). However, it's been known that not all tobacco smokers suffer from the disease, which also does occur in nonsmokers as well (Lamprecht *et al.*, 2011). Many other environmental risk factors for COPD have been identified, with various levels of evidence, that may play an important role especially in developing countries (Eisner *et al.*, 2010; van Gemert *et al.*, 2015). Among others, these risk factors include environmental (secondhand) tobacco smoke (Yin *et al.*, 2007), outdoor air pollution (Gauderman *et al.*, 2007; Gan *et al.*, 2013), indoor air pollution and biomass smoke (Hu *et al.*, 2010; Gall *et al.*, 2013), asthma and airway hyperresponsiveness (de Marco *et al.*, 2011). Genes also appear to play a role: hereditary alpha-1 antitrypsin deficiency is a well known risk factor for COPD, although it accounts for only 1-2% of all cases; further genetic loci have been linked to accelerated lung function decline, or are being investigated (Foreman *et al.*, 2012). Occupation, the subject of the present thesis, has also been identified as a risk factor for chronic bronchitis and COPD in a variety of studies (Balmes *et al.*, 2003; Omland *et al.*, 2014; Alif *et al.*, 2016).

Lung function declines naturally with increasing age, and an accelerated lung function decline has long been considered as the proximate cause of COPD. However, it is now clear that COPD can frequently arise with a normal lung function decline, if optimal lung growth has not been achieved from childhood until early adulthood (Lange *et al.*, 2015) (Figure 1.1). There are several factors in early life that affect lung development, collectively termed “childhood disadvantage factors”, such as childhood asthma, parental smoking, lower respiratory infections in early childhood and low birth weight; these factors are important predictors of lung function in later, adult life (Lawlor *et al.*, 2005; Stern *et al.*, 2007; Svanes *et al.*, 2010). In fact, more than half of COPD cases may be due to abnormal lung development rather than accelerated lung function decline (Lange *et al.*, 2015).

Figure 1.1: Trajectories of lung function over time (adapted from Lange et al., 2015)



Airflow limitation, as measured by forced spirometry, is the defining feature of COPD; as such a diagnosis of COPD requires spirometry, ideally made after administrator of bronchodilation in order to exclude reversible airway obstruction from conditions such as asthma. Chronic respiratory symptoms such as progressive dyspnoea, cough and sputum production (i.e. chronic bronchitis) are also characteristic of COPD, however they may not be present on or reliably reported by all patients. As a result, COPD is usually defined in epidemiological studies by airflow limitation alone. Of the available diagnostic modalities, spirometry is the most objective and reproducible measurement of lung function, and has been adequately standardized (Miller *et al.*, 2005). Spirometry measures the volume of air forcibly exhaled from the point of maximal inspiration (Forced Vital Capacity, FVC) and the volume of air exhaled during the first second of forced expiration (Forced Expiratory Volume in one second, FEV1). The ratio of the two measurements (FEV1/FVC) is also calculated, which the most frequently used measurement to diagnose airflow limitation.

Interpretation of spirometric lung function parameters must be done with respect to reference values based on age, height, sex or race (Pellegrino *et al.*, 2005). Reference equations constructed from large epidemiological studies are used for this purpose, such as the European Community for Coal and Steel equations (Quanjer *et al.*, 1993), the NHANES III equations (Hankinson *et al.*, 1999) and more recently the multi-ethnic Global Lung Initiative (GLI-2012) equations (Quanjer *et al.*, 2012), which are the current gold standard. Based on these, absolute lung function values can be expressed as

“percent predicted” values with reference to the predicted lung function value given age, height, sex and race.

Two criteria can be used to define airflow limitation as part of COPD diagnosis. One is a fixed FEV1/FVC ratio of under 0.7, which is simple and widely used both in clinical practice and in epidemiological studies. However, the fixed FEV1/FVC ratio has been shown to lead to more frequent COPD diagnosis in the elderly, and less frequent in middle age patients or those with mild disease (van Dijk *et al.*, 2015; Kainu *et al.*, 2016). An alternative is to use cut-off values based on a Lower Limit of Normal (LLN) for FEV1/FVC, which classifies a given proportion of the population (usually the bottom 5% of the distribution) as having an abnormally low FEV1/FVC ratio. This requires the use of a reference equation, and the LLN is highly dependent on the equation chosen (Roche *et al.*, 2008). Using an LLN criterion may lead to more reliable and clinically relevant classification of both normal spirometry and of airflow limitation (Pellegrino *et al.*, 2005; Vaz Fragoso *et al.*, 2015, 2016). Nevertheless, there is still no complete consensus on the choice between a fixed ratio and the LLN, as there is some evidence that older persons with FEV1/FVC<0.7 but >LLN may suffer higher morbidity compared to those with FEV1/FVC>0.7 (Mannino *et al.*, 2007; Wollmer & Engström, 2013).

Regardless of the criterion used to diagnose airflow limitation in COPD, the classification of its severity is based on FEV1 expressed as percent predicted; according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, four categories are identified (Table 1.1). However, although a low FEV1 in addition to low FEV1/FVC increases the risk of patient-reported adverse outcomes (van Dijk *et al.*, 2015), the correlation of FEV1 with respiratory symptoms or overall health status is rather weak (Jones, 2009).

Table 1.1: Classification of airflow limitation severity in COPD

Category	Severity	Criterion
GOLD 1:	Mild	FEV1 >= 80% predicted
GOLD 2:	Moderate	50% <= FEV1 < 80% predicted
GOLD 3:	Severe	30% <= FEV1 < 50% predicted
GOLD 4:	Very Severe	FEV1 < 30% predicted

Chronic bronchitis is a useful term associated with COPD, with both clinical and prognostic value. It can be defined in different ways , but the classical definition has been “chronic cough and chronic sputum production for at least 3 months per year for two consecutive years”. It is the result of mucus metaplasia of the airway epithelium,

due to chronic inflammation by irritants such as tobacco smoke or bacterial/viral infections; mucus is overproduced by goblet cells of the epithelium, and also cleared less from the airways due to ciliary dysfunction. Chronic bronchitis is common in the population, but is not found in all patients with COPD; its prevalence among COPD patients has ranged from 14% to 74% in epidemiologic studies (Kim & Criner, 2013). It is also associated with smoking; in a 30-year longitudinal study from Finland, the cumulative incidence of chronic bronchitis was 42% in current smokers, 26% in ex-smokers and 22% in never smokers (Pelkonen *et al.*, 2006). In another study, the prevalence of chronic bronchitis among participants with COPD was 14.4%, but also 6.2% among participants without COPD (de Oca *et al.*, 2012). Importantly, chronic bronchitis is associated with the number and severity of COPD exacerbations (Burgel *et al.*, 2009; Kim *et al.*, 2011), frequency of COPD-related hospitalizations (Vestbo *et al.*, 1996; Guerra *et al.*, 2009), as well as with overall quality of life (Kim *et al.*, 2011; de Oca *et al.*, 2012). In addition, it has been associated with increased respiratory and all-cause mortality (Sherman *et al.*, 1992; Pelkonen *et al.*, 2006; Guerra *et al.*, 2009). Finally, chronic bronchitis has been associated with both accelerated lung function decline and increase COPD risk in several studies (Sherman *et al.*, 1992; Vestbo *et al.*, 1996; de Marco *et al.*, 2007; Guerra *et al.*, 2009; Kohansal *et al.*, 2009; Allinson *et al.*, 2016), even though older studies had failed to find a link (Fletcher & Peto, 1977).

1.2 The link between occupation and COPD

Occupation is an important determinant of respiratory health, and there is an entire category of occupational lung disease entities, that includes the pneumoconioses, hypersensitivity pneumonitis, occupational pleural disease and occupational respiratory cancers (Reid & Reid, 2013; Seaman *et al.*, 2015). Occupational asthma is probably the most frequently recognized respiratory illness linked to occupation (Bernstein *et al.*, 2006; Kogevinas *et al.*, 2007).

In contrast to the above, there is not a distinct clinical category of COPD that is clearly identified as occupational, and respiratory physicians do not often make a diagnosis of “occupational COPD” (Eisner *et al.*, 2010). There are several reasons for that. Certain occupations expose workers to irritants and other noxious substances such as dusts, endotoxins, gases & fumes, metals, pesticides, solvents and other chemicals, which exert a toxic influenca on the airway epithelium and could cause lung function decline and COPD. However, there are no particular clinical features of COPD that differentiate occupational- from non-occupational-related cases. On the other hand, the condition

develops slowly over many years through the concurrent interplay of many different risk factors, of which tobacco smoking exerts an overriding influence. COPD patients commonly have many risk factors, unlike for example occupational asthma which can often be linked to certain occupations or certain workplace hazards.

As a result, demonstrating an association between occupation and COPD relies on detecting an excess of cases among occupationally exposed populations. However this is also difficult for several reasons. First, exposed workers tend to be healthier at baseline and have higher lung function, the so-called “healthy worker effect” or “healthy hire effect”; this may occur as a result of less healthy workers avoiding strenuous or exposed jobs (Olivieri *et al.*, 2010). Second, cross-sectional workforce-based studies often suffer from a “healthy worker survivor effect”, as diseased workers leave their jobs early and cannot be followed up; this leads to underestimation of the effect of occupational exposures (Li & Sung, 1999; Shah, 2009). A third difficulty arises because of the multiple potential confounders in the relationship between COPD and occupation, the most important of which is tobacco smoking. Smoking is associated with the choice of occupation and also strongly associated with lung function decline and COPD; as such it needs to be closely adjusted for in any relevant epidemiological study in order to reduce residual confounding, but this can be hard to do in practice.

There are two epidemiological settings to study the relationship between occupation and COPD. The first is workplace-based studies, whereby workers doing a particular exposed job are examined or compared with their non-exposed colleagues at the same setting. Such longitudinal studies for example have been performed in miners (Holman *et al.*, 1987; Hnizdo *et al.*, 1990; Attfield & Hodous, 1992), tunnel workers (Ulvestad *et al.*, 2001) and concrete-manufacturing workers (Meijer *et al.*, 2001). Exposure assessment is relatively easier to perform in such studies, and in more detail; the drawback is that these studies focus on a few particular occupations and exposures, they are more susceptible to healthy worker survivor bias especially if follow-up is incomplete, and are less generalizable to the overall population. On the other hand are population-based (or community-based) studies, which enroll and follow random samples of the general population and can include many different types of occupational exposures. Population-based studies, especially if longitudinal rather than cross-sectional or case-control, are more generalizable and are less susceptible to healty worker survivor bias. However, it is more difficult to assess occupational exposure in such studies. The most common method employed by these studies in the past is to enquire each participant directly about his/her past or current exposures, i.e. self-report (Eisner *et al.*, 2010). However, self-report of past occupational exposures is prone to

differential misclassification or recall bias due to potential overreporting of exposure by diseased/symptomatic indivuduals, and/or underreporting of exposure by healthy individuals.

For this reason, Job-Exposure Matrices (JEMs) have been developed as a way to assess occupational exposures in a more objective way. A JEM is a cross-tabulation between jobs and possible occupational exposures, providing a degree of exposure (or probability of exposure) to each agent for each given job (Kauppinen, 1994). Job-exposure matrices can be classified as general-purpose or specific; a general-purpose JEM covers all jobs of a comprehensive classification of occupation, whereas a specific matrix is restricted to job titles occurring within an industry, or even within one facility. In terms of exposure metrics, a JEM can provide binary (exposed/unexposed), categorical (e.g. none/low/high exposure) or quantitative measures of exposure. The job axis of a JEM usually employs one of the available standardized classification of occupations in order to assign degrees of exposure (Mannetje & Kromhout, 2003); therefore occupational information in an epidemiological study (job titles and industries) must be coded accordingly. This procedure is usually done manually by expert coders, but can be also done automatically by computer software or even by the study participants themselves, using simple computer tools employing decision trees (Patel *et al.*, 2012; De Matteis *et al.*, 2017). A JEM can also employ a time axis, enabling the assignment of different degrees of exposure for different time periods.

General-purpose JEMs have been used as a reliable, easy and low-cost tool for exposure assessment in large population-based or register-based epidemiological studies. Their consistency in assessing occupational exposures irrespective of outcome or other confounders has been much appreciated. However, the main drawback of a JEM is the potential for non-differential misclassification, as real variations and heterogeneity within a given job code are ignored; this typically leads to attenuation of the exposure-effect association and hence may mask the risks under study (Kauppinen *et al.*, 1992; Bouyer *et al.*, 1995). The degree of misclassification can be attenuated by formal inclusion of an expert assessment step in the application of a JEM (Kennedy *et al.*, 2000), although this can be complex and time-consuming especially for large studies. Another issue is applicability of a JEM to different countries and populations; the same job code can have very different exposures in various countries according to local conditions, availability of protective measures, etc. In addition, application of a JEM requires the collected occupational information to be coded in the same classification as the JEM's job axis; if that is not the case, then recoding may be needed. This requires that the occupational data are at the same level of detail, and can be done either by using

the original information or by conversion of the available codes (Kromhout & Vermeulen, 2001).

Despite these important limitations, a large body of literature has been accumulated demonstrating an association between occupational exposures and COPD, chronic bronchitis or lung function decline (Eisner *et al.*, 2010; Omland *et al.*, 2014), to the degree that the association has been repeatedly described as causal (Naidoo, 2012; Martinez & Delclos, 2015). It has even been estimated that between 15-20% of all COPD or chronic bronchitis cases are attributable to occupational exposures (Balmes *et al.*, 2003). Nevertheless, important questions remain. First of all, the majority of the evidence has been cross-sectional rather than longitudinal, and many older studies have only assessed occupational exposures by self-report, or have not fully adjusted for important confounders such as smoking and age. Very few studies have directly assessed COPD incidence, in a prospective fashion, and particularly using post-bronchodilator spirometry in order to better distinguish from asthma. There is still a need of better quality evidence, from large studies with sufficient follow-up and tight control of confounders. Second, population-based studies have mostly focused on a narrow range of exposures, usually expressed as some combination of “vapours, gases, dusts and fumes” (VGDF) (Cullinan, 2012). Only recently attention has been given to other potential occupational respiratory irritants such as pesticides (de Jong *et al.*, 2014b). Finally, there are open questions about the effects of occupational exposures in men and women, their possible interaction with smoking, as well as how occupation affects the clinical phenotype and quality of life in COPD cases (Martinez & Delclos, 2015). As a result, further research on the relationship between occupation and COPD is still warranted.

2.OBJECTIVES

The main objective of this thesis was to explore in detail the associations between particular occupational exposures and COPD risk in the framework of the European Community Respiratory Health Survey (ECRHS), a large longitudinal community-based study, thereby providing new and stronger evidence for the link between occupation and COPD.

To address this overall aim, the following specific objectives were outlined:

- To evaluate the effect of occupational exposures on prospectively-evaluated **COPD incidence** over a long period of follow-up in the ECRHS study and with tight control of potential confounders. Also to estimate the proportion of total COPD cases that is attributable to such occupational exposures (Paper I)
- To evaluate the effect of occupational exposures on chronic respiratory symptoms incidence, primarily **chronic bronchitis**, over the course of the ECRHS study (Paper II).
- To determine in detail the effect of occupational exposures on annual **lung function decline**, taking care to minimize residual confounding, and taking into account both the natural variability of lung function decline *and* the correlation between spirometric parameters FEV1 and FVC (Paper III).

In all three above cases, extra consideration was given to assessing effect modification by sex and by smoking, to the maximum possible extent.

Additional methodological work has been conducted related to the objectives of this thesis; the PhD candidate has participated in the revision of a Job-Exposure Matrix for occupational asthmagens, namely the Occupational Asthma-specific JEM (OAsJEM). This work has been currently submitted as a paper to the journal *Occupational and Environmental Medicine*, and is not presented here but has been undertaken as part of the PhD project.

3. METHODS

This chapter provides an overview of the ECRHS study, which has been the primary data source for the analyses presented in this thesis, and of the ALOHA(+) JEM that has been the main exposure assessment tool used.

3.1 The European Community Respiratory Health Survey (ECRHS)

The European Community Respiratory Health Survey (ECRHS) is a large international multi-centre longitudinal community-based study that started in 1991-1993. At that time it recruited more than 18,000 young adults aged 20-44 from more than 35 study centres (predominantly, but not exclusively in Europe), collecting a variety of health-related and other information about factors known or hypothesized to be associated with the risk of developing asthma and atopy. The specific objectives of the initial study were as follows (Burney *et al.*, 1994):

1. To estimate the variation in the prevalence of asthma, asthma-like symptoms and bronchial lability in Europe.
2. To estimate variation in exposure to known or suspected risk factors for asthma; to measure their association with asthma; and to further assess the extent to which they explain variations in prevalence across Europe.
3. To estimate the variation in treatment practice for asthma in the European Community.

A two-stage sampling strategy was employed. Multiple areas of about 150,000 population each and marked by pre-existing administrative boundaries were enrolled in the study; it was attempted to include at least three areas in each participating country in order to enable studying both “within country” and “between country” variation. A short “screening questionnaire” was administered in each study area with the aim of obtaining 3,000 responders, 1,500 for each sex, aged 20-44 years. Then out of these a further random sample of 300 men and 300 women per study area was selected, as well as (in most centres) an additional “symptomatic sample” of about 100-150 persons based on their reporting respiratory symptoms at the screening questionnaire.

Then participants in both the random sample and the symptomatic sample completed a more detailed “main questionnaire”, and underwent further tests including spirometry (under a standardized protocol, and without administration of a bronchodilator), measurement of bronchial responsiveness (metacholine challenge), skin prick tests and serum IgE measurements. Items on the main questionnaire were adapted from other, standardized questionnaires to the maximum extent possible. Among other information, participants were asked about their current or most recent employment, as well as two extra questions: “have you ever had to change or leave your job because it affected your breathing?” and “have you ever worked in a job which exposed you to vapours, gases, dusts or fumes?”, and in case of a positive response, what was that job. These questions essentially amount to self-reporting of occupational exposures by the participants themselves. Jobs recorded at this initial survey were coded according to the Office of Populations Censuses and Surveys (OPCS-2) classification, which consists of 350 unique job codes.

The ECRHS II was a follow-up survey of this cohort (the initial survey subsequently became known as ECRHS I), performed between 1998 and 2003. A majority of study centres agreed to participate in this second wave (29 centres in total, from 14 countries). All participants that completed the second stage of the ECRHS I (i.e. all participants in the random sample and the symptomatic sample) were eligible to participate in the ECRHS II. The objectives of the study were significantly expanded, as did the information collected (which now included blood sampling for genetic analyses, an indoor environmental assessment, as well as a significantly expanded questionnaire). Spirometry was again performed, without bronchodilation, and metacholine challenge testing was repeated. The questions on occupations were now significantly expanded; now participants were asked to report all jobs performed for at least three continuous months since the initial study visit. Thus **a complete job history was recorded for each participant**, thereby permitting objective exposure assessment via application of a Job-Exposure Matrix. Occupations and industries were reported as free text and were subsequently coded according to the International Standard Classification of Occupations '88 (ISCO-88) by trained local coders. The ISCO-88 classification consists of 506 unique job codes organized in a tree-like structure into 10 major, 28 sub-major and 143 minor groups; a basic criterion for classifying jobs according to this system is the skill and specialization level required.

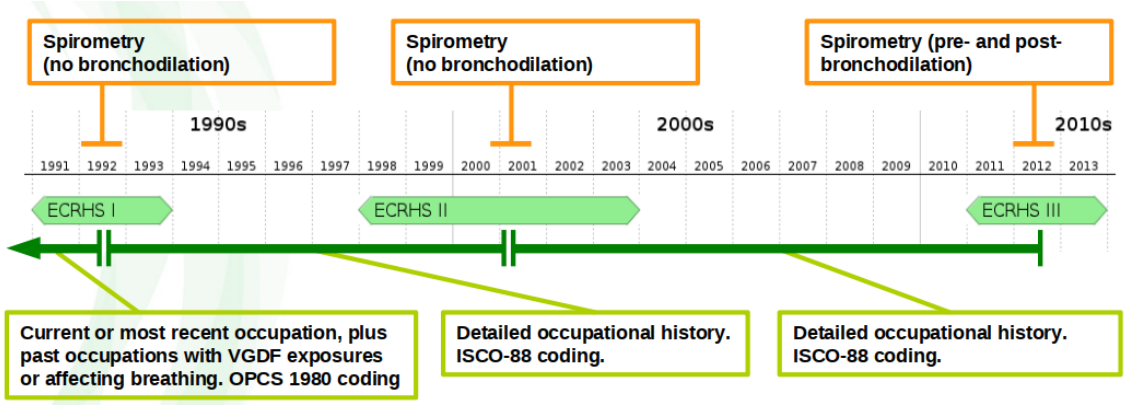
Ten years later, ECRHS III was undertaken as second follow-up of the original cohort (third wave of data collection). The aims of ECRHS III were as follows:

1. Describe change in respiratory symptom prevalence in adults as they age

2. Assess change in IgE sensitisation to common allergens in adults as they age
3. Determine whether the prognosis of asthma is influenced by any observed change in atopic status
4. Assess whether atopic status and asthma as measured over a twenty year period is associated with lung function decline or the development of COPD in older adults
5. Describe the association of obesity and physical exercise with asthma, lung function, lung function decline and the prognosis of asthma

In 27 centres, participants in the second stage of ECRHS I (the "random sample" and the "symptomatic sample") were sent again a screening questionnaire, and the respondents were invited to a local study centre. The questionnaires administered were further expanded, and now included a quality of life tool, a food frequency questionnaire, the International Physical Activity Questionnaire, a body shape questionnaire, a sleep questionnaire and an exposure to sunlight questionnaire. Additional measurements were obtained, such as exhaled nitric oxide (FeNO) and bio-impendance. **Spirometry was** further standardized (including the use of a single spirometer device at all centres), and **performed both with, and without administration of bronchodilation**, thereby enabling better differentiation between reversible (more characteristic of asthma) and non-reversible (more characteristic of COPD) airflow limitation. Again, full occupational histories were collected from participants up to their previous study visit, and coded in the ISCO-88 classification; jobs were recorded if performed for at least three continuous months and for 20 or more hours per week.

The timeline of the study is illustrated below:



For the longitudinal analyses performed as part of this thesis, only jobs reported after the initial study visit (ECRHS I) were considered, so as to ensure a homogeneity in the assessment of exposures and objectivity via application of a JEM. Occupational exposures before the ECRHS I were not considered, primarily because they were assessed by self-report, as full job histories were not recorded. Where necessary this has been taken into account in the analysis (e.g. for lung function decline).

3.2 The ALOHA(+) Job-Exposure Matrix

An “ad hoc JEM” was developed for the initial study (ECRHS I) to objectively estimate exposure to three agents: biological dusts, mineral dusts, and gases & fumes (Sunyer *et al.*, 1998). This JEM was semi-quantitative, in that it assigned each job code three degrees of exposure to each agent: none, low and high exposure. The ad hoc JEM incorporated no time axis, and used the 350 codes of the OPCS-2 classification on its job axis.

With the upgraded and more detailed occupational information collected as part of ECRHS II, and the switch to ISCO-88 coding, the ad hoc JEM was in need of an upgrade. Therefore the ALOHA JEM was developed, using the same principles but moving to ISCO-88 for its job axis; it also provides semi-quantitative exposure estimates for biological dust, mineral dusts and gases & fumes, as well as their composite (Vapors, Gases, Dusts and Fumes - VGDF) (Matheson *et al.*, 2005). Specificity in assessing exposures was prioritized over sensitivity during the development of the JEM (Kromhout *et al.*, 2004). The ALOHA JEM has been applied not only within the ECRHS (Sunyer *et al.*, 2005), but also in numerous other studies (Sadhra *et al.*, 2017).

The ALOHA(+) JEM is a further extension, that includes not only the previous four exposures, but also pesticides (further divided into three categories: insecticides, herbicides and fungicides), solvents (aromatic, chlorinated and other solvents) and metals (de Jong *et al.*, 2014b). It thus provides a more complete assessment of potential harmful occupational exposures.

4.RESULTS

4.1 Paper I: Occupational exposures and 20-year incidence of COPD: The European Community Respiratory Health Survey

4.2 Paper II: Occupational exposures and incidence of chronic bronchitis symptoms over two decades of follow-up: the European Community Respiratory Health Survey

4.3 Paper III: Lung function decline and COPD prevalence in relation to occupational exposures in the ECRHS study

4.1 Paper I

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4.2 Paper II

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

Theodore Lytras, Manolis Kogevinas, Jan-Paul Zock, occupational working group and study centres of the ECRHS

Draft manuscript, about to be submitted for publication

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

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Abstract

Background: Occupational exposures have been associated with an increased risk of chronic bronchitis (CB), i.e. cough and phlegm for at least three months in two consequtive years. However, few studies have examined this association prospectively, using objectively-assessed occupational exposures. Our objective was to examine the effect of occupational exposures on CB incidence in the European Community Respiratory Health Survey (ECRHS).

Methods: General population samples aged 20-44 were randomly selected in 1991-1993, and followed up twice after approximately 10 and 20 years. Respiratory symptoms were assessed at each study visit via a questionnaire, and spirometry was performed. Participants with neither chronic cough nor chronic phlegm at baseline were included in the analysis. Coded job histories during follow-up were linked to a Job-Exposure Matrix, generating occupational exposure estimates to twelve categories of agents. Their association with CB incidence over both follow-up visits was examined with Poisson regression models fitted using Generalized Estimating Equations (GEE). Covariate missingness was handled using multiple imputation.

Findings: 8,933 participants fulfilled the inclusion criteria, contributing 13,324 observations over both follow-up visits. CB incidence proportion was 1.5% at the first follow-up and 2.1% at the second. Only participants exposed to metals had a higher incidence of CB (RR=1.69, 95% CI: 1.15 – 2.49). However, exposure to mineral dust increased the incidence of chronic phlegm (RR=1.72, 95% CI: 1.44 – 2.06); gases/fumes and solvents also increased the incidence of chronic phlegm but only in men, while pesticides did the same in women only.

Interpretation: 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 Obstructive Pulmonary Disease (COPD) is a major public health issue that is a leading cause of mortality and morbidity worldwide [1]. The disease is characterized by largely persistent airflow limitation, respiratory symptoms and frequent symptom exacerbations [2]; tobacco smoking is the primary risk factor, although a number of other environmental factors have been identified [3], including occupational exposures [4]. 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 present in a varying proportion of COPD patients [5], but also in persons without airflow limitation, especially among smokers [6]. Besides its detrimental impact on quality of life [7], 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 [6,8–10], even among those without airflow limitation [11].

Although occupation is currently considered an established risk factor for COPD [12], only few studies have specifically examined the association between CB and certain occupational exposures, particularly dusts and fumes, and most such studies have been cross-sectional [4]. 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 symptoms with CB, but only with chronic phlegm for mineral dust and gases/fumes exposure [13]. Now the ECRHS has accumulated 20 years of follow-up, allowing a relative aging of the study population. Therefore 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 [14]. 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.

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. The population for this study 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 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 [15]. 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 that were performed for at least 8 hours a week for at least three months. Each such employment was recorded in free text and subsequently coded in the International Classification of Occupations-88 (ISCO-88) by trained local coders. Occupational exposures were assessed by linking the ISCO-88 occupational codes to the semi-quantitative ALOHA(+) Job-Exposure Matrix (JEM) [16]. For every job code, the JEM assigns three grades 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

The outcomes of interest were CB, and also chronic cough and chronic phlegm separately. Associations between these outcomes and occupational exposures were examined in Poisson regression models fitted using Generalized Estimating Equations (GEE) with an exchangeable working correlation matrix [17]. 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 [18]. All models were adjusted for age, sex, lifetime smoking pack-years, current smoking, Socioeconomic Status (SES), current asthma and severity of airflow limitation. We also included quadratic terms for age and lifetime smoking pack-years, in order to account for potential non-linear relationships between these important covariates and CB incidence [19]. 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). Three sensitivity analyses were performed; one without adjustment for severity of airflow limitation, one excluding all incident asthma cases, and another both excluding incident asthma cases and without adjustment for severity of airflow limitation. Comparisons between models were performed using the Quasi-likelihood Information Criterion (QIC) statistic [20]; 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 [21]; 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 [22], using packages “geepack”, “mice” and “QICpack”.

Results

Figure 1 illustrates the flow of ECRHS participants into our final study sample; in total 8933 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, Netherlands, Norway, Spain, Sweden, Switzerland, UK and the USA). Median age at baseline was 34.4. Of those participants, 4515 participated in both follow-up visits, 3500 only in ECRHS II and 918 only in ECRHS III. The descriptive characteristics of the study population are summarized on Table 1. 118 participants (1.5%) had CB at the ECRHS II, and the percentage increased to 2.1% at the ECRHS III (p=0.013). The proportion of participants with occupational exposures ranged from 1.4% (to herbicides at ECRHS II) up to 40.5% (to gases/fumes at ECRHS III). Substantial correlations between individual exposures were noted, particularly among pesticide and solvent 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, compared to no exposure, resulted in an increased incidence of CB (RR=1.69, 95% CI: 1.15 – 2.49); other exposures did not show a statistically significant effect, although mineral dust came very close (RR=1.34, 95% CI: 0.99 – 1.82). Exclusion of incident asthma cases from the analysis resulted in increased effect estimates, for both metals exposure (RR=2.18, 95% CI: 1.40 – 3.40) and mineral dust (RR=1.50, 95% CI: 1.04 – 2.16), while omitting adjustment for severity of airway obstruction did not meaningfully impact the 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 seemed to have a stronger effect on CB incidence among non-smokers (RR=2.41, 95% CI: 1.23 – 4.72) than among smokers (RR=1.49, 95% CI: 0.94 – 2.34).

With respect to the outcome of chronic cough, only exposure to metals showed an effect on incidence (RR=1.28, 95% CI: 1.01 – 1.63), 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 however, we observed increased

incidence for exposure to metals, aromatic and chlorinated solvents, mineral dust, gases & 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 & fumes (RR=1.52, 95% CI: 1.21 – 1.90), VGDF (RR=1.63, 95% CI: 1.29 – 2.05) 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=2.12, 95% CI: 1.11 – 4.06 and RR=2.05, 95% CI: 1.04 – 4.05 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 a dose-response relationship between VGDF exposure and chronic phlegm; any high exposure to VGDF resulted in an RR of 1.56 (95% CI: 1.26 – 1.92) compared to no exposure, while only low exposure to VGDF had a lower effect (RR=1.20, 95% CI: 1.02 – 1.41).

Discussion

Our study is the first large prospective population-based study to clearly show that metals exposure over a long period of follow up increases the incidence of CB, particularly in never smokers. Only one smaller population-based study has recently associated exposure to metals with fixed airflow obstruction [23], and an industry-based study linked metals to deterioriation in lung function [24]. This is the first study to use CB as outcome, and estimate incidence rather than CB prevalence in a prospective fashion. 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 [25]; impairment of pulmonary surfactant may be involved, via an inflammatory or autoimmune mechanism [24].

Many workers in these occupations were also exposed to mineral dust, which also showed a trend toward 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, and helpers/cleaners in offices, hotels and other establishments, which occured frequently in women. A number of population-based studies have associated dusts exposure in general with CB symptoms [4], but only one cross-sectional study has done so specifically for mineral dust, showing an even higher risk in ever smokers [26]. 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 much 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 exposure and outcome definitions as our study [27]. 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 in men. In addition we found increased chronic phlegm incidence only among women exposed to insecticides and fungicides; although the numbers of cases were small, this finding deserves further attention as pesticides have recently been associated with accelerated lung function decline [28] and airway obstruction [29]. Chronic phlegm, otherwise named “chronic mucus hypersecretion”, 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 [30]. There is recent evidence that chronic phlegm may represent an early developmental phase of COPD particularly among smokers [9], at least for some COPD cases [31]. 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.

The prevalence of chronic respiratory symptoms, including chronic bronchitis, is higher among patients with COPD [32]. The severity of airflow limitation may be associated, if only weakly, with CB symptoms [32,33]. Therefore we decided a priori to adjust our analyses for the severity of airflow limitation; however it was found not to substantially affect the estimated relationship between CB and occupational exposures. In contrast, exclusion of incident asthma cases resulted in higher effect estimates for both mineral dust and metals exposure, particularly with CB as outcome. Exclusion of participants with asthma essentially increased the specificity of the study questions for the ascertainment of CB, thereby reducing non-differential misclassification of outcome which would 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 most of the participants represented their entire working life; therefore lifetime occupational exposures could be assessed for a variety of agents, and in an objective way using a JEM rather than self-report, which

could be more vulnerable to recall or reporting bias. We were able to tightly control for a number of important confounders, 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 is a problem in any large population-based study. In addition, the multi-centre and multi-country design increases the generalizability of the findings.

On the other hand, the study has certain limitations. The incidence of CB in our cohort was very low (about 2%) compared to other studies, and lower than the reported prevalence of 3.4%-22% for the general population. This is probably due to the still fairly young age of our cohort, and diminishes the study's statistical power to detect associations. The proportion of occupationally exposed women was much lower than that of men, as in most occupational epidemiology studies, making inference about women more difficult. Future studies should try to 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 may still be insufficient to do subgroup analyses or to reliably assess heterogeneity across study centres and countries.

In conclusion, this study provides strong prospective evidence about the association of occupational exposures with chronic bronchitis and chronic phlegm, illustrating their role in the pathogenesis of COPD. Future research should investigate further 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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Table 1: Characteristics of the study population, N=8933 participants without cough or phlegm at baseline (ECRHS I)

	ECRHS II	ECRHS III
Number of participants followed up	7958	5366
Median age at follow-up (y)	43.1	54.4
% male	47.2	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	52.6	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 exposure)		
Biological dust	25.8	30.5
Mineral Dust	20.0	23.1
Gases & fumes	35.8	40.5
Vapors, Gases, Dusts & Fumes	40.4	45.6
Herbicides	1.4	1.8
Insecticides	2.2	2.9
Fungicides	2.3	3.3
All pesticides	3.1	4.1
Aromatic solvents	12.4	14.5
Chlorinated solvents	9.8	11.9
Other solvents	22.3	26.7
Metals	9.1	10.9
% missing information		
Lifetime smoking pack-years	9.3	30.4
Current smoking	1.1	18.1
Current asthma	1.3	1.5
Socioeconomic status	0.5	3.7
Lung function	18.0	15.1

Table 2: Associations between occupational exposures and incidence of CB, chronic cough and chronic phlegm. N=8933 participants without cough or phlegm at baseline (ECRHS I) followed-up at ECRHS II and III (n=13324 observations)

	Chronic Bronchitis			Cough only			Phlegm only		
	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)
Biological dust	161/9635 (1.7%)	68/3689 (1.8%)	1.01 (0.76 – 1.33)	487/9635 (5.1%)	188/3689 (5.1%)	0.94 (0.80 – 1.11)	389/9635 (4.0%)	179/3689 (4.9%)	1.15 (0.96 – 1.36)
Mineral Dust	166/10498 (1.6%)	63/2826 (2.2%)	1.34 (0.99 – 1.82)	511/10498 (4.9%)	164/2826 (5.8%)	1.11 (0.92 – 1.33)	378/10498 (3.6%)	190/2826 (6.7%)	**1.72 (1.44 – 2.06)**
Gases & fumes	133/8303 (1.6%)	96/5021 (1.9%)	1.14 (0.87 – 1.48)	416/8303 (5.0%)	259/5021 (5.2%)	0.97 (0.83 – 1.13)	303/8303 (3.6%)	265/5021 (5.3%)	**1.34 (1.14 – 1.57)**
Vapors, Gases, Dusts & Fumes	125/7664 (1.6%)	104/5660 (1.8%)	1.09 (0.84 – 1.41)	386/7664 (5.0%)	289/5660 (5.1%)	0.97 (0.83 – 1.13)	274/7664 (3.6%)	294/5660 (5.2%)	**1.37 (1.16 – 1.60)**
Herbicides	225/13113 (1.7%)	4/211 (1.9%)	1.09 (0.40 – 3.00)	662/13113 (5.0%)	13/211 (6.2%)	1.21 (0.71 – 2.06)	555/13113 (4.2%)	13/211 (6.2%)	1.32 (0.77 – 2.27)
Insecticides	224/12991 (1.7%)	5/333 (1.5%)	0.85 (0.35 – 2.05)	657/12991 (5.1%)	18/333 (5.4%)	1.05 (0.67 – 1.65)	550/12991 (4.2%)	18/333 (5.4%)	1.16 (0.73 – 1.83)
Fungicides	224/12962 (1.7%)	5/362 (1.4%)	0.79 (0.32 – 1.93)	656/12962 (5.1%)	19/362 (5.2%)	1.02 (0.65 – 1.60)	548/12962 (4.2%)	20/362 (5.5%)	1.19 (0.77 – 1.84)
All pesticides	222/12855 (1.7%)	7/469 (1.5%)	0.86 (0.40 – 1.83)	651/12855 (5.1%)	24/469 (5.1%)	1.01 (0.68 – 1.50)	545/12855 (4.2%)	23/469 (4.9%)	1.04 (0.69 – 1.58)
Aromatic solvents	197/11558 (1.7%)	32/1766 (1.8%)	1.06 (0.72 – 1.56)	578/11558 (5.0%)	97/1766 (5.5%)	1.09 (0.88 – 1.35)	471/11558 (4.1%)	97/1766 (5.5%)	**1.26 (1.02 – 1.56)**
Chlorinated solvents	200/11908 (1.7%)	29/1416 (2.0%)	1.20 (0.81 – 1.79)	593/11908 (5.0%)	82/1416 (5.8%)	1.14 (0.90 – 1.43)	486/11908 (4.1%)	82/1416 (5.8%)	**1.31 (1.04 – 1.65)**
Other solvents	177/10115 (1.7%)	52/3209 (1.6%)	0.94 (0.69 – 1.28)	525/10115 (5.2%)	150/3209 (4.7%)	0.91 (0.76 – 1.08)	422/10115 (4.2%)	146/3209 (4.5%)	1.09 (0.91 – 1.31)
Metals	196/12017 (1.6%)	33/1307 (2.5%)	**1.69 (1.15 – 2.49)**	595/12017 (5.0%)	80/1307 (6.1%)	**1.28 (1.01 – 1.63)**	487/12017 (4.1%)	81/1307 (6.2%)	**1.44 (1.14 – 1.82)**

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.

Table 3: Associations between occupational exposures and incidence of chronic phlegm, stratified by gender. N=8933 participants without cough or phlegm at baseline (ECRHS I) followed-up at ECRHS II and III (n=13324 observations)

	Men			Women		
	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)
Biological dust	209/4759 (4.4%)	79/1546 (5.1%)	1.10 (0.86 – 1.41)	180/4876 (3.7%)	100/2143 (4.7%)	1.19 (0.94 – 1.51)
Mineral Dust	152/4325 (3.5%)	136/1980 (6.9%)	**1.77 (1.41 – 2.22)**	226/6173 (3.7%)	54/846 (6.4%)	**1.65 (1.23 – 2.20)**
Gases & fumes*	124/3446 (3.6%)	164/2859 (5.7%)	**1.52 (1.21 – 1.90)**	179/4857 (3.7%)	101/2162 (4.7%)	1.17 (0.93 – 1.49)
Vapors, Gases, Dusts & Fumes*	108/3167 (3.4%)	180/3138 (5.7%)	**1.63 (1.29 – 2.05)**	166/4497 (3.7%)	114/2522 (4.5%)	1.15 (0.91 – 1.45)
Herbicides	280/6156 (4.5%)	8/149 (5.4%)	1.10 (0.56 – 2.18)	275/6957 (4.0%)	5/62 (8.1%)	1.91 (0.79 – 4.59)
Insecticides*	279/6072 (4.6%)	9/233 (3.9%)	0.79 (0.42 – 1.48)	271/6919 (3.9%)	9/100 (9.0%)	**2.12 (1.11 – 4.06)**
Fungicides*	276/6033 (4.6%)	12/272 (4.4%)	0.92 (0.53 – 1.61)	272/6929 (3.9%)	8/90 (8.9%)	**2.05 (1.04 – 4.05)**
All pesticides*	274/5953 (4.6%)	14/352 (4.0%)	0.81 (0.48 – 1.35)	271/6902 (3.9%)	9/117 (7.7%)	1.86 (0.97 – 3.55)
Aromatic solvents	207/4917 (4.2%)	81/1388 (5.8%)	**1.35 (1.06 – 1.73)**	264/6641 (4.0%)	16/378 (4.2%)	0.99 (0.61 – 1.63)
Chlorinated solvents	222/5222 (4.3%)	66/1083 (6.1%)	**1.36 (1.05 – 1.78)**	264/6686 (3.9%)	16/333 (4.8%)	1.16 (0.72 – 1.88)
Other solvents*	198/4612 (4.3%)	90/1693 (5.3%)	**1.27 (1.00 – 1.62)**	224/5503 (4.1%)	56/1516 (3.7%)	0.90 (0.68 – 1.20)
Metals	212/5140 (4.1%)	76/1165 (6.5%)	**1.53 (1.19 – 1.96)**	275/6877 (4.0%)	5/142 (3.5%)	0.86 (0.37 – 2.04)

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)

Figures

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

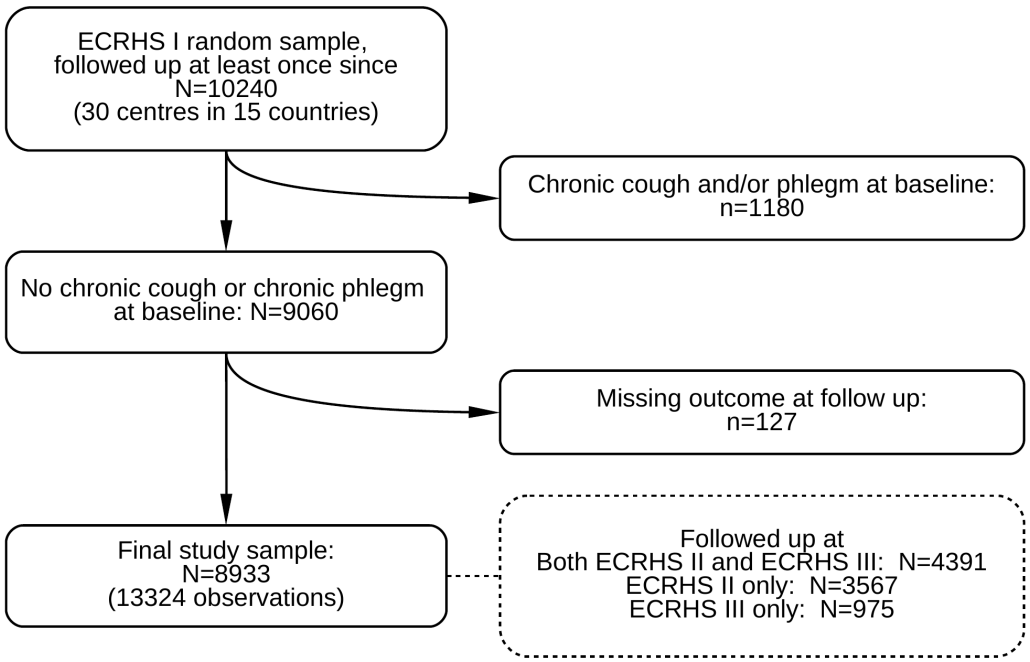
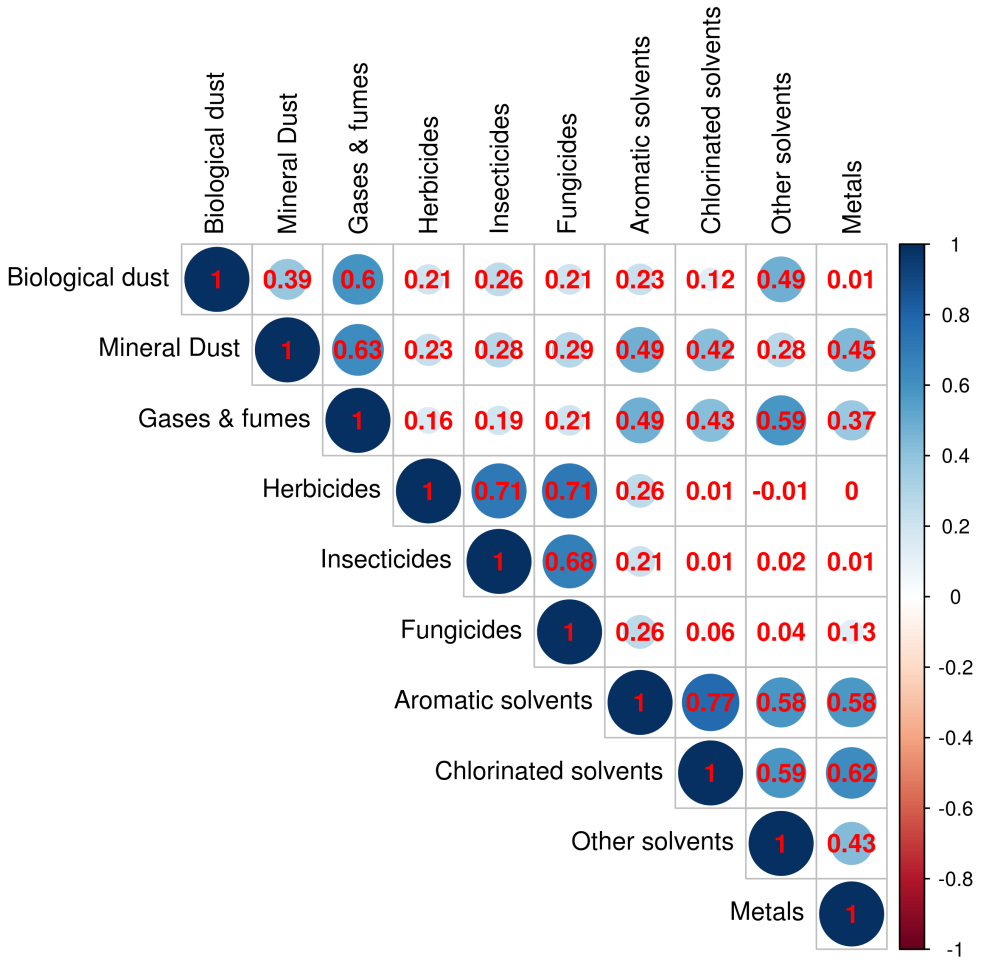


Figure 2: Correlation map (Spearman's rho) between occupational exposures in the study population (n=13324 observations)



ONLINE SUPPLEMENT

Supplementary Table 1: Sensitivity analyses for the association between occupational exposures and incidence of CB, chronic cough and chronic phlegm. N=8933 participants followed-up at ECRHS II and III (n=13324 observations)

(a) Sensitivity analysis 1: no adjustment for degree of airway obstruction

	Chronic Bronchitis			Cough only			Phlegm only		
	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)
Biological dust	161/9635 (1.7%)	68/3689 (1.8%)	1.03 (0.78 – 1.36)	487/9635 (5.1%)	188/3689 (5.1%)	0.95 (0.81 – 1.12)	389/9635 (4.0%)	179/3689 (4.9%)	1.16 (0.98 – 1.37)
Mineral Dust	166/10498 (1.6%)	63/2826 (2.2%)	**1.36 (1.01 – 1.85)**	511/10498 (4.9%)	164/2826 (5.8%)	1.12 (0.93 – 1.34)	378/10498 (3.6%)	190/2826 (6.7%)	**1.73 (1.44 – 2.07)**
Gases & fumes	133/8303 (1.6%)	96/5021 (1.9%)	1.16 (0.89 – 1.50)	416/8303 (5.0%)	259/5021 (5.2%)	0.98 (0.84 – 1.14)	303/8303 (3.6%)	265/5021 (5.3%)	**1.35 (1.15 – 1.59)**
Vapors, Gases, Dusts & Fumes	125/7664 (1.6%)	104/5660 (1.8%)	1.10 (0.85 – 1.42)	386/7664 (5.0%)	289/5660 (5.1%)	0.98 (0.84 – 1.14)	274/7664 (3.6%)	294/5660 (5.2%)	**1.38 (1.17 – 1.61)**
Herbicides	225/13113 (1.7%)	4/211 (1.9%)	1.13 (0.42 – 3.06)	662/13113 (5.0%)	13/211 (6.2%)	1.22 (0.72 – 2.08)	555/13113 (4.2%)	13/211 (6.2%)	1.36 (0.79 – 2.33)
Insecticides	224/12991 (1.7%)	5/333 (1.5%)	0.85 (0.35 – 2.06)	657/12991 (5.1%)	18/333 (5.4%)	1.05 (0.67 – 1.66)	550/12991 (4.2%)	18/333 (5.4%)	1.17 (0.74 – 1.85)
Fungicides	224/12962 (1.7%)	5/362 (1.4%)	0.79 (0.32 – 1.93)	656/12962 (5.1%)	19/362 (5.2%)	1.02 (0.65 – 1.60)	548/12962 (4.2%)	20/362 (5.5%)	1.20 (0.77 – 1.86)
All pesticides	222/12855 (1.7%)	7/469 (1.5%)	0.87 (0.41 – 1.86)	651/12855 (5.1%)	24/469 (5.1%)	1.01 (0.68 – 1.50)	545/12855 (4.2%)	23/469 (4.9%)	1.06 (0.71 – 1.60)
Aromatic solvents	197/11558 (1.7%)	32/1766 (1.8%)	1.09 (0.75 – 1.60)	578/11558 (5.0%)	97/1766 (5.5%)	1.11 (0.90 – 1.38)	471/11558 (4.1%)	97/1766 (5.5%)	**1.27 (1.03 – 1.58)**
Chlorinated solvents	200/11908 (1.7%)	29/1416 (2.0%)	1.25 (0.84 – 1.84)	593/11908 (5.0%)	82/1416 (5.8%)	1.16 (0.92 – 1.46)	486/11908 (4.1%)	82/1416 (5.8%)	**1.33 (1.06 – 1.67)**
Other solvents	177/10115 (1.7%)	52/3209 (1.6%)	0.95 (0.70 – 1.29)	525/10115 (5.2%)	150/3209 (4.7%)	0.92 (0.77 – 1.09)	422/10115 (4.2%)	146/3209 (4.5%)	1.10 (0.91 – 1.31)
Metals	196/12017 (1.6%)	33/1307 (2.5%)	**1.70 (1.15 – 2.50)**	595/12017 (5.0%)	80/1307 (6.1%)	**1.29 (1.01 – 1.63)**	487/12017 (4.1%)	81/1307 (6.2%)	**1.44 (1.14 – 1.83)**

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.

(b) Sensitivity analysis 2: incident asthma cases excluded

	Chronic Bronchitis			Cough only			Phlegm only		
	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)
Biological dust	109/8647 (1.3%)	41/3266 (1.3%)	0.94 (0.66 – 1.34)	361/8647 (4.2%)	130/3266 (4.0%)	0.92 (0.76 – 1.12)	288/8647 (3.3%)	130/3266 (4.0%)	1.17 (0.95 – 1.43)
Mineral Dust	105/9396 (1.1%)	45/2517 (1.8%)	**1.50 (1.04 – 2.16)**	365/9396 (3.9%)	126/2517 (5.0%)	1.20 (0.97 – 1.48)	273/9396 (2.9%)	145/2517 (5.8%)	**1.81 (1.47 – 2.24)**
Gases & fumes	84/7431 (1.1%)	66/4482 (1.5%)	1.20 (0.87 – 1.65)	298/7431 (4.0%)	193/4482 (4.3%)	1.00 (0.83 – 1.20)	217/7431 (2.9%)	201/4482 (4.5%)	**1.40 (1.16 – 1.69)**
Vapors, Gases, Dusts & Fumes	80/6851 (1.2%)	70/5062 (1.4%)	1.11 (0.81 – 1.52)	277/6851 (4.0%)	214/5062 (4.2%)	0.99 (0.83 – 1.18)	194/6851 (2.8%)	224/5062 (4.4%)	**1.45 (1.20 – 1.74)**
Herbicides	148/11726 (1.3%)	2/187 (1.1%)	0.79 (0.19 – 3.29)	482/11726 (4.1%)	9/187 (4.8%)	1.14 (0.59 – 2.20)	407/11726 (3.5%)	11/187 (5.9%)	1.52 (0.86 – 2.70)
Insecticides	148/11612 (1.3%)	2/301 (0.7%)	0.48 (0.12 – 1.93)	478/11612 (4.1%)	13/301 (4.3%)	1.00 (0.58 – 1.71)	404/11612 (3.5%)	14/301 (4.7%)	1.18 (0.70 – 1.98)
Fungicides	147/11594 (1.3%)	3/319 (0.9%)	0.72 (0.23 – 2.29)	477/11594 (4.1%)	14/319 (4.4%)	1.04 (0.62 – 1.77)	402/11594 (3.5%)	16/319 (5.0%)	1.31 (0.81 – 2.13)
All pesticides	146/11492 (1.3%)	4/421 (1.0%)	0.71 (0.26 – 1.93)	473/11492 (4.1%)	18/421 (4.3%)	1.00 (0.63 – 1.59)	400/11492 (3.5%)	18/421 (4.3%)	1.09 (0.68 – 1.73)
Aromatic solvents	124/10339 (1.2%)	26/1574 (1.7%)	1.40 (0.91 – 2.15)	416/10339 (4.0%)	75/1574 (4.8%)	1.18 (0.92 – 1.52)	343/10339 (3.3%)	75/1574 (4.8%)	**1.32 (1.03 – 1.70)**
Chlorinated solvents	128/10649 (1.2%)	22/1264 (1.7%)	1.47 (0.94 – 2.30)	428/10649 (4.0%)	63/1264 (5.0%)	1.23 (0.94 – 1.61)	357/10649 (3.4%)	61/1264 (4.8%)	**1.32 (1.01 – 1.73)**
Other solvents	115/9061 (1.3%)	35/2852 (1.2%)	1.00 (0.69 – 1.45)	384/9061 (4.2%)	107/2852 (3.8%)	0.90 (0.73 – 1.11)	310/9061 (3.4%)	108/2852 (3.8%)	1.10 (0.89 – 1.36)
Metals	123/10737 (1.1%)	27/1176 (2.3%)	**2.18 (1.40 – 3.40)**	429/10737 (4.0%)	62/1176 (5.3%)	**1.33 (1.01 – 1.75)**	354/10737 (3.3%)	64/1176 (5.4%)	**1.51 (1.16 – 1.98)**

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.

(c) Sensitivity analysis 3: incident asthma cases excluded, and no adjustment for degree of airway obstruction

	Chronic Bronchitis			Cough only			Phlegm only		
	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)
Biological dust	109/8647 (1.3%)	41/3266 (1.3%)	0.96 (0.67 – 1.36)	361/8647 (4.2%)	130/3266 (4.0%)	0.93 (0.76 – 1.12)	288/8647 (3.3%)	130/3266 (4.0%)	1.17 (0.96 – 1.43)
Mineral Dust	105/9396 (1.1%)	45/2517 (1.8%)	**1.52 (1.05 – 2.19)**	365/9396 (3.9%)	126/2517 (5.0%)	1.21 (0.98 – 1.49)	273/9396 (2.9%)	145/2517 (5.8%)	**1.82 (1.47 – 2.25)**
Gases & fumes	84/7431 (1.1%)	66/4482 (1.5%)	1.22 (0.89 – 1.68)	298/7431 (4.0%)	193/4482 (4.3%)	1.01 (0.84 – 1.21)	217/7431 (2.9%)	201/4482 (4.5%)	**1.41 (1.17 – 1.71)**
Vapors, Gases, Dusts & Fumes	80/6851 (1.2%)	70/5062 (1.4%)	1.13 (0.83 – 1.55)	277/6851 (4.0%)	214/5062 (4.2%)	1.00 (0.84 – 1.19)	194/6851 (2.8%)	224/5062 (4.4%)	**1.45 (1.21 – 1.76)**
Herbicides	148/11726 (1.3%)	2/187 (1.1%)	0.83 (0.20 – 3.43)	482/11726 (4.1%)	9/187 (4.8%)	1.16 (0.60 – 2.22)	407/11726 (3.5%)	11/187 (5.9%)	1.55 (0.87 – 2.76)
Insecticides	148/11612 (1.3%)	2/301 (0.7%)	0.49 (0.12 – 2.00)	478/11612 (4.1%)	13/301 (4.3%)	1.01 (0.59 – 1.74)	404/11612 (3.5%)	14/301 (4.7%)	1.20 (0.71 – 2.01)
Fungicides	147/11594 (1.3%)	3/319 (0.9%)	0.73 (0.23 – 2.32)	477/11594 (4.1%)	14/319 (4.4%)	1.05 (0.62 – 1.77)	402/11594 (3.5%)	16/319 (5.0%)	1.32 (0.81 – 2.15)
All pesticides	146/11492 (1.3%)	4/421 (1.0%)	0.72 (0.27 – 1.96)	473/11492 (4.1%)	18/421 (4.3%)	1.01 (0.64 – 1.61)	400/11492 (3.5%)	18/421 (4.3%)	1.10 (0.69 – 1.75)
Aromatic solvents	124/10339 (1.2%)	26/1574 (1.7%)	1.41 (0.92 – 2.17)	416/10339 (4.0%)	75/1574 (4.8%)	1.18 (0.92 – 1.52)	343/10339 (3.3%)	75/1574 (4.8%)	**1.33 (1.03 – 1.71)**
Chlorinated solvents	128/10649 (1.2%)	22/1264 (1.7%)	1.47 (0.94 – 2.31)	428/10649 (4.0%)	63/1264 (5.0%)	1.23 (0.94 – 1.61)	357/10649 (3.4%)	61/1264 (4.8%)	**1.32 (1.01 – 1.73)**
Other solvents	115/9061 (1.3%)	35/2852 (1.2%)	0.99 (0.69 – 1.44)	384/9061 (4.2%)	107/2852 (3.8%)	0.90 (0.73 – 1.11)	310/9061 (3.4%)	108/2852 (3.8%)	1.10 (0.89 – 1.36)
Metals	123/10737 (1.1%)	27/1176 (2.3%)	**2.20 (1.41 – 3.43)**	429/10737 (4.0%)	62/1176 (5.3%)	**1.34 (1.02 – 1.76)**	354/10737 (3.3%)	64/1176 (5.4%)	**1.52 (1.16 – 1.98)**

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.

Supplementary Table 2: Association between occupational exposures and incidence of CB, chronic cough and chronic phlegm, <u>stratified by intensity of exposure</u> (only low exposure / ever high exposure, vs unexposed). N=8933 participants followed-up at ECRHS II and III (n=13324 observations)

	Chronic Bronchitis		Cough only		Phlegm only	
	Only low	Ever high	Only low	Ever high	Only low	Ever high
Biological dust	1.03 (0.77 – 1.37)	0.86 (0.42 – 1.77)	0.98 (0.83 – 1.16)	0.85 (0.57 – 1.28)	1.18 (0.99 – 1.41)	0.95 (0.62 – 1.43)
Mineral Dust	1.35 (0.98 – 1.87)	1.41 (0.89 – 2.22)	1.10 (0.91 – 1.34)	1.09 (0.82 – 1.46)	**1.61 (1.33 – 1.95)**	**1.47 (1.13 – 1.91)**
Gases & fumes	1.22 (0.94 – 1.58)	0.91 (0.55 – 1.50)	1.01 (0.87 – 1.18)	0.92 (0.69 – 1.22)	**1.23 (1.05 – 1.45)**	**1.43 (1.11 – 1.84)**
Vapors, Gases, Dusts & Fumes	1.10 (0.84 – 1.43)	1.17 (0.80 – 1.71)	0.96 (0.82 – 1.11)	1.03 (0.82 – 1.28)	**1.20 (1.02 – 1.41)**	**1.56 (1.26 – 1.92)**
Herbicides	1.63 (0.60 – 4.39)	NA*	1.55 (0.91 – 2.67)	0.87 (0.29 – 2.60)	1.30 (0.67 – 2.52)	1.24 (0.48 – 3.16)
Insecticides	1.33 (0.50 – 3.52)	0.68 (0.17 – 2.71)	1.00 (0.53 – 1.90)	1.15 (0.63 – 2.10)	0.98 (0.50 – 1.93)	1.42 (0.79 – 2.53)
Fungicides	0.87 (0.28 – 2.75)	0.67 (0.17 – 2.72)	0.97 (0.52 – 1.80)	1.13 (0.62 – 2.07)	1.08 (0.59 – 2.00)	1.24 (0.67 – 2.29)
All pesticides	1.24 (0.56 – 2.78)	0.90 (0.29 – 2.81)	1.17 (0.73 – 1.87)	1.10 (0.62 – 1.95)	0.96 (0.56 – 1.65)	1.35 (0.77 – 2.36)
Aromatic solvents	1.10 (0.75 – 1.62)	0.76 (0.19 – 2.98)	1.11 (0.89 – 1.38)	1.12 (0.60 – 2.10)	1.21 (0.97 – 1.51)	1.53 (0.88 – 2.66)
Chlorinated solvents	1.11 (0.70 – 1.76)	**2.00 (1.12 – 3.59)**	1.18 (0.92 – 1.52)	1.10 (0.72 – 1.70)	1.27 (0.98 – 1.64)	**1.56 (1.08 – 2.25)**
Other solvents	0.98 (0.72 – 1.34)	0.72 (0.23 – 2.22)	0.92 (0.77 – 1.10)	1.04 (0.61 – 1.76)	1.08 (0.90 – 1.30)	1.53 (0.96 – 2.44)
Metals	**1.76 (1.15 – 2.70)**	1.59 (0.89 – 2.85)	**1.42 (1.10 – 1.83)**	0.96 (0.63 – 1.46)	**1.41 (1.09 – 1.84)**	**1.50 (1.07 – 2.12)**

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.

* Not applicable (no chronic bronchitis cases with ever high exposure to herbicides)

Supplementary Table 3: Association between occupational exposures and incidence of CB, chronic cough and chronic phlegm, stratified by sex and smoking status. N=8933 participants followed-up at ECRHS II and III (n=13324 observations)

(a) Stratified by sex

	Chronic Bronchitis		Cough only		Phlegm only	
	Male	Female	Male	Female	Male	Female
Biological dust	0.97 (0.62 – 1.51)	1.04 (0.72 – 1.49)	0.97 (0.75 – 1.24)	0.92 (0.74 – 1.14)	1.10 (0.86 – 1.41)	1.19 (0.94 – 1.51)
Mineral Dust	1.23 (0.82 – 1.85)	1.51 (0.97 – 2.34)	1.06 (0.84 – 1.33)	1.19 (0.91 – 1.56)	**1.77 (1.41 – 2.22)**	**1.65 (1.23 – 2.20)**
Gases & fumes	1.21 (0.82 – 1.78)	1.08 (0.76 – 1.54)	1.02 (0.81 – 1.27)	0.93 (0.75 – 1.15)	**1.52 (1.21 – 1.90)**	1.17 (0.93 – 1.49)
Vapors, Gases, Dusts & Fumes	1.17 (0.79 – 1.73)	1.02 (0.72 – 1.45)	1.02 (0.82 – 1.27)	0.93 (0.76 – 1.14)	**1.63 (1.29 – 2.05)**	1.15 (0.91 – 1.45)
Herbicides	0.79 (0.19 – 3.27)	1.76 (0.44 – 7.06)	1.37 (0.74 – 2.52)	0.88 (0.29 – 2.63)	1.10 (0.56 – 2.18)	1.91 (0.79 – 4.59)
Insecticides	0.76 (0.24 – 2.35)	1.02 (0.25 – 4.18)	1.03 (0.59 – 1.78)	1.09 (0.50 – 2.41)	0.79 (0.42 – 1.48)	**2.12 (1.11 – 4.06)**
Fungicides	0.65 (0.21 – 2.08)	1.11 (0.27 – 4.55)	1.04 (0.62 – 1.75)	0.98 (0.41 – 2.33)	0.92 (0.53 – 1.61)	**2.05 (1.04 – 4.05)**
All pesticides	0.84 (0.34 – 2.05)	0.92 (0.23 – 3.73)	1.03 (0.65 – 1.62)	0.96 (0.43 – 2.11)	0.81 (0.48 – 1.35)	1.86 (0.97 – 3.55)
Aromatic solvents	1.11 (0.70 – 1.77)	0.93 (0.43 – 1.99)	1.13 (0.88 – 1.46)	0.99 (0.65 – 1.52)	**1.35 (1.06 – 1.73)**	0.99 (0.61 – 1.63)
Chlorinated solvents	1.40 (0.87 – 2.23)	0.78 (0.32 – 1.88)	1.16 (0.88 – 1.52)	1.09 (0.71 – 1.70)	**1.36 (1.05 – 1.78)**	1.16 (0.72 – 1.88)
Other solvents	1.08 (0.70 – 1.68)	0.82 (0.53 – 1.27)	0.96 (0.74 – 1.23)	0.87 (0.68 – 1.11)	**1.27 (1.00 – 1.62)**	0.90 (0.68 – 1.20)
Metals	**1.72 (1.12 – 2.65)**	1.53 (0.57 – 4.14)	1.25 (0.97 – 1.63)	1.45 (0.82 – 2.57)	**1.53 (1.19 – 1.96)**	0.86 (0.37 – 2.04)

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.

(b) Stratified by smoking status (ever smokers / never smokers)

	Chronic Bronchitis		Cough only		Phlegm only	
	Never smokers	Ever smokers	Never smokers	Ever smokers	Never smokers	Ever smokers
Biological dust	1.20 (0.73 – 1.98)	0.96 (0.69 – 1.34)	1.00 (0.76 – 1.32)	0.93 (0.76 – 1.13)	1.25 (0.93 – 1.67)	1.12 (0.91 – 1.37)
Mineral Dust	1.66 (0.95 – 2.91)	1.27 (0.90 – 1.79)	1.18 (0.85 – 1.63)	1.09 (0.89 – 1.35)	**1.76 (1.28 – 2.41)**	**1.71 (1.39 – 2.11)**
Gases & fumes	1.33 (0.83 – 2.13)	1.09 (0.81 – 1.47)	1.05 (0.81 – 1.37)	0.94 (0.79 – 1.13)	**1.38 (1.05 – 1.81)**	**1.34 (1.11 – 1.61)**
Vapors, Gases, Dusts & Fumes	1.28 (0.81 – 2.02)	1.03 (0.77 – 1.39)	1.09 (0.85 – 1.39)	0.93 (0.78 – 1.10)	**1.49 (1.15 – 1.93)**	**1.32 (1.10 – 1.59)**
Herbicides	2.37 (0.67 – 8.36)	0.52 (0.08 – 3.53)	1.62 (0.73 – 3.56)	1.00 (0.47 – 2.14)	1.71 (0.74 – 3.93)	1.17 (0.57 – 2.40)
Insecticides	1.75 (0.49 – 6.24)	0.52 (0.14 – 2.03)	1.27 (0.58 – 2.75)	0.95 (0.53 – 1.71)	1.34 (0.59 – 3.09)	1.09 (0.62 – 1.94)
Fungicides	1.60 (0.44 – 5.74)	0.49 (0.12 – 1.92)	1.24 (0.59 – 2.58)	0.92 (0.52 – 1.64)	1.12 (0.48 – 2.60)	1.23 (0.74 – 2.06)
All pesticides	1.33 (0.37 – 4.81)	0.71 (0.27 – 1.88)	1.10 (0.53 – 2.26)	0.97 (0.59 – 1.58)	1.00 (0.43 – 2.32)	1.08 (0.67 – 1.76)
Aromatic solvents	1.27 (0.61 – 2.67)	1.03 (0.66 – 1.61)	1.29 (0.89 – 1.88)	1.04 (0.80 – 1.34)	1.09 (0.71 – 1.68)	**1.35 (1.06 – 1.72)**
Chlorinated solvents	1.58 (0.75 – 3.29)	1.14 (0.72 – 1.80)	1.31 (0.86 – 2.00)	1.10 (0.84 – 1.45)	1.10 (0.68 – 1.79)	**1.41 (1.09 – 1.83)**
Other solvents	1.06 (0.61 – 1.85)	0.90 (0.63 – 1.31)	1.02 (0.76 – 1.37)	0.87 (0.70 – 1.08)	1.20 (0.89 – 1.64)	1.04 (0.84 – 1.30)
Metals	**2.41 (1.23 – 4.72)**	1.49 (0.94 – 2.34)	1.44 (0.94 – 2.22)	1.23 (0.92 – 1.62)	1.36 (0.86 – 2.16)	**1.48 (1.13 – 1.93)**

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.

Supplementary Table 4: Association between occupational exposures and incidence of CB, chronic cough and chronic phlegm: complete case analysis. N=6186 participants followed-up at ECRHS II and III (n=9046 observations)

	Chronic Bronchitis			Cough only			Phlegm only		
	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)	Unexposed	Exposed	RR (95%CI)
Biological dust	161/9635 (1.7%)	68/3689 (1.8%)	1.01 (0.73 – 1.39)	487/9635 (5.1%)	188/3689 (5.1%)	0.95 (0.79 – 1.15)	389/9635 (4.0%)	179/3689 (4.9%)	1.16 (0.95 – 1.42)
Mineral Dust	166/10498 (1.6%)	63/2826 (2.2%)	**1.49 (1.04 – 2.13)**	511/10498 (4.9%)	164/2826 (5.8%)	1.13 (0.91 – 1.40)	378/10498 (3.6%)	190/2826 (6.7%)	**1.90 (1.54 – 2.35)**
Gases & fumes	133/8303 (1.6%)	96/5021 (1.9%)	1.17 (0.86 – 1.59)	416/8303 (5.0%)	259/5021 (5.2%)	1.00 (0.83 – 1.20)	303/8303 (3.6%)	265/5021 (5.3%)	**1.39 (1.14 – 1.68)**
Vapors, Gases, Dusts & Fumes	125/7664 (1.6%)	104/5660 (1.8%)	1.05 (0.78 – 1.43)	386/7664 (5.0%)	289/5660 (5.1%)	0.99 (0.82 – 1.18)	274/7664 (3.6%)	294/5660 (5.2%)	**1.36 (1.12 – 1.64)**
Herbicides	225/13113 (1.7%)	4/211 (1.9%)	1.26 (0.39 – 4.05)	662/13113 (5.0%)	13/211 (6.2%)	1.44 (0.79 – 2.61)	555/13113 (4.2%)	13/211 (6.2%)	1.66 (0.93 – 2.96)
Insecticides	224/12991 (1.7%)	5/333 (1.5%)	0.98 (0.37 – 2.61)	657/12991 (5.1%)	18/333 (5.4%)	1.18 (0.71 – 1.97)	550/12991 (4.2%)	18/333 (5.4%)	1.27 (0.76 – 2.12)
Fungicides	224/12962 (1.7%)	5/362 (1.4%)	0.88 (0.32 – 2.40)	656/12962 (5.1%)	19/362 (5.2%)	1.23 (0.75 – 1.99)	548/12962 (4.2%)	20/362 (5.5%)	1.29 (0.79 – 2.11)
All pesticides	222/12855 (1.7%)	7/469 (1.5%)	1.03 (0.46 – 2.34)	651/12855 (5.1%)	24/469 (5.1%)	1.13 (0.73 – 1.77)	545/12855 (4.2%)	23/469 (4.9%)	1.12 (0.70 – 1.78)
Aromatic solvents	197/11558 (1.7%)	32/1766 (1.8%)	1.10 (0.70 – 1.73)	578/11558 (5.0%)	97/1766 (5.5%)	1.06 (0.81 – 1.38)	471/11558 (4.1%)	97/1766 (5.5%)	**1.44 (1.13 – 1.85)**
Chlorinated solvents	200/11908 (1.7%)	29/1416 (2.0%)	1.23 (0.77 – 1.97)	593/11908 (5.0%)	82/1416 (5.8%)	1.02 (0.76 – 1.35)	486/11908 (4.1%)	82/1416 (5.8%)	**1.39 (1.07 – 1.81)**
Other solvents	177/10115 (1.7%)	52/3209 (1.6%)	0.88 (0.61 – 1.26)	525/10115 (5.2%)	150/3209 (4.7%)	0.83 (0.67 – 1.03)	422/10115 (4.2%)	146/3209 (4.5%)	1.12 (0.91 – 1.39)
Metals	196/12017 (1.6%)	33/1307 (2.5%)	1.54 (0.97 – 2.46)	595/12017 (5.0%)	80/1307 (6.1%)	1.18 (0.89 – 1.56)	487/12017 (4.1%)	81/1307 (6.2%)	**1.41 (1.08 – 1.85)**

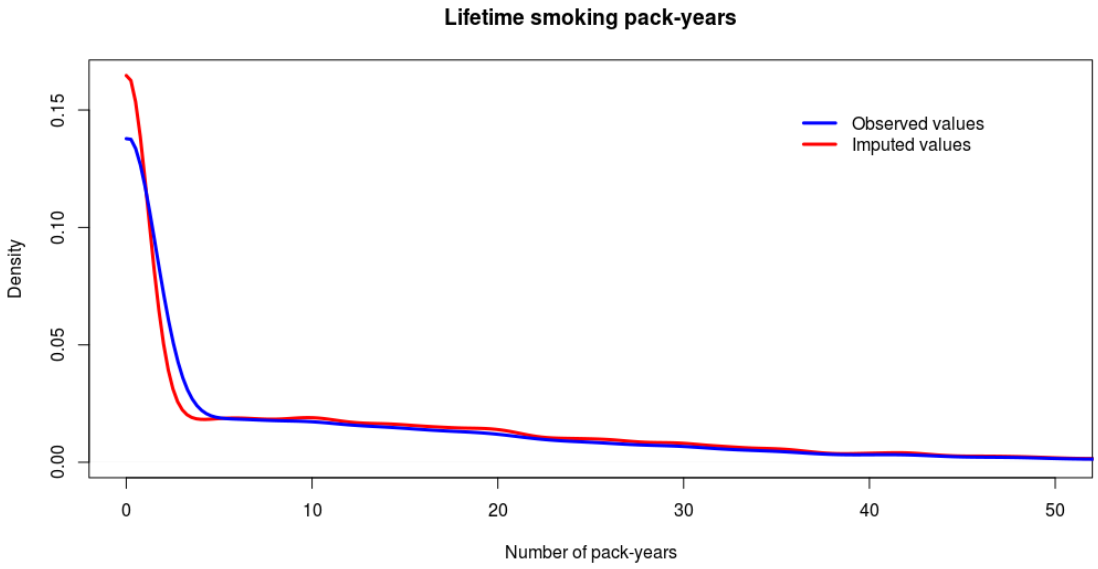
Adjusted for age, sex, lifetime smoking pack-years, current smoking, socioeconomic status (SES), current asthma and severity of airflow limitation.

Details about the multiple imputation procedure

Multiple imputation was employed to handle covariate missingness only (not outcome missingness due to drop-out). The most frequent covariates affected by missingness were lung function measurements (at both surveys, i.e. ECRHS II and III), plus current smoking status and lifetime smoking pack-years (only at ECRHS III) (see Table 1 in the manuscript). Very few observations had missing values on current asthma and SES.

Multiple imputation with chained equations was performed using the R package "mice", version 2.30. The procedure was applied on the long-format dataset (n=13324 observations from N=8933 study participants). The imputation method was set to logistic regression for binary variables (current asthma and current smoking), polynomial regression for categorical variables (SES and degree of airflow limitation), and predictive mean matching for continuous variables (lifetime smoking pack-years). All variables used in the main model were used as predictors in the imputation model, including all occupational exposures, outcomes (chronic cough and chronic phlegm separately) and a survey indicator (ECRHS II or III). The passive imputation function of the "mice" package was used to ensure that the imputed value for current smoking would be set to FALSE if the imputed lifetime pack-years were zero.

Fifty imputed datasets were created with 10 Gibbs sampler iterations each; convergence was assessed by visually examining the traceplots, and was deemed very satisfactory. The distribution of imputed values for lifetime pack-years was compared to the observed values using a density plot, and was found to be very similar (figure below).



4.1 Paper III

Lung function decline and COPD prevalence in relation to occupational exposures in the ECRHS study

Theodore Lytras, Manolis Kogevinas, Jan-Paul Zock, occupational working group and study centres of the ECRHS

Preliminary paper, not submitted for publication; a participant-level pooled analysis with the SAPALDIA cohort is currently being undertaken based on the exact analytical methods described here, to be published later.

Lung function decline and COPD prevalence in relation to occupational exposures in the ECRHS study

Theodore Lytras[1,2], Manolis Kogevinas[1,2,3,4], Jan-Paul Zock[1,2,3], occupational working group and study centres of the ECRHS

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Abstract

Few longitudinal studies have assessed the relationship between occupational exposures and lung function decline in a general population. Our objective was to examine this potential association within the European Community Respiratory Health Survey (ECRHS). General population samples aged 20 to 50 were randomly selected in 1991-1993, and followed up 10 and 20 years later. Spirometry (without bronchodilation) was performed at each visit. Coded job histories during follow-up visits were linked to a Job-Exposure Matrix, generating cumulative exposure estimates for 12 occupational exposures. FEV1 and FVC were jointly modelled in linear mixed-effects models, fitted in a Bayesian framework. The prevalence of COPD was estimated via model-based predictions for any combination of covariates. A total of 21,773 lung function measurements from 9,765 study participants were analyzed. We found accelerated declines in the FEV1/FVC ratio for male smokers exposed to dusts, gases, fumes and pesticides; similar but non-significant effects were observed in female smokers, while for never smokers any possible effect was much smaller. These results strengthen the evidence base about occupational exposures as a risk factor for COPD.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an important cause of population morbidity and mortality, characterized by a low level of lung function and persistent airflow limitation [1]. Lung function declines naturally with age, and an accelerated decline is the proximate cause of COPD. The most important risk factor for accelerated lung function decline is tobacco smoking, which is associated with the vast majority of COPD cases. Other environmental risk factors, however, also play a role in the pathogenesis of COPD; one of these is occupation, to which 15-20% of all cases have been attributed [2]. A large number of studies, both population- and industry-based, have demonstrated an asociation between COPD and a variety of occupational exposures, such as dusts, gases and fumes [3]. Most of these studies have been cross-sectional though; few studies have examined the relationship between longitudinal lung function decline and occupational exposures as estimated by a Job-Exposure Matrix (JEM) [4–6].

A previous analysis from the first 10-year follow-up of the European Community Respiratory Health Survey (ECRHS) did not show a steeper decline in lung function in people exposed to vapors, gases, dusts or fumes [4]. The cohort however was fairly young (30-55 years old at the time), and the follow-up time may have been too short to detect an association. The ECRHS has now completed a second follow-up after a mean of 20 years, including more participants over 50 years of age, while we additionally have further exposure estimates (such as against pesticides, chlorocarbons and heavy metals) from the recently extended ALOHA(+) JEM. Meanwhile some open questions remain about the effect of occupational exposures on lung function decline, such as its magnitude and its interaction with sex and smoking.

Consequently, the aim of the present study was to explore the association of occupational exposures, estimated via the ALOHA(+) JEM, with longitudinal lung function decline in the general population, over two decades of follow-up in the ECRHS cohort.

Methods

The ECRHS is a multicentre longitudinal study initiated in 1991–1993 which enrolled random general population samples aged 20 to 44 years in 55 centres from 23 countries [7]. Participants at baseline (ECRHS I) completed a detailed questionnaire via face-to-face interview and underwent a clinical examination, spirometry and other measurements. They were followed again between 1998 and 2002 (ECRHS II), and a

second time between 2010 and 2012 (ECRHS III). During both follow-ups, participants were asked to provide a detailed list of their occupations and industries from jobs held since the last study visit; these were recorded in free text and subsequently coded in the International Classification of Occupations-88 (ISCO-88) standard by trained local coders. Ethical approval for each centre was obtained from their respective competent bodies.

The population for this study includes all participants who completed spirometry at baseline (ECRHS I) and were followed up at least once (at ECRHS II and/or ECRHS III). Spirometries were performed without bronchodilation and according to the ATS/ERS standards for reproducibility, keeping the maximum Forced Volume Capacity (FVC) and Forced Expiratory Volume in 1 second (FEV_1) per participant. Occupational exposures were determined by linking the participants ISCO-88 coded occupations to the semi-quantitative ALOHA(+) JEM [5]. This JEM assigns, for every ISCO-88 job code, three grades of exposure (none, low, high) to twelve agents (biological dusts, mineral dusts, gases/fumes, herbicides, insecticides, fungicides, aromatic solvents, chlorinated solvents, other solvents, and metals) including two composites of the above (All pesticides, and Vapors/Gases/Dusts/Fumes – VGDF). For each participant a cumulative exposure to each agent in intensity-years was calculated, by multiplying the duration of each job with the intensity of exposure (0 for none, 1 for low, and 4 for high).

Covariates used for adjustment included sex, height at each visit (including its square, to allow for non-linear associations), current asthma, current smoking, lifetime smoking pack-years, Socioeconomic Status (SES) and early life disadvantage score; the latter is a composite variable that includes maternal smoking, maternal asthma, paternal asthma, childhood asthma (before age 10), and having a serious respiratory infection before age 5 [8]. 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?”. 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).

Associations between cumulative occupational exposures and absolute lung function (FEV_1, FVC and the FEV_1/FVC ratio) were assessed using linear mixed-effects models (for full details see the online supplement). FEV_1 and FVC were jointly modelled, and all models included participant-level random intercepts and slopes, taking account of the correlations both between intercepts and slopes and between FEV_1 and FVC. For each

ALOHA(+) exposure agent we fitted two joint models, one using absolute FEV_1 and FVC and one using their logarithms as the outcome; from the latter, log-linear model we calculated the effects of exposures on the FEV_1/FVC ratio, as the difference between model parameters for log(FEV_1) and log(FVC). Also from the log-linear model we estimated the effect of exposures on the prevalence of COPD, as model-based predictions (Risk Ratios) for any age and combination of covariates; COPD was defined as a pre-bronchodilator FEV_1/FVC ratio less than the Lower Limit of Normal (LLN) using the GLI equations [9].

The fixed-effects part for all models included the above mentioned covariates and also interaction terms between cumulative exposure and sex, and between cumulative exposure and ever being a smoker; therefore all exposure effect estimates were stratified by sex and smoking status (ever smokers vs. never smokers). In addition, we fitted a pair of "null" models, i.e. with covariates only and not exposure, in order to assess how well the overall model describes the longitudinal function decline in our study population.

The models were fitted in a Bayesian framework with the JAGS software, setting non-informative priors for all parameters, and using 4 chains and 12,000 iterations per chain, discarding the first 2,000 as burn-in; convergence was checked by visual inspection of the MCMC traceplots and by the Gelman-Rubin statistic. Furthermore, all models included a fully Bayesian imputation sub-model for handling item (covariate) missingness, with hyperparameters set to non-informative priors. In order to address differential loss to follow-up, we used an Inverse response-Propensity Weighting (IPW) scheme appropriate for panel studies [10]; probability of response at each study wave was estimated using logistic regression, as a function of covariates at previous waves. These covariates included age at baseline (ECRHS I), smoking status (current / ex- / never smoker), SES and chronic respiratory symptoms including asthma symptoms. Covariate missingness in the response probability model was handled by multiple imputation and pooling [11]. Finally as a sensitivity analysis, we refit all models without any weights and compared the results. All analyses were performed with the R statistical environment, version 3.3.3 [12].

Results

Table 1 highlights the characteristics of the study population. We analyzed a total of 21,773 lung function measurements from 9,765 study participants across 29 centres who completed at least one follow-up visit, with a mean maximum follow-up duration of

15.6 years. Of these participants, 4,973 completed both visits over a mean duration of 20.0 years. Slightly less than half of our sample had never smoked, and about a third were current smokers at baseline, dropping almost by half to 18.1% at the second follow-up. Almost half of all participants had been occupationally exposed to VGDF at some point during follow-up (44.8%), whereas fewer had been exposed to pesticides (3.8%), solvents (27.4%) or metals (10.9%). Men were overall more likely than women to be occupationally exposed to most agents, with the exeption of biological dust (Table 2). In addition, many exposures showed substantial overlap with each other (Figure 1).

Lifetime smoking pack-years were missing in 11.6% of all observations, and had to be imputed in our models as described above; also current smoking status was missing in 5.3%, current asthma in 0.8% and SES in 2% of all observations.

Lung function in our study population naturally declined with advancing age across both follow-ups, and the “null” model (with covariates only) appeared reliable in describing both mean lung function by age as well as the variability around the mean (Supplemental Figure 1).

Table 3 shows the main results of our analysis, i.e. the mean additional lung function change (negative sign means a larger decline, positive sign means a smaller decline) per intensity-year of occupational exposure to each ALOHA(+) agent, stratified by sex and smoking status. Quantile-based 95% Credible Intervals (CrI, the Bayesian analogue to the Confidence Interval) are presented. The effects are very small for all three lung function parameters and for all exposures, but some patterns emerge. Significant (95% CrI does not include zero) additional declines in the FEV_1/FVC ratio are seen in men who have smoked (current or ex-smokers), for most exposures except solvents. For dusts, gases/fumes and their composite VGDF these reductions appear to be driven by a slower decline in FVC compared to FEV1; on the other hand, for pesticides a more clear-cut decline in FEV_1 is observed (for all pesticides: -2.76 ml/intensity-year, 95% CrI: -4.48 to -1.00). Similar non-significant trends towards FEV_1/FVC decline for these occupational exposures are observed also in women who have smoked, in particular particular for VGDF (-0.026 %/intensity-year, 95% CrI: -0.052 to 0). For men and women who have never smoked, any possible effect of occupational exposures on the FEV1/FVC ratio appear much smaller; an interesting finding is an accelerated decline in both FEV_1 and FVC of about -2 ml/intensity-year for non-smoking women exposed to biological dust. In addition, women working in occupations with aromatic and chlorinated solvent exposure appeared to have slower declines in both FEV_1 and FVC, with no overall effect on the FEV1/FVC ratio decline.

The observed FEV_1/FVC reductions in ever smokers, although small, can accumulate over the years (see Supplemental Table 1) and translate to a measurable higher risk of COPD; the exact amount depends on the baseline COPD risk, which is a function of age, pack-years of smoking and other covariates. This is illustrated by Figure 2, which shows model-based predictions of COPD risk in smokers after occupational exposure, compared to no exposure. For men at 65 years of age, the predicted Relative Risk of COPD after a lifetime of low-exposure to VGDF (45 intensity-years) is 1.10 (95% CrI: 1.05 to 1.18), and for pesticides it is 1.17 (95% CrI: 1.03 to 1.36).

Due to the substantial overlap between different occupational exposures in many jobs and for many study participants, it is difficult to disentangle the effect of each exposure. For example, all 370 participants with pesticide exposure were also exposed to VGDF. In order to distinguish between the effect of VGDF and that of pesticides on lung function decline, we fit the model with both exposures included, thereby estimating the effect of one controlled for the other. The results are shown in Table 4. The effect of VGDF on the FEV1/FVC ratio for smoking men remained virtually unchanged (-0.03 %/intensity-year, 95% CrI: -0.043 to -0.017) while the additional (conditional on VGDF) effect of pesticides was not significant (-0.021 %intensity-year, 95% CrI: -0.064 to 0.021). Similarly, most participants exposed to metals were also exposed to mineral dust. In a model with both exposures, the effect of metals on all parameters became not significant, while mineral dust appeared to cause accelerated decline of the FEV1/FVC ratio in smoking men (-0.041 %/intensity-year, 95% CrI: -0.061 to -0.021), due to a slower decline in FVC.

The results from the sensitivity analysis (models fit without observation IPW weights) did not appreciably differ from those of the main analysis (Supplemental Table 2).

Discussion

In this study we showed that occupational exposures, despite having different effects on FEV1 and FVC separately, were consistently associated with accelerated declines in the FEV1/FVC ratio especially among male smokers. This was true for biological dust, mineral dust, pesticides and metals exposure, while solvents did not appear to have any effect. This extra lung function decline associated with occupational exposures can result in increased COPD risk later in life.

The study provides important prospective evidence about the role of occupation in long-term lung function decline for a variety of exposures, in particular dusts, gases/fumes and pesticides. Although dusts and fumes have been associated with increased risk of

COPD in multiple studies [2,3], few have examined longitudinal lung function decline, and fewer have done so in a general population setting [5,6,13–15]. In comparison to industry-based studies, general population cohorts can provide more generalizable information by including all types of exposures across all industries, and by adjusting for socioeconomic status and other covariates. Therefore this study expands the evidence base for the role of occupation in accelerated lung function decline and COPD risk.

Our analysis was stratified a priori by sex and smoking status, thus assuming different effect of occupational exposures for men and women, and for never smokers vs. ever smokers. Although the sample size was not sufficient to demonstrate effect modification by smoking status, the effect of almost all occupational exposures tended to be lower for never smokers, particularly with respect to FEV1/FVC. This is consistent with other studies that have observed interaction between the effects of occupation and smoking on lung function decline and COPD risk [5,16–18]. Smoking has been known to induce inflammation and impair the host defense mechanisms of the lung [19–21]; as a result it could potentiate the effect of occupational exposures on lung function decline. Sex differences also may exist both due to biological differences and because of differences in the exact jobs that comprise each exposed category. For certain exposures in our study, namely biological dust, gases/fumes and VGDF, we found very similar effects on the FEV1/FVC ratio in female smokers as in male smokers. However, due to the lower percentage of women working in exposed occupations, these estimates suffer from lower precision. We also found an accelerated decline in both FEV1 and FVC, with a normal FEV1/FVC ratio, in non-smoking women exposed to biological dust; this indicates a potential increased risk of restrictive, rather than obstructive lung disease in these women and warrants further inverstigation.

Occupational pesticide exposure has been associated with accelerated FEV1 and FEV1/FVC decline in one previous longitudinal study, particularly for smokers [5]; our results further confirm and expand on this finding. Of note, pesticides have been linked with both obstructive and restrictive lung disease, possibly dependent on the exact kind of agent [22]. In this study we found significant declines in FEV1 and FEV1/FVC for smoking men exposed to pesticides, but also a smaller decline in FVC. After adjusting for concurrent VGDF exposure however, the FVC decline became significant and the effect on the FEV1/FVC ratio was reduced. These findings indicate that pesticides might indeed be a heterogenous exposure in terms of its effect on lung function, causing obstruction, restriction or both. Future studies must try to distinguish in detail between

the different subgroups of pesticides, which is challenging to do in a population-based study.

Another interesting finding is the slower FVC decline among smoking men exposed to dusts, gases and fumes, with a normal FEV1 decline, resulting in an accelerated FEV1/FVC decline. This could point to a “healthy hire” effect, where the healthiest workers are employed in the more physically demanding jobs, which also expose them to more respiratory health hazards. Such an effect has been described earlier for pre-existing asthma before employment [23,24], and may also affect here the relationship between respiratory health and occupation in a general population setting. A similar phenomenon appears to be at play for women (both smokers and non-smokers) exposed to aromatic and chlorinated solvents in our study, who had much slower declines in both FEV1 and FVC, with a normal FEV1/FVC ratio. These observations highlight the importance of jointly modelling both spirometric parameters; indeed in our linear mixed-effects models we found positive correlations not only between the participant-level random intercepts and slopes for both FEV1 and FVC, but also between the intercepts for FEV1 and FVC and between the slopes for FEV1 and FVC (data not shown). Modelling this dependence between FEV1 and FVC is a requisite for epidemiological studies of lung function, as is examining not only FEV1 but also its ratio with FVC.

Strengths of the current study include its prospective population-based design and long follow-up of 20 years. Full job histories were collected for the study period and cumulative occupational exposures were calculated using a JEM instead of self-report; the latter could be vulnerable to recall bias, especially given the long follow-up. Lung function was modelled in detail, using random intercepts and slopes; in addition we controlled for multiple confounders, including socioeconomic status, current asthma and especially lifetime smoking pack-years, in order to avoid confounding by intensity of smoking. Fully Bayesian imputation was employed for missing covariates, under an ignorable missingness assumption, and IPW weighting was applied to adjust for any differential loss to follow-up.

On the other hand, there are certain limitations. Although the sample size is large, it was still insufficient in many cases to generate precise estimates for relatively small effects on lung function decline, especially as regards women. For the same reason, we cannot fully disentangle the effect of multiple overlapping exposures, which would require a large number of small subroup analyses. The application of a JEM may ensure more objective exposure estimates, but some heterogeneity in the exposure categories cannot be avoided, as well as some misclassification. We could not assess heterogeneity of the

results across study centres or countries, also because the -necessary- inclusion of participant-level random effects left almost no variance to be explained by study centre. Residual confounding cannot be completely ruled out, and we observed indirect evidence suggestive of a potential “healthy hire” bias which could blunt the effects of occupational exposures on lung function decline.

In conclusion, long-term occupational exposure to dusts, gases, fumes and pesticides over two decades of follow-up was associated with an accelerated decline in the FEV1/FVC ratio, particularly in male smokers, and therefore an increased risk of airway obstruction and COPD. Although the observed effects are small, these results strengthen the case for occupation as a modifiable risk factor for COPD, in agreement with previous studies. Future research should try to provide more data about women in exposed occupations, and about the interaction of occupational exposures with smoking.

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Table 1: Characteristics of study participants followed up, by study wave

	ECRHS I	ECRHS II	ECRHS III
Number of participants	9765	8725	6013
% men	48	48.1	47.9
Mean age	34	42.8	54.1
% current asthma	7.9	9.9	11.2
% never smokers	44.8	45.5	49
% current smokers	34.5	29	18.1
Mean cumulative smoking pack-years	7.2	9.7	10.9
% of participants exposed			
Biological dust	-	26.6	30.7
Mineral Dust	-	21.1	23.9
Gases & fumes	-	37.4	41.3
Vapors, Gases, Dusts & Fumes	-	41.9	46.1
Herbicides	-	1.5	1.8
Insecticides	-	2.3	2.9
Fungicides	-	2.4	3.4
All pesticides	-	3.2	4.3
Aromatic solvents	-	13.1	14.9
Chlorinated solvents	-	10.3	12.2
Other solvents	-	23	26.9
Metals	-	9.5	11.4
Mean cumulative exposures since previous follow-up (intensity-years)			
Biological dust	-	2.2	4.7
Mineral Dust	-	2.4	4.7
Gases & fumes	-	3.9	7.7
Vapors, Gases, Dusts & Fumes	-	5.3	10.6
Herbicides	-	0.1	0.3
Insecticides	-	0.3	0.6
Fungicides	-	0.3	0.6
All pesticides	-	0.4	0.7
Aromatic solvents	-	1	1.9
Chlorinated solvents	-	1.2	2.1
Other solvents	-	1.8	3.7
Metals	-	1.3	2.3

Table 2: Proportion of participants with any occupational exposure during follow-up, stratified by gender

	% of men ever exposed	% of women ever exposed
Biological dust	25.5	32.5
Mineral Dust	33.6	13.4
Gases & fumes	47.9	33.2
Vapors, Gases, Dusts & Fumes	51.8	38.2
Herbicides	2.5	1
Insecticides	3.8	1.6
Fungicides	4.7	1.4
All pesticides	5.9	1.8
Aromatic solvents	23.6	5.9
Chlorinated solvents	18.7	5.2
Other solvents	28.4	22.7
Metals	20.1	2.4

Table 3: Effect of occupational exposures on lung function decline, per intensity-year of exposure, stratified by gender and smoking status.

(a) Additional annual FEV_1 change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Biological dust	-0.513 (-1.823 to 0.762)	**-2.154 (-3.746 to -0.637)**	0.449 (-0.533 to 1.405)	-1.192 (-2.653 to 0.271)
Mineral Dust	-0.223 (-1.332 to 0.842)	-0.139 (-1.938 to 1.667)	-0.492 (-1.228 to 0.22)	-0.408 (-2.163 to 1.371)
Gases & fumes	-0.218 (-1.172 to 0.728)	-0.889 (-2.343 to 0.561)	0.137 (-0.498 to 0.773)	-0.534 (-1.934 to 0.84)
Vapors, Gases, Dusts & Fumes	-0.018 (-0.745 to 0.722)	-0.559 (-1.701 to 0.6)	0.008 (-0.505 to 0.529)	-0.532 (-1.62 to 0.587)
Herbicides	-1.703 (-6.211 to 3.203)	-0.881 (-6.602 to 4.969)	**-3.318 (-5.905 to -0.738)**	-2.496 (-8.232 to 3.003)
Insecticides	-0.379 (-3.237 to 2.427)	0.667 (-3.149 to 4.584)	**-2.209 (-4.181 to -0.336)**	-1.163 (-4.516 to 2.236)
Fungicides	0.524 (-2.571 to 3.689)	2.461 (-1.511 to 6.503)	**-2.889 (-4.811 to -1.02)**	-0.952 (-4.475 to 2.649)
All pesticides	0.179 (-2.474 to 3.027)	1.252 (-2.475 to 5.007)	**-2.761 (-4.479 to -0.998)**	-1.688 (-5.053 to 1.737)
Aromatic solvents	0.673 (-1.367 to 2.626)	3.013 (-0.72 to 6.617)	0.123 (-1.332 to 1.607)	2.462 (-0.954 to 5.865)
Chlorinated solvents	0.186 (-1.309 to 1.695)	**3.806 (0.048 to 7.609)**	**-1.06 (-2.079 to -0.044)**	2.56 (-0.957 to 6.231)
Other solvents	-0.115 (-1.897 to 1.571)	-0.669 (-2.54 to 1.162)	0.75 (-0.554 to 2.037)	0.196 (-1.303 to 1.697)
Metals	0.146 (-1.263 to 1.517)	1.506 (-2.244 to 5.269)	-0.865 (-1.822 to 0.068)	0.495 (-3.195 to 4.227)

(b) Additional annual FVC change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Biological dust	0.395 (-1.107 to 1.902)	**-2.222 (-4.083 to -0.406)**	**1.711 (0.535 to 2.863)**	-0.906 (-2.627 to 0.82)
Mineral Dust	0.904 (-0.377 to 2.198)	-0.405 (-2.548 to 1.723)	**1.049 (0.188 to 1.912)**	-0.26 (-2.364 to 1.862)
Gases & fumes	0.574 (-0.552 to 1.69)	-0.66 (-2.458 to 1.065)	**1.456 (0.699 to 2.21)**	0.222 (-1.466 to 1.883)

	Men, never smokers	Women, never smokers	Men, ever smokers	Women, ever smokers
Vapors, Gases, Dusts & Fumes	0.831 (-0.038 to 1.72)	-0.409 (-1.758 to 0.958)	**1.288 (0.684 to 1.911)**	0.048 (-1.246 to 1.378)
Herbicides	-2.044 (-7.325 to 3.823)	-3.955 (-11.019 to 3.178)	-2.692 (-5.757 to 0.359)	-4.604 (-11.535 to 2.313)
Insecticides	-1.379 (-4.696 to 1.966)	-1.655 (-6.148 to 2.981)	-0.803 (-3.146 to 1.422)	-1.079 (-5.132 to 2.915)
Fungicides	-0.149 (-4.198 to 3.727)	0.123 (-4.647 to 4.934)	-1.768 (-4.006 to 0.428)	-1.496 (-5.871 to 2.798)
All pesticides	-0.551 (-3.781 to 2.893)	-0.767 (-5.217 to 3.724)	-1.485 (-3.561 to 0.596)	-1.701 (-5.819 to 2.396)
Aromatic solvents	1.92 (-0.588 to 4.206)	**4.952 (0.646 to 9.189)**	0.769 (-0.932 to 2.538)	3.801 (-0.274 to 7.886)
Chlorinated solvents	1.356 (-0.471 to 3.2)	**6.626 (2.052 to 11.169)**	-0.734 (-1.949 to 0.461)	**4.536 (0.353 to 8.846)**
Other solvents	1.225 (-0.813 to 3.258)	0.543 (-1.634 to 2.731)	1.165 (-0.42 to 2.713)	0.482 (-1.302 to 2.248)
Metals	1.26 (-0.37 to 2.876)	0.608 (-3.792 to 5.014)	0.174 (-0.958 to 1.259)	-0.479 (-4.779 to 3.835)

(c) Additional annual FEV_1/FVC change (relative, in %) per intensity-year of exposure (95% CrI).

	Men, never smokers	Women, never smokers	Men, ever smokers	Women, ever smokers
Biological dust	-0.019 (-0.051 to 0.012)	-0.018 (-0.056 to 0.019)	**-0.029 (-0.052 to -0.005)**	-0.027 (-0.063 to 0.008)
Mineral Dust	-0.023 (-0.05 to 0.005)	0.003 (-0.042 to 0.049)	**-0.044 (-0.061 to -0.027)**	-0.018 (-0.062 to 0.026)
Gases & fumes	-0.011 (-0.033 to 0.012)	-0.01 (-0.045 to 0.026)	**-0.03 (-0.046 to -0.015)**	-0.029 (-0.062 to 0.003)
Vapors, Gases, Dusts & Fumes	-0.014 (-0.032 to 0.004)	-0.008 (-0.036 to 0.019)	**-0.032 (-0.044 to -0.019)**	-0.026 (-0.052 to 0)
Herbicides	-0.018 (-0.131 to 0.096)	0.051 (-0.089 to 0.191)	-0.042 (-0.104 to 0.019)	0.027 (-0.094 to 0.149)
Insecticides	0.014 (-0.057 to 0.087)	0.045 (-0.051 to 0.141)	**-0.053 (-0.095 to -0.009)**	-0.022 (-0.102 to 0.06)
Fungicides	0.011 (-0.065 to 0.089)	0.058 (-0.044 to 0.161)	**-0.047 (-0.09 to -0.004)**	0 (-0.082 to 0.083)
All pesticides	0.012 (-0.058 to 0.081)	0.041 (-0.051 to 0.135)	**-0.051 (-0.091 to -0.011)**	-0.022 (-0.101 to 0.058)

	Men, never smokers	Women, never smokers	Men, ever smokers	Women, ever smokers
Aromatic solvents	-0.017 (-0.067 to 0.033)	-0 (-0.092 to 0.091)	-0.023 (-0.06 to 0.012)	-0.007 (-0.092 to 0.078)
Chlorinated solvents	-0.018 (-0.058 to 0.02)	-0.006 (-0.102 to 0.091)	-0.022 (-0.048 to 0.003)	-0.01 (-0.1 to 0.082)
Other solvents	-0.027 (-0.069 to 0.015)	-0.022 (-0.067 to 0.024)	-0.014 (-0.046 to 0.017)	-0.01 (-0.045 to 0.025)
Metals	-0.017 (-0.052 to 0.018)	0.038 (-0.054 to 0.131)	**-0.037 (-0.06 to -0.014)**	0.019 (-0.071 to 0.109)

All estimates adjusted for height (including its square), current smoking, smoking pack-years, current asthma, socioeconomic status and early life disadvantage score.

Table 4: Combined effect of VGDF and pesticide exposure on lung function decline, per intensity-year of exposure, stratified by gender and smoking status.

(a) Additional annual FEV_1 change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Vapors, Gases, Dusts & Fumes	-0.046 (-0.829 to 0.739)	-0.685 (-1.947 to 0.531)	0.242 (-0.298 to 0.781)	-0.397 (-1.589 to 0.816)
All pesticides	0.211 (-2.879 to 3.186)	2.082 (-1.963 to 6.143)	**-3.005 (-4.865 to -1.121)**	-1.134 (-4.687 to 2.39)

(b) Additional annual FVC change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Vapors, Gases, Dusts & Fumes	**0.989 (0.045 to 1.941)**	-0.247 (-1.768 to 1.24)	**1.512 (0.87 to 2.153)**	0.276 (-1.113 to 1.713)
All pesticides	-1.738 (-5.178 to 1.71)	-0.605 (-5.314 to 4.164)	**-2.985 (-5.12 to -0.787)**	-1.852 (-6.229 to 2.443)

(c) Additional annual FEV_1/FVC change (relative, in %) per intensity-year of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Vapors, Gases, Dusts & Fumes	-0.017 (-0.036 to 0.002)	-0.014 (-0.044 to 0.015)	**-0.03 (-0.043 to -0.017)**	-0.027 (-0.055 to 0.001)
All pesticides	0.03 (-0.041 to 0.102)	0.061 (-0.041 to 0.161)	-0.021 (-0.064 to 0.021)	0.009 (-0.075 to 0.096)

All estimates also adjusted for height (including its square), current smoking, smoking pack-years, current asthma, socioeconomic status and early life disadvantage score.

Table 5: Combined effect of mineral dust and metals exposure on lung function decline, per intensity-year of exposure, stratified by gender and smoking status.

(a) Additional annual FEV_1 change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Mineral dust	-0.438 (-1.691 to 0.859)	-0.709 (-2.728 to 1.33)	-0.169 (-1.027 to 0.689)	-0.439 (-2.417 to 1.495)
Metals	0.432 (-1.303 to 2.008)	2.066 (-1.989 to 6.185)	-0.771 (-1.852 to 0.35)	0.863 (-3.081 to 4.891)

(b) Additional annual FVC change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Mineral dust	0.469 (-1.043 to 1.96)	-0.99 (-3.424 to 1.402)	**1.386 (0.372 to 2.393)**	-0.073 (-2.437 to 2.195)
Metals	1.04 (-0.855 to 2.949)	1.489 (-3.324 to 6.399)	-0.8 (-2.087 to 0.521)	-0.351 (-5.069 to 4.413)

(c) Additional annual FEV_1/FVC change (relative, in %) per intensity-year of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Mineral dust	-0.02 (-0.051 to 0.011)	-0.003 (-0.052 to 0.046)	**-0.041 (-0.061 to -0.021)**	-0.024 (-0.071 to 0.023)
Metals	-0.007 (-0.046 to 0.033)	0.036 (-0.064 to 0.137)	-0.008 (-0.034 to 0.019)	0.035 (-0.06 to 0.131)

All estimates also adjusted for height (including its square), current smoking, smoking pack-years, current asthma, socioeconomic status and early life disadvantage score.

Figures

Figure 1: Matrix of correlations (Spearman's rho) between cumulative occupational exposures in the study population (in intensity-years) as estimated by the ALOHA(+) JEM

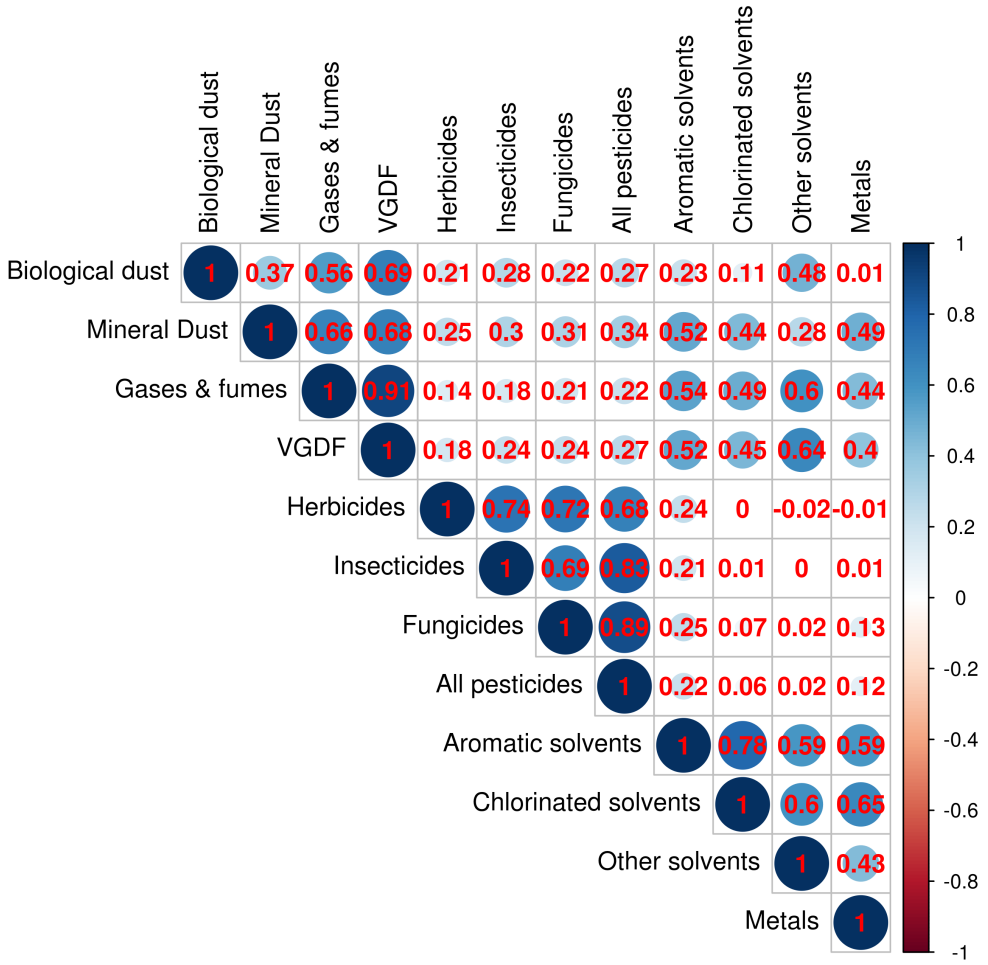
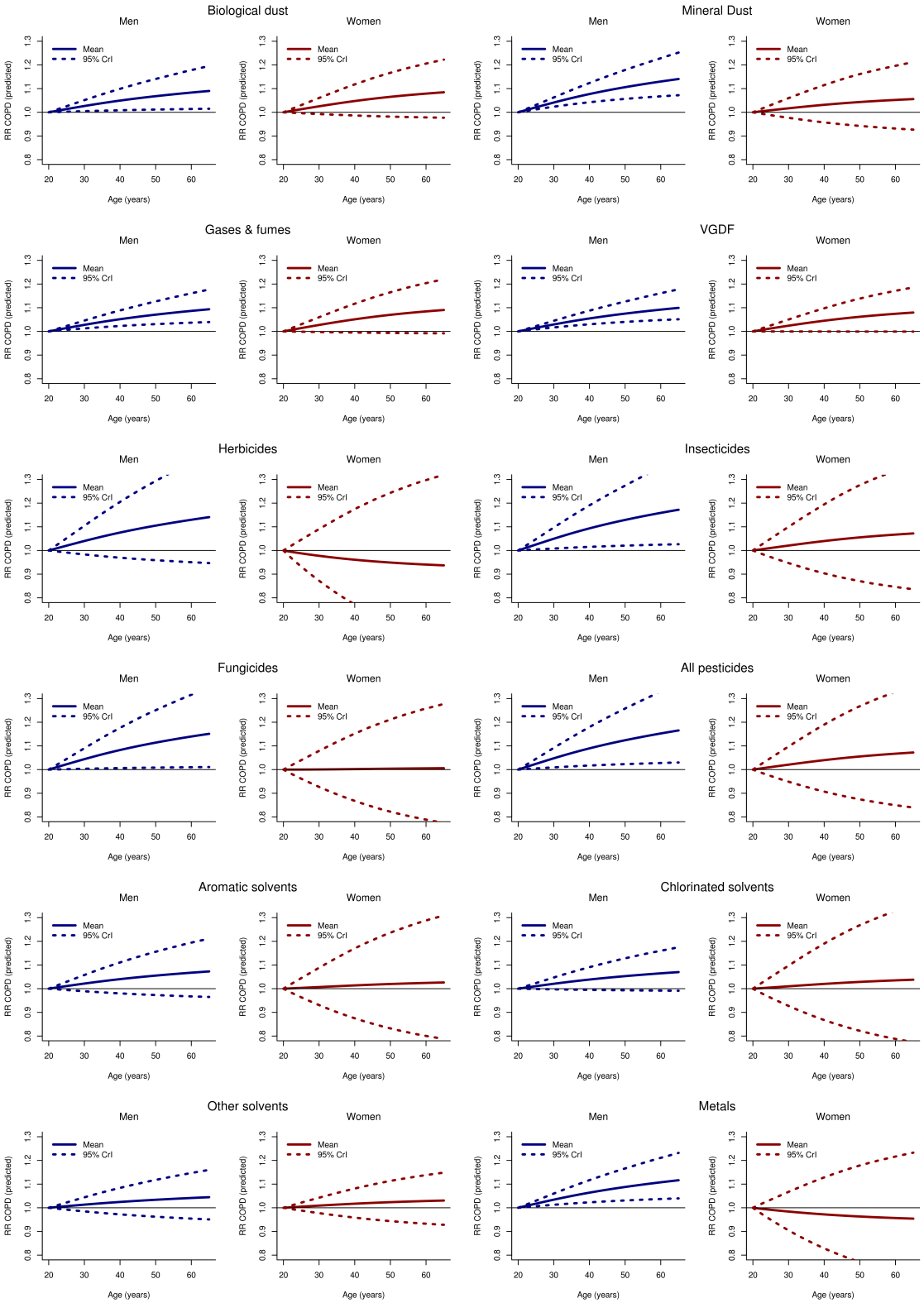


Figure 2: Model-predicted Relative Risk of COPD by age in ever smokers, for continuous low-intensity occupational exposure from age 20 onwards, versus no occupational exposure. Height set to cohort mean by gender, smoking pack-years set to cohort mean by age and gender.


Biological dust
Men
Women
Mineral Dust
Men
Women
Gases & fumes
Men
Women
VGDF
Men
Women
Herbicides
Men
Women
Insecticides
Men
Women
Fungicides
Men
Women
All pesticides
Men
Women
Aromatic solvents
Men
Women
Chlorinated solvents
Men
Women
Other solvents
Men
Women
Metals
Men
Women
Mean
95% CrI
RR COPD (predicted)
Age (years)

SUPPLEMENT

Details about the statistical methodology used

The fixed-effects part of the main model (the one including cumulative occupational exposures) jointly modelled absolute FEV_1 and FVC (or their logarithm) as a function of age and other covariates at each time point. Random intercepts and slopes for every participant were included, both for FEV_1 and FVC; their correlations were modelled via a 4x4 unstructured covariance matrix, using an inverse Wishart prior. Correlation coefficients (Equation 1) were all set on a uniform U(-1,1) prior, all standard deviations (random effects and residual) on uniform priors with a high upper limit, and all fixed-effects coefficients were set on normal priors with zero mean and high variance.

Equation 1: Correlation matrix between FEV_1 random intercept, FEV_1 random slope, FVC random intercept and FVC random slope.

$$\begin{bmatrix} 1 & \rho_{u1} & \rho_{ua} & \rho_{Q1} \\ \rho_{u1} & 1 & \rho_{Q2} & \rho_{ub} \\ \rho_{ua} & \rho_{Q2} & 1 & \rho_{u2} \\ \rho_{Q1} & \rho_{ub} & \rho_{u2} & 1 \end{bmatrix}$$

Equation 2: Full equation of the model (Y_{ij} : lung function for participant *j* at time *i*, $k_{FEV1,}, k_{FVC}$: binary indicators for lung function parameter, *Z*: random effect terms)

$$\begin{aligned} Y_{ij} = {} & k_{FEV1}(\beta_1 + \beta_2 cumexp_{ij} + \beta_3 age_{ij} + \beta_4 female_j age_{ij} + \beta_5 female_j + \beta_6 female_j cumexp_{ij} + \\ & + \beta_7 everSmoked_{ij} cumexp_{ij} + \beta_8 height_j + \beta_9 height_j^2 + \beta_{10} currentSmoker_{ij} + \beta_{11} cumPackYears_{ij} + \\ & + \beta_{12} SES_j^{mid} + \beta_{13} SES_j^{low} + \beta_{14} disadvScore_j + \beta_{15} currentAsthma_{ij}) + \\ & k_{FVC}(\beta_{16} + \beta_{17} cumexp_{ij} + \beta_{18} age_{ij} + \beta_{19} female_j age + \beta_{20} female_j + \beta_{21} female_j cumexp_{ij} + \\ & + \beta_{22} everSmoked_{ij} cumexp_{ij} + \beta_{23} height_j + \beta_{24} height_j^2 + \beta_{25} currentSmoker_{ij} + \beta_{26} cumPackYears_{ij} + \\ & + \beta_{27} SES_j^{mid} + \beta_{28} SES_j^{low} + \beta_{29} disadvScore_j + \beta_{30} currentAsthma_{ij}) + \\ & + k_{FEV1}(Z_{a1} + Z_{b1} age_{ij}) + k_{FVC}(Z_{a2} + Z_{b2} age_{ij}) \end{aligned}$$

We tried adding a centre-level random effect as well; however this explained only a tiny amount of the overall variance, many orders of magnitude smaller than the participant-level random effects. Thus the centre-level random effect was dropped, so as not to needlessly complicate the models.

We also set priors on three fixed covariates, namely current asthma, SES, current smoking and total smoking pack-years, in order to do Bayesian imputation of any missing values. For current asthma and current smoking we used binomial priors with non-informative Beta(0.5,0.5) hyperpriors. For SES we used a categorical prior with a non-informative Dirichlet(0.5,0.5,0.5) hyperprior. For total smoking pack-years we

modelled the smoking pack-years since the previous follow-up as a zero-inflated gamma distribution; we set a binomial prior on the probability of having smoked, and a gamma prior on the number of pack-years conditional on having smoked, with the hyperparameters of the two priors estimated from the observed data at each time point.

The full JAGS code of the model was as follows:

```
data {
    zero[1] <- 0
    zero[2] <- 0
    zero[3] <- 0
    zero[4] <- 0

    noninf[1] <- 0.5
    noninf[2] <- 0.5
    noninf[3] <- 0.5
}

model {

  # Random intercept and slope for each participant
  for(j in 1:K ) {
    u1[j,1:4] ~ dmnorm(zero, tau.u)
  }

  # Variance-covariance matrix of the participant random effects
  R.u[1,1] <- pow(sigma.a1, 2)
  R.u[2,2] <- pow(sigma.b1, 2)
  R.u[3,3] <- pow(sigma.a2, 2)
  R.u[4,4] <- pow(sigma.b2, 2)
  R.u[1,2] <- rho.u1 * sigma.a1 * sigma.b1
  R.u[2,1] <- R.u[1,2]
  R.u[3,4] <- rho.u2 * sigma.a2 * sigma.b2
  R.u[4,3] <- R.u[3,4]
  R.u[1,3] <- rho.ua * sigma.a1 * sigma.a2
  R.u[3,1] <- R.u[1,3]
  R.u[2,4] <- rho.ub * sigma.b1 * sigma.b2
  R.u[4,2] <- R.u[2,4]
  R.u[1,4] <- rho.Q1 * sigma.a1 * sigma.b2
  R.u[4,1] <- R.u[1,4]
  R.u[2,3] <- rho.Q2 * sigma.b1 * sigma.a2
  R.u[3,2] <- R.u[2,3]

  tau.u ~ dwish(R.u, 4)
  sigma.u <- inverse(tau.u)
    # with priors:
  sigma.a1 ~ dunif(0, 40)
  sigma.b1 ~ dunif(0, 40)
```

```
  sigma.a2 ~ dunif(0, 40)
  sigma.b2 ~ dunif(0, 40)
  rho.u1 ~ dunif(-1,1)
  rho.u2 ~ dunif(-1,1)
  rho.Q2 ~ dunif(-1,1)
  rho.ua <- rho.u1 * rho.Q2
  rho.ub <- rho.Q2 * rho.u2
  rho.Q1 <- rho.u1 * rho.Q2 * rho.u2

  # Define model for each observational unit
  for(i in 1:N ) {
    mu[i] <-    beta[1]*FEV1[i] + beta[2]*FEV1[i]*X[i] +
beta[3]*FEV1[i]*age[i] +
                beta[4]*FEV1[i]*age[i]*female[i] +
                beta[5]*FEV1[i]*female[i] + beta[6]*FEV1[i]*X[i]*female[i] +
                beta[7]*FEV1[i]*X[i]*everSmoked[pid[i], survey[i]] +
                beta[8]*FEV1[i]*height[i] + beta[9]*FEV1[i]*height[i]^2 +
                beta[10]*FEV1[i]*cursmoke[i] +
                beta[11]*FEV1[i]*packyrs[pid[i],survey[i]] +
                beta[12]*FEV1[i]*SESmid[pid[i]] +
beta[13]*FEV1[i]*SESlow[pid[i]] +
                beta[14]*FEV1[i]*disadv[i] + beta[15]*FEV1[i]*asthma[i] +

                beta[16]*FVC[i] + beta[17]*FVC[i]*X[i] +
beta[18]*FVC[i]*age[i] +
                beta[19]*FVC[i]*age[i]*female[i] +
                beta[20]*FVC[i]*female[i] + beta[21]*FVC[i]*X[i]*female[i] +
                beta[22]*FVC[i]*X[i]*everSmoked[pid[i], survey[i]] +
                beta[23]*FVC[i]*height[i] + beta[24]*FVC[i]*height[i]^2 +
                beta[25]*FVC[i]*cursmoke[i] +
                beta[26]*FVC[i]*packyrs[pid[i],survey[i]] +
                beta[27]*FVC[i]*SESmid[pid[i]] +
beta[28]*FVC[i]*SESlow[pid[i]] +
                beta[29]*FVC[i]*disadv[i] + beta[30]*FVC[i]*asthma[i] +

                u1[pid[i],1]*FEV1[i] + u1[pid[i],2]*FEV1[i]*age[i] +
                u1[pid[i],3]*FVC[i] + u1[pid[i],4]*FVC[i]*age[i]

    Y[i] ~ dnorm(mu[i], tau.res*weight[i])
  }

  # Residual variance
  tau.res <- pow(sigma.res,-2)
  sigma.res ~ dunif(0,1000)

  # Priors:
  # Fixed intercept and slope
  for (b in 1:30) {
    beta[b] ~ dnorm(0.0,1.0E-5)
```

```
  }


# Imputation models for missing covariates

  for(i in 1:N ) {
    # Smoking
    cursmoke[i] ~ dbern(theta.smoke)
    asthma[i] ~ dbern(theta.asthma)
  }

  for (j in 1:K) {
    # SES
    SES[j] ~ dcat(p.SES)
    SESmid[j] <- equals(SES[j], 2)
    SESlow[j] <- equals(SES[j], 3)

    for (t in 1:3) {
      pyb[j,t] ~ dgamma(gaj[j, t] , gbj[j, t])
      gaj[j, t] <- ga[t] * smoked[j, t] + 0.0001
      gbj[j, t] <- gb[t] * smoked[j, t] + 0.0001
      smoked[j, t] ~ dbern(pSmk[t])
    }
    packyrs[j,1] <- pyb[j,1]
    packyrs[j,2] <- pyb[j,2] + packyrs[j,1]
    packyrs[j,3] <- pyb[j,3] + packyrs[j,2]
    everSmoked[j,1] <- packyrs[j,1]>0
    everSmoked[j,2] <- packyrs[j,2]>0
    everSmoked[j,3] <- packyrs[j,3]>0
  }

  for (t in 1:3) {
    ga[t] <- gmean[t]^2/gsd[t]^2
    gb[t] <- gmean[t]/gsd[t]^2
    logit(pSmk[t]) <- bSmk[t]
    bSmk[t] ~ dnorm(0.0,1.0E-5)
  }

  # Priors for hyperparameters
  theta.smoke ~ dbeta(0.5,0.5)
  theta.asthma ~ dbeta(0.5,0.5)
  p.SES[1:3] ~ ddirch(noninf[1:3])

}
```

The same specification was used both in the linear (absolute FEV_1 and FVC as outcome) and in the log-linear ($\log(FEV_1)$ and log(FVC) as outcome) models. From the

log-linear model, inference was made on the FEV_1/FVC ratio by taking the difference between coefficients for $\log(FEV_1)$ and $\log(FVC)$; thus, after exponentiation, effect estimates on the FEV_1/FVC ratio are percentages on a relative scale, not absolute differences on a % scale. From the predictive distribution of the $\log(FEV_1/FVC)$ ratio (whose variance takes into account the residual variance, the variance of the random effects and the latter's correlations, over the whole MCMC chain) it is possible to calculate the prevalence of COPD defined as pre-bronchodilator $FEV_1/FVC < LLN$. Thus, for various combinations of age, covariates and exposures, the Relative Risk (RR) of COPD versus the unexposed was calculated. To reflect the fact that the FEV_1/FVC ratio can not be over 100% or below 0%, we assumed that $-\log(FEV_1/FVC)$ follows a gamma distribution with shape (k) and scale (θ) calculated according to its estimated mean and variance.

Inverse Response Propensity Weighting scheme

The IPW scheme used to account for differential losses to follow-up was based on the method of Little and David (1983) for non-attrition nonresponse in panel studies. This was done to account for the fact that one centre (Aarhus) did not participate in ECRHS II but participated in ECRHS III. Three logistic regression models were fitted:

(1) one estimating $P(R_2=1 \mid Z, X_1)$, i.e. the probability of response at ECRHS II given design variables and covariates at ECRHS I, using the entire study population,

(2) one estimating $P(R_3=1 \mid Z, X_1, R_2=0)$, i.e. the probability of response at ECRHS III for non-respondents at ECRHS II, given design variables and covariates at ECRHS I, and

(3) $P(R_2=1 \mid Z, X_1, X_2, R_2=1)$, i.e. the probability of response at ECRHS III for respondents at ECRHS II, given design variables and covariates up to ECRHS I.

The respondents at ECRHS1 are all weighted by 1. Respondents at ECRHS2 are weighted by $w_2 = 1 / P(R_2=1 \mid Z, X_1)$, using model 1 above. Respondents at ECRHS3 are weighted by $w_3 = w_2 * w_{3|2}$, where $w_{3|2} = 1 / P(R_3=1 \mid Z, X_1, R_2=0)$ using model 2 above for non-respondents at ECRHS2 and $w_{3|2} = P(R_2=1 \mid Z, X_1, X_2, R_2=1)$ using model 3 above for respondents at ECHRS2.

The covariates selected for inclusion in set Z (adjusted for in all three regressions) were: age at baseline, and SES (socioeconomic status, 3 categories, based on age of completion of formal education).

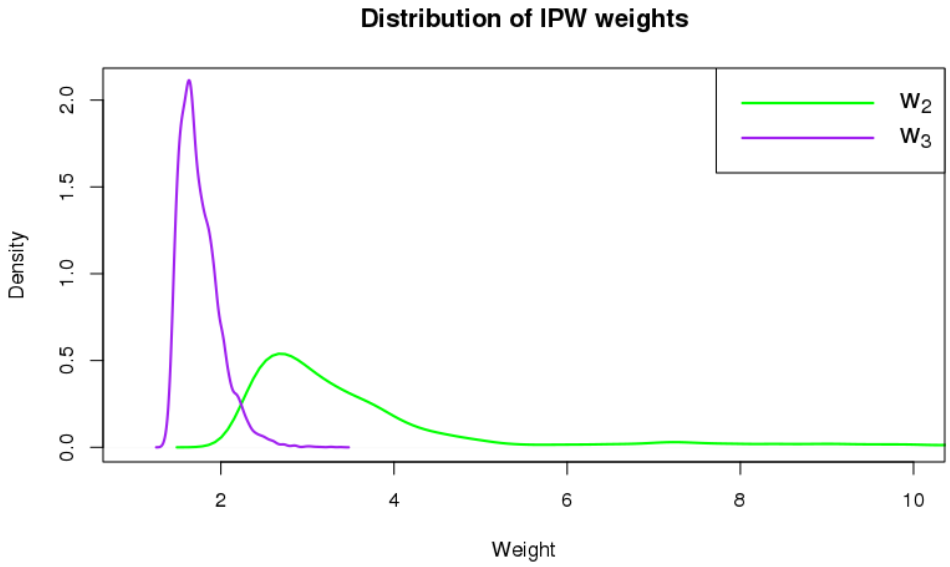
The covariates for set X_1 (also adjusted for in all three regressions) were current smoking status, plus the chronic respiratory symptoms reported on questions 1-13 of the ECRHS I main questionnaire; of the latter, the most important were selected based on a series of likelihood ratio tests, and the final covariates included in set X_1 were as follows:

Q1	Have you had wheezing or whistling in your chest at any time in the last 12 months?
Q3	Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?
Q4	Have you had an attack of shortness of breath that came on following strenuous activity at any time in the last 12 months?
Q5	Have you been woken by an attack of shortness of breath at any time in the last 12 months?
Q6	Have you been woken by an attack of coughing at any time in the last 12 months?
Q7	Do you usually cough first thing in the morning in the winter?
Q9	Do you usually bring up any phlegm from your chest first thing in the morning in the winter?
Q11	Do you ever have trouble with your breathing?
Q12	Are you disabled from walking by a condition other than heart or lung disease?

Note that Q13 (“Have you ever had asthma?”) was not a strong predictor of response at ECRHS2, and thus was not included in the set.

In similar fashion, set X_2 included current smoking status at ECRHS II plus the chronic respiratory symptoms reported at ECRHS II; of these, only Q8 (“Do you usually cough during the day, or at night, in the winter?”) and Q14 (“Have you ever had asthma?”) were significant additional predictors of response at ECRHS III *on top* of the predictors of sets Z and X_1, as determined by likelihood ratio tests, and were thus retained in set X_2.

To handle item (covariate) non-response and obtain weights for all available study participants, multiple imputation was employed (50 datasets) and the three logistic regressions were applied in each dataset with the end result (log odds of response) pooled, before calculating the weights w_2 and w_3.. The distribution of weights per study wave was examined to make sure there were no extreme values. Also all models were fitted without any weighting as a sensitivity analysis, and no substantial differences were found.


Distribution of IPW weights
Density
0.0
0.5
1.0
1.5
2.0
2
4
6
8
10
Weight
W2
W3

Supplemental Table 1: Effect of occupational exposures on lung function decline after 25 intensity-years of exposure, stratified by sex and smoking status.

(a) Additional FEV_1 change (absolute, in ml) after 25 intensity-years of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Biological dust	-12.8	**-53.8**	11.2	-29.8
	(-45.6 to 19)	**(-93.7 to -15.9)**	(-13.3 to 35.1)	(-66.3 to 6.8)
Mineral Dust	-5.6	-3.5	-12.3	-10.2
	(-33.3 to 21.1)	(-48.5 to 41.7)	(-30.7 to 5.5)	(-54.1 to 34.3)
Gases & fumes	-5.4	-22.2	3.4	-13.4
	(-29.3 to 18.2)	(-58.6 to 14)	(-12.4 to 19.3)	(-48.3 to 21)
Vapors, Gases,	-0.5	-14	0.2	-13.3
Dusts & Fumes	(-18.6 to 18.1)	(-42.5 to 15)	(-12.6 to 13.2)	(-40.5 to 14.7)
Herbicides	-42.6	-22	**-83**	-62.4
	(-155.3 to 80.1)	(-165 to 124.2)	**(-147.6 to -18.5)**	(-205.8 to 75.1)
Insecticides	-9.5	16.7	**-55.2**	-29.1
	(-80.9 to 60.7)	(-78.7 to 114.6)	**(-104.5 to -8.4)**	(-112.9 to 55.9)
Fungicides	13.1	61.5	**-72.2**	-23.8
	(-64.3 to 92.2)	(-37.8 to 162.6)	**(-120.3 to -25.5)**	(-111.9 to 66.2)
All pesticides	4.5	31.3	**-69**	-42.2
	(-61.9 to 75.7)	(-61.9 to 125.2)	**(-112 to -25)**	(-126.3 to 43.4)
Aromatic	16.8	75.3	3.1	61.6
solvents	(-34.2 to 65.6)	(-18 to 165.4)	(-33.3 to 40.2)	(-23.9 to 146.6)
Chlorinated	4.7	**95.2**	**-26.5**	64
solvents	(-32.7 to 42.4)	**(1.2 to 190.2)**	**(-52 to -1.1)**	(-23.9 to 155.8)
Other solvents	-2.9	-16.7	18.8	4.9
	(-47.4 to 39.3)	(-63.5 to 29)	(-13.9 to 50.9)	(-32.6 to 42.4)
Metals	3.7	37.7	-21.6	12.4
	(-31.6 to 37.9)	(-56.1 to 131.7)	(-45.6 to 1.7)	(-79.9 to 105.7)

(b) Additional FVC change (absolute, in ml) after 25 intensity-years of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Biological dust	9.9	**-55.5**	**42.8**	-22.6
	(-27.7 to 47.5)	**(-102.1 to -10.1)**	**(13.4 to 71.6)**	(-65.7 to 20.5)

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Mineral Dust	22.6	-10.1	**26.2**	-6.5
	(-9.4 to 55)	(-63.7 to 43.1)	**(4.7 to 47.8)**	(-59.1 to 46.6)
Gases & fumes	14.4	-16.5	**36.4**	5.5
	(-13.8 to 42.3)	(-61.5 to 26.6)	**(17.5 to 55.3)**	(-36.7 to 47.1)
Vapors, Gases,	20.8	-10.2	**32.2**	1.2
Dusts & Fumes	(-0.9 to 43)	(-44 to 24)	**(17.1 to 47.8)**	(-31.2 to 34.5)
Herbicides	-51.1	-98.9	-67.3	-115.1
	(-183.1 to 95.6)	(-275.5 to 79.5)	(-143.9 to 9)	(-288.4 to 57.8)
Insecticides	-34.5	-41.4	-20.1	-27
	(-117.4 to 49.2)	(-153.7 to 74.5)	(-78.7 to 35.6)	(-128.3 to 72.9)
Fungicides	-3.7	3.1	-44.2	-37.4
	(-105 to 93.2)	(-116.2 to 123.3)	(-100.1 to 10.7)	(-146.8 to 70)
All pesticides	-13.8	-19.2	-37.1	-42.5
	(-94.5 to 72.3)	(-130.4 to 93.1)	(-89 to 14.9)	(-145.5 to 59.9)
Aromatic	48	**123.8**	19.2	95
solvents	(-14.7 to 105.2)	**(16.1 to 229.7)**	(-23.3 to 63.5)	(-6.9 to 197.1)
Chlorinated	33.9	**165.6**	-18.3	**113.4**
solvents	(-11.8 to 80)	**(51.3 to 279.2)**	(-48.7 to 11.5)	**(8.8 to 221.2)**
Other solvents	30.6	13.6	29.1	12.1
	(-20.3 to 81.4)	(-40.9 to 68.3)	(-10.5 to 67.8)	(-32.6 to 56.2)
Metals	31.5	15.2	4.3	-12
	(-9.2 to 71.9)	(-94.8 to 125.3)	(-24 to 31.5)	(-119.5 to 95.9)

(c) Additional FEV_1/FVC change (relative, in %) after 25 intensity-years of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Biological dust	-0.486	-0.453	**-0.713**	-0.68
	(-1.269 to 0.3)	(-1.381 to 0.482)	**(-1.285 to -0.135)**	(-1.553 to 0.202)
Mineral Dust	-0.567	0.083	**-1.097**	-0.451
	(-1.233 to 0.114)	(-1.05 to 1.225)	**(-1.512 to -0.68)**	(-1.547 to 0.65)
Gases & fumes	-0.271	-0.255	**-0.747**	-0.731
	(-0.827 to 0.289)	(-1.121 to 0.642)	**(-1.136 to -0.363)**	(-1.537 to 0.075)
Vapors, Gases,	-0.346	-0.206	**-0.786**	-0.647
Dusts & Fumes	(-0.79 to 0.101)	(-0.892 to 0.488)	**(-1.091 to -0.482)**	(-1.283 to 0.008)
Herbicides	-0.448	1.294	-1.056	0.676
	(-3.226 to 2.418)	(-2.213 to 4.883)	(-2.57 to 0.465)	(-2.332 to 3.787)

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Insecticides	0.355	1.134	**-1.305**	-0.539
	(-1.412 to 2.189)	(-1.276 to 3.578)	**(-2.345 to -0.233)**	(-2.527 to 1.502)
Fungicides	0.265	1.461	**-1.17**	0.009
	(-1.618 to 2.259)	(-1.088 to 4.101)	**(-2.225 to -0.098)**	(-2.03 to 2.088)
All pesticides	0.3	1.032	**-1.266**	-0.545
	(-1.428 to 2.039)	(-1.276 to 3.424)	**(-2.257 to -0.265)**	(-2.497 to 1.464)
Aromatic solvents	-0.431	-0.012	-0.585	-0.167
	(-1.664 to 0.825)	(-2.276 to 2.311)	(-1.48 to 0.299)	(-2.276 to 1.977)
Chlorinated solvents	-0.452	-0.143	-0.554	-0.245
	(-1.443 to 0.511)	(-2.511 to 2.312)	(-1.19 to 0.077)	(-2.461 to 2.072)
Other solvents	-0.662	-0.554	-0.356	-0.248
	(-1.706 to 0.378)	(-1.666 to 0.607)	(-1.14 to 0.429)	(-1.122 to 0.626)
Metals	-0.426	0.962	**-0.915**	0.466
	(-1.283 to 0.447)	(-1.329 to 3.316)	**(-1.477 to -0.357)**	(-1.754 to 2.766)

All estimates adjusted for height (including its square), sex, current smoking, smoking pack-years, current asthma, socioeconomic status and early life disadvantage score.

Supplemental Table 2: Unweighted (no inverse response-propensity IPW weighting) estimates for the effect of occupational exposures on lung function decline, per intensity-year of exposure.

(a) Additional annual FEV_1 change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Biological dust	-0.351	**-2.18**	0.378	-1.45
	(-1.678 to 0.93)	**(-3.802 to -0.553)**	(-0.646 to 1.404)	(-3.014 to 0.103)
Mineral Dust	-0.135	-0.191	-0.462	-0.517
	(-1.271 to 1.023)	(-2.094 to 1.74)	(-1.201 to 0.274)	(-2.392 to 1.387)
Gases & fumes	-0.128	-0.998	0.239	-0.631
	(-1.071 to 0.822)	(-2.493 to 0.487)	(-0.452 to 0.926)	(-2.05 to 0.813)
Vapors, Gases,	0.088	-0.577	0.038	-0.627
Dusts & Fumes	(-0.666 to 0.826)	(-1.763 to 0.622)	(-0.506 to 0.583)	(-1.743 to 0.507)
Herbicides	-0.964	-0.767	**-3.425**	-3.228
	(-5.869 to 4.023)	(-7.253 to 5.588)	**(-6.296 to -0.597)**	(-9.516 to 2.95)
Insecticides	0.124	0.798	**-2.103**	-1.429
	(-2.999 to 3.13)	(-3.292 to 4.875)	**(-4.116 to -0.097)**	(-5.009 to 2.209)
Fungicides	0.971	2.54	**-2.651**	-1.082
	(-2.107 to 4.042)	(-1.738 to 6.824)	**(-4.681 to -0.576)**	(-4.708 to 2.582)
All pesticides	0.53	1.197	**-2.586**	-1.919
	(-2.369 to 3.384)	(-2.791 to 5.183)	**(-4.454 to -0.713)**	(-5.493 to 1.629)
Aromatic	0.588	2.388	0.373	2.172
solvents	(-1.428 to 2.62)	(-1.303 to 6.135)	(-1.213 to 1.971)	(-1.406 to 5.778)
Chlorinated	0.194	3.647	-0.994	2.458
solvents	(-1.422 to 1.812)	(-0.382 to 7.71)	(-2.082 to 0.091)	(-1.326 to 6.207)
Other solvents	0.035	-0.707	0.857	0.116
	(-1.753 to 1.815)	(-2.665 to 1.209)	(-0.5 to 2.224)	(-1.435 to 1.628)
Metals	0.098	1.479	-0.848	0.533
	(-1.426 to 1.549)	(-2.363 to 5.345)	(-1.856 to 0.149)	(-3.275 to 4.281)

(b) Additional annual FVC change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Biological dust	0.68	**-2.231**	**1.744**	-1.167
	(-0.806 to 2.125)	**(-4.135 to -0.328)**	**(0.56 to 2.945)**	(-2.942 to 0.627)

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Mineral Dust	0.872	-0.607	**1.099**	-0.38
	(-0.424 to 2.21)	(-2.81 to 1.648)	**(0.246 to 1.961)**	(-2.572 to 1.828)
Gases & fumes	0.537	-0.763	**1.362**	0.062
	(-0.53 to 1.592)	(-2.495 to 0.955)	**(0.56 to 2.16)**	(-1.59 to 1.717)
Vapors, Gases,	0.866	-0.427	**1.252**	-0.041
Dusts & Fumes	(-0.042 to 1.7)	(-1.8 to 0.93)	**(0.62 to 1.877)**	(-1.331 to 1.272)
Herbicides	-2.078	-4.199	-2.641	-4.762
	(-7.878 to 3.831)	(-11.732 to 3.268)	(-5.955 to 0.632)	(-12.105 to 2.561)
Insecticides	-1.101	-1.537	-0.596	-1.031
	(-4.659 to 2.386)	(-6.195 to 3.203)	(-2.933 to 1.768)	(-5.206 to 3.271)
Fungicides	-0.05	0.257	-1.509	-1.202
	(-3.652 to 3.548)	(-4.59 to 5.243)	(-3.827 to 0.891)	(-5.446 to 3.177)
All pesticides	-0.401	-0.778	-1.261	-1.638
	(-3.667 to 2.853)	(-5.457 to 3.854)	(-3.419 to 0.91)	(-5.807 to 2.55)
Aromatic	1.585	4.18	0.859	3.454
solvents	(-0.78 to 3.905)	(-0.081 to 8.434)	(-0.986 to 2.702)	(-0.664 to 7.609)
Chlorinated	1.015	**5.618**	-0.601	4.001
solvents	(-0.828 to 2.875)	**(1.054 to 10.181)**	(-1.858 to 0.638)	(-0.307 to 8.292)
Other solvents	1.339	0.495	1.275	0.432
	(-0.678 to 3.383)	(-1.813 to 2.758)	(-0.307 to 2.849)	(-1.365 to 2.215)
Metals	0.882	0.259	0.287	-0.337
	(-0.82 to 2.546)	(-4.157 to 4.725)	(-0.876 to 1.439)	(-4.716 to 4.033)

(c) Additional annual FEV_1/FVC change (relative, in %) per intensity-year of exposure (95% CrI).

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Biological dust	-0.022	-0.018	**-0.031**	-0.028
	(-0.056 to 0.013)	(-0.059 to 0.023)	**(-0.058 to -0.005)**	(-0.067 to 0.012)
Mineral Dust	-0.019	0.007	**-0.044**	-0.018
	(-0.048 to 0.011)	(-0.042 to 0.057)	**(-0.063 to -0.025)**	(-0.066 to 0.031)
Gases & fumes	-0.01	-0.013	**-0.025**	-0.029
	(-0.034 to 0.015)	(-0.051 to 0.025)	**(-0.042 to -0.008)**	(-0.065 to 0.007)
Vapors, Gases,	-0.012	-0.009	**-0.03**	-0.026
Dusts & Fumes	(-0.032 to 0.007)	(-0.038 to 0.021)	**(-0.044 to -0.016)**	(-0.055 to 0.003)

	Men, never smokers	**Women, never smokers**	**Men, ever smokers**	**Women, ever smokers**
Herbicides	-0	0.059	-0.048	0.012
	(-0.127 to 0.127)	(-0.108 to 0.227)	(-0.12 to 0.026)	(-0.138 to 0.162)
Insecticides	0.018	0.048	**-0.055**	-0.026
	(-0.057 to 0.095)	(-0.058 to 0.152)	**(-0.105 to -0.004)**	(-0.117 to 0.063)
Fungicides	0.02	0.06	-0.049	-0.009
	(-0.064 to 0.105)	(-0.055 to 0.174)	(-0.1 to 0.003)	(-0.102 to 0.084)
All pesticides	0.018	0.043	**-0.053**	-0.029
	(-0.056 to 0.091)	(-0.059 to 0.148)	**(-0.1 to -0.007)**	(-0.117 to 0.06)
Aromatic solvents	-0.011	-0.004	-0.021	-0.013
	(-0.066 to 0.042)	(-0.101 to 0.096)	(-0.061 to 0.019)	(-0.105 to 0.08)
Chlorinated solvents	-0.012	0.006	-0.023	-0.006
	(-0.054 to 0.03)	(-0.1 to 0.112)	(-0.052 to 0.006)	(-0.105 to 0.094)
Other solvents	-0.027	-0.023	-0.014	-0.01
	(-0.073 to 0.018)	(-0.071 to 0.025)	(-0.049 to 0.021)	(-0.049 to 0.029)
Metals	-0.012	0.043	**-0.039**	0.016
	(-0.049 to 0.025)	(-0.054 to 0.141)	**(-0.064 to -0.013)**	(-0.078 to 0.111)

All estimates adjusted for height (including its square), sex, current smoking, smoking pack-years, current asthma, socioeconomic status and early life disadvantage score.

Supplemental Table 3: Effect of occupational exposures on lung function decline, per intensity-year of exposure, stratified by sex only.

(a) Additional annual FEV_1 change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Male	Female
Biological dust	0.071 (-0.81 to 0.922)	**-1.615 (-3.005 to -0.264)**
Mineral Dust	-0.43 (-1.058 to 0.191)	-0.296 (-2.036 to 1.374)
Gases & fumes	0.017 (-0.541 to 0.59)	-0.667 (-1.968 to 0.611)
Vapors, Gases, Dusts & Fumes	-0.02 (-0.474 to 0.442)	-0.5 (-1.54 to 0.554)
Herbicides	**-2.966 (-5.389 to -0.52)**	-1.899 (-7.077 to 3.271)
Insecticides	**-1.751 (-3.402 to -0.044)**	-0.739 (-3.893 to 2.488)
Fungicides	**-2.038 (-3.64 to -0.441)**	0.108 (-3.196 to 3.474)
All pesticides	**-2.026 (-3.595 to -0.449)**	-0.753 (-3.875 to 2.46)
Aromatic solvents	0.326 (-0.928 to 1.568)	2.774 (-0.519 to 6.07)
Chlorinated solvents	-0.689 (-1.584 to 0.198)	2.802 (-0.802 to 6.417)
Other solvents	0.556 (-0.584 to 1.707)	-0.078 (-1.464 to 1.339)
Metals	-0.577 (-1.397 to 0.238)	0.906 (-2.737 to 4.582)

(b) Additional annual FVC change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Male	Female
Biological dust	**1.209 (0.161 to 2.237)**	-1.458 (-3.106 to 0.129)
Mineral Dust	**1.011 (0.268 to 1.743)**	-0.334 (-2.389 to 1.684)
Gases & fumes	**1.192 (0.532 to 1.869)**	-0.127 (-1.654 to 1.397)
Vapors, Gases, Dusts & Fumes	**1.146 (0.603 to 1.69)**	-0.083 (-1.343 to 1.178)
Herbicides	-2.53 (-5.389 to 0.38)	-4.252 (-10.537 to 1.913)
Insecticides	-0.904 (-2.939 to 1.112)	-1.271 (-5.116 to 2.638)
Fungicides	-1.256 (-3.202 to 0.648)	-0.737 (-4.72 to 3.298)
All pesticides	-1.174 (-3.068 to 0.695)	-1.228 (-4.952 to 2.586)
Aromatic solvents	1.164 (-0.321 to 2.657)	**4.362 (0.538 to 8.354)**
Chlorinated solvents	-0.121 (-1.162 to 0.921)	**4.975 (0.783 to 9.171)**
Other solvents	1.245 (-0.099 to 2.567)	0.475 (-1.193 to 2.132)
Metals	0.492 (-0.465 to 1.459)	-0.023 (-4.25 to 4.252)

(c) Additional annual FEV_1/FVC change (relative, in %) per intensity-year of exposure (95% CrI).

	Male	Female
Biological dust	**-0.026 (-0.047 to -0.005)**	-0.024 (-0.056 to 0.008)
Mineral Dust	**-0.039 (-0.053 to -0.024)**	-0.009 (-0.05 to 0.033)
Gases & fumes	**-0.025 (-0.038 to -0.011)**	-0.023 (-0.054 to 0.008)
Vapors, Gases, Dusts & Fumes	**-0.027 (-0.037 to -0.016)**	-0.019 (-0.043 to 0.006)
Herbicides	-0.038 (-0.096 to 0.02)	0.038 (-0.077 to 0.153)
Insecticides	-0.037 (-0.076 to 0.002)	0.001 (-0.078 to 0.079)
Fungicides	-0.034 (-0.074 to 0.005)	0.015 (-0.066 to 0.097)
All pesticides	-0.036 (-0.073 to 0)	-0.002 (-0.079 to 0.074)
Aromatic solvents	-0.021 (-0.051 to 0.009)	-0.006 (-0.087 to 0.075)
Chlorinated solvents	-0.021 (-0.043 to 0)	-0.012 (-0.101 to 0.077)
Other solvents	-0.019 (-0.048 to 0.01)	-0.012 (-0.045 to 0.021)
Metals	**-0.031 (-0.051 to -0.012)**	0.027 (-0.062 to 0.116)

All estimates adjusted for height (including its square), sex, current smoking, smoking pack-years, current asthma, socioeconomic status and early life disadvantage score.

Supplemental Table 4: Effect of occupational exposures on lung function decline, per intensity-year of exposure, stratified by smoking status only.

(a) Additional annual FEV_1 change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Never smokers	Ever smokers
Biological dust	-1.08 (-2.3 to 0.126)	0.051 (-0.855 to 0.954)
Mineral Dust	-0.209 (-1.261 to 0.866)	-0.452 (-1.138 to 0.226)
Gases & fumes	-0.34 (-1.199 to 0.536)	0.042 (-0.558 to 0.641)
Vapors, Gases, Dusts & Fumes	-0.133 (-0.843 to 0.574)	-0.095 (-0.589 to 0.399)
Herbicides	-1.133 (-5.337 to 3.077)	**-3.22 (-5.737 to -0.73)**
Insecticides	-0.009 (-2.718 to 2.65)	**-1.997 (-3.777 to -0.244)**
Fungicides	0.923 (-1.946 to 3.789)	**-2.48 (-4.252 to -0.658)**
All pesticides	0.411 (-2.146 to 2.965)	**-2.558 (-4.255 to -0.905)**
Aromatic solvents	1.017 (-0.856 to 2.906)	0.394 (-0.974 to 1.767)
Chlorinated solvents	0.349 (-1.244 to 1.976)	-0.819 (-1.822 to 0.179)
Other solvents	-0.325 (-1.962 to 1.268)	0.536 (-0.521 to 1.586)
Metals	0.214 (-1.147 to 1.596)	-0.835 (-1.784 to 0.09)

(b) Additional annual FVC change (absolute, in ml) per intensity-year of exposure (95% CrI).

	Never smokers	Ever smokers
Biological dust	-0.532 (-1.961 to 0.899)	1.06 (-0.034 to 2.153)
Mineral Dust	0.709 (-0.494 to 1.971)	**0.948 (0.117 to 1.763)**
Gases & fumes	0.34 (-0.672 to 1.383)	**1.286 (0.572 to 1.995)**
Vapors, Gases, Dusts & Fumes	0.597 (-0.272 to 1.43)	**1.072 (0.491 to 1.661)**
Herbicides	-2.266 (-7.204 to 2.783)	**-3.158 (-6.153 to -0.149)**
Insecticides	-1.297 (-4.497 to 1.795)	-0.888 (-2.965 to 1.2)
Fungicides	-0.093 (-3.411 to 3.168)	-1.727 (-3.868 to 0.459)
All pesticides	-0.615 (-3.599 to 2.434)	-1.52 (-3.562 to 0.473)
Aromatic solvents	**2.34 (0.171 to 4.538)**	1.094 (-0.556 to 2.741)
Chlorinated solvents	1.6 (-0.255 to 3.41)	-0.376 (-1.582 to 0.8)
Other solvents	0.985 (-0.942 to 2.836)	0.907 (-0.36 to 2.175)
Metals	1.207 (-0.298 to 2.844)	0.119 (-0.996 to 1.221)

(c) Additional annual FEV_1/FVC change (relative, in %) per intensity-year of exposure (95% CrI).

	Never smokers	Ever smokers
Biological dust	-0.019 (-0.048 to 0.011)	**-0.028 (-0.049 to -0.007)**
Mineral Dust	-0.018 (-0.045 to 0.008)	**-0.042 (-0.058 to -0.025)**
Gases & fumes	-0.012 (-0.033 to 0.01)	**-0.029 (-0.044 to -0.015)**
Vapors, Gases, Dusts & Fumes	-0.013 (-0.03 to 0.004)	**-0.031 (-0.042 to -0.019)**
Herbicides	0.002 (-0.107 to 0.113)	-0.03 (-0.088 to 0.027)
Insecticides	0.019 (-0.05 to 0.087)	**-0.046 (-0.086 to -0.006)**
Fungicides	0.023 (-0.05 to 0.097)	-0.038 (-0.078 to 0.002)
All pesticides	0.017 (-0.05 to 0.083)	**-0.045 (-0.083 to -0.008)**
Aromatic solvents	-0.015 (-0.064 to 0.035)	-0.021 (-0.055 to 0.013)
Chlorinated solvents	-0.018 (-0.057 to 0.021)	-0.021 (-0.046 to 0.003)
Other solvents	-0.024 (-0.062 to 0.013)	-0.012 (-0.038 to 0.013)
Metals	-0.014 (-0.049 to 0.022)	**-0.035 (-0.057 to -0.012)**

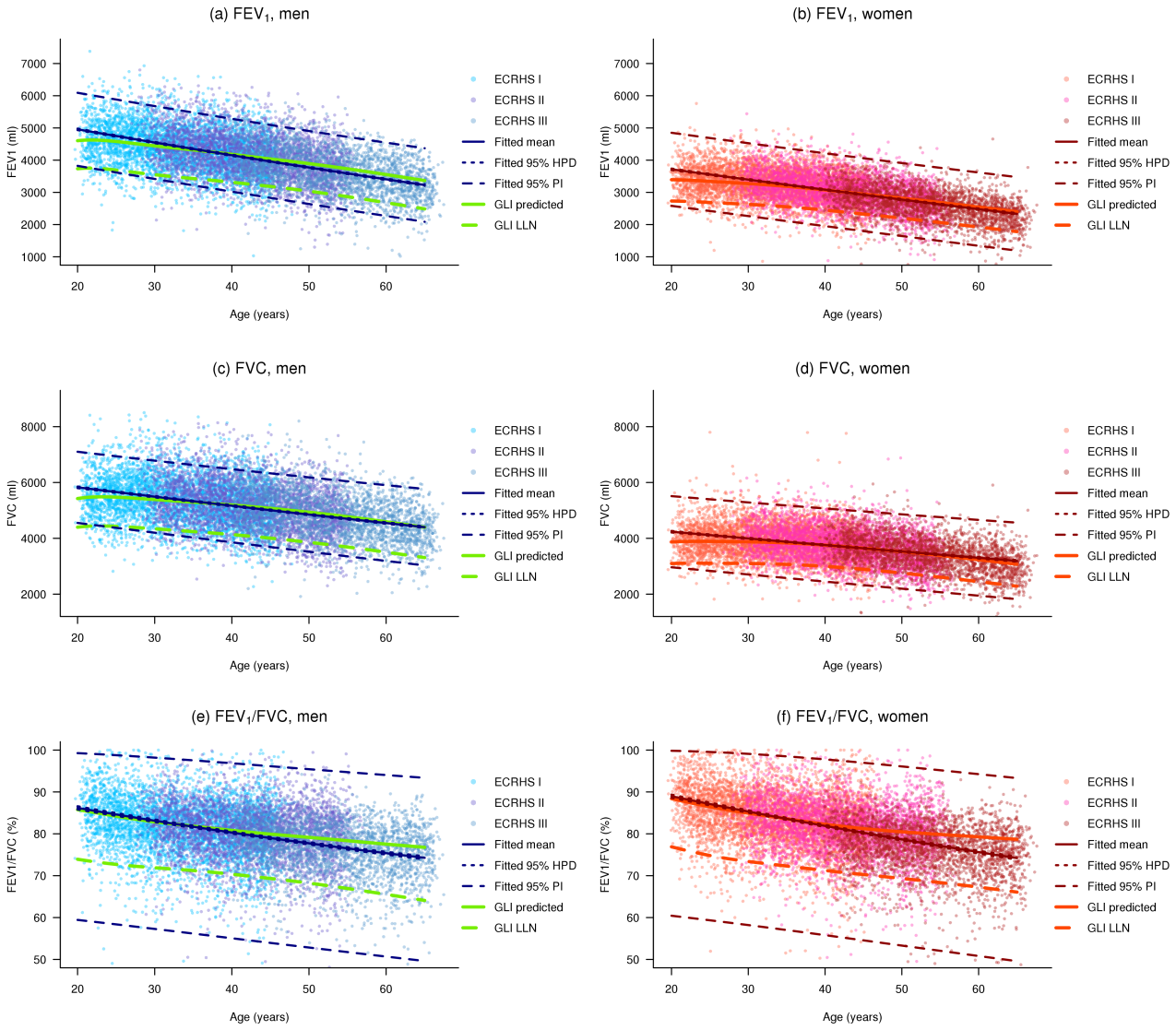
All estimates adjusted for height (including its square), sex, current smoking, smoking pack-years, current asthma, socioeconomic status and early life disadvantage score.

Supplemental Table 5: Effect of occupational exposures on lung function decline, per intensity-year of exposure, not stratified by sex or smoking status

	Additional FEV1 change (ml/year)	Additional FVC change (ml/year)	Additional relative FEV1/FVC change (%/year)
Biological dust	-0.391 (-1.127 to 0.323)	0.466 (-0.41 to 1.302)	**-0.025 (-0.042 to -0.008)**
Mineral Dust	-0.385 (-0.96 to 0.194)	**0.892 (0.204 to 1.587)**	**-0.035 (-0.049 to -0.021)**
Gases & fumes	-0.098 (-0.616 to 0.427)	**0.977 (0.372 to 1.585)**	**-0.024 (-0.036 to -0.011)**
Vapors, Gases, Dusts & Fumes	-0.101 (-0.517 to 0.321)	**0.945 (0.459 to 1.442)**	**-0.026 (-0.035 to -0.016)**
Herbicides	**-2.732 (-4.852 to -0.59)**	**-2.92 (-5.479 to -0.371)**	-0.023 (-0.074 to 0.028)
Insecticides	**-1.564 (-3.049 to -0.1)**	-0.99 (-2.769 to 0.754)	-0.029 (-0.063 to 0.005)
Fungicides	**-1.632 (-3.128 to -0.136)**	-1.216 (-3.011 to 0.596)	-0.024 (-0.059 to 0.011)
All pesticides	**-1.78 (-3.178 to -0.372)**	-1.181 (-2.795 to 0.486)	-0.03 (-0.063 to 0.002)
Aromatic solvents	0.575 (-0.56 to 1.702)	**1.518 (0.161 to 2.869)**	-0.019 (-0.048 to 0.009)
Chlorinated solvents	-0.48 (-1.344 to 0.38)	0.189 (-0.846 to 1.201)	-0.02 (-0.042 to 0.001)
Other solvents	0.296 (-0.586 to 1.176)	0.911 (-0.128 to 1.94)	-0.016 (-0.037 to 0.006)
Metals	-0.511 (-1.292 to 0.272)	0.48 (-0.456 to 1.419)	**-0.028 (-0.048 to -0.009)**

All estimates adjusted for height (including its square), sex, current smoking, smoking pack-years, current asthma, socioeconomic status and early life disadvantage score.

Supplemental Figure 1: Lung function decline with age in the ECRHS study population, fitted values by age according to "null" model (without occupational exposures), and predicted values according to GLI-2012. Height set to cohort mean by gender, smoking pack-years set to cohort mean by age and gender.



HPD: Highest Posterior Density interval; PI: Prediction Interval; LLN: Lower Limit of Normal.

5.DISCUSSION

The main contribution of the current thesis is that it substantially expands the evidence base for the role of occupational exposures in COPD, both in strengthening the association for previously studied exposures such as dusts, gases and fumes, and in establishing it for new exposures such as pesticides, solvents and metals. In addition, the studies shed light on the interplay of occupational exposures with smoking and gender. This is a difficult and complex task, marked by several conceptual and analytical hurdles.

There are three facets in the relationship between occupational exposures and COPD, that are clinically and pathogenically important. The first is the effect of these exposures on the rate of lung function decline, which is the main determinant for the development of COPD, although not the only one (Lange *et al.*, 2015). The second is their association with chronic bronchitis (CB) and other respiratory symptoms; CB is consequential both as a predictor of lung function decline, and as an independent predictor of subsequent morbidity and mortality due to COPD, especially among smokers. The third is the end effect of occupational exposures on COPD incidence itself, defined using post-bronchodilation spirometry; this is the most important not just in terms of establishing causality, but for estimating the magnitude of the association, overall and across subgroups, as well as the proportion of disease accounted for by occupational exposures. Associations with all three of these outcomes must be interpreted in tandem, and assessing each of them presents unique and specific challenges.

5.1 Contribution to current knowledge

Our results indicate that many occupational exposures (biological dust, mineral dust, gases & fumes, VGDF, pesticides and metals) resulted in accelerated lung function decline, especially as regards the FEV1/FVC ratio. This additional lung function decline was more pronounced in ever smokers compared to never smokers, and also tended to be higher in men compared to women (although the results for women suffered from low precision). Biological dust exposure was also shown to affect COPD incidence directly and account for a substantial proportion of COPD cases in the population (10.5%), as did gases & fumes and pesticide exposure, the latter causing less cases in the population though (4.4% of the total). The combination of any of these three main

groups of occupational exposures accounted for 21.0% of COPD cases in our study population, which is remarkable considering that this is a general population sample from several developed countries and of relatively young age with respect to COPD onset. It also confirms and expands on the previous published estimate of 15-20% of all COPD cases being attributable to occupation (Balmes *et al.*, 2003). On the other hand, these exposures were not associated with increased CB incidence, except for gases & fumes which increased the incidence of chronic phlegm (RR = 1.34, 95% CI 1.14 – 1.57), particularly in men. This suggest a particular phenotype of COPD associated with biological dust, namely one that does not always involve chronic mucus hypersecretion.

Pesticides are a relatively new focus of attention on the literature about respiratory health, and have been previously linked to occupational asthma (Hoppin *et al.*, 2009), COPD, chronic bronchitis, lung cancer and other outcomes (Hoppin *et al.*, 2006; Ye *et al.*, 2013). Pesticides have also been recently associated with accelerated lung function decline and airway obstruction (de Jong *et al.*, 2014a; b). In our analyses pesticides were found to cause rapidly accelerated FEV1 decline, but only in ever smokers (-2.6 ml per intensity-year of exposure, the highest among all occupational exposures). At the same time smokers exposed to pesticides had also accelerated FVC decline, particularly those exposed to herbicides, which points to pesticides causing not only obstructive but also restrictive lung defects (Peiris-John *et al.*, 2005), with a normal or – in our case – lower FEV1/FVC ratio. In our analysis of the ECRHS cohort, pesticides actually doubled the incidence of COPD in both men and women. In addition, they doubled the incidence of chronic phlegm but only in women, having no effect in men. Therefore it appears that the effect of pesticides on lung function and COPD is complex, is mediated by different pathogenetic mechanisms and depends on both smoking status and sex.

Mineral dust and metals exposure were found to be associated with accelerated FEV1/FVC decline, particularly in male smokers, although for metals the effect disappeared when adjusting for simultaneous mineral dust exposure. Nevertheless, none of these two agents appeared to be associated with increased COPD incidence in our analyses. It should be emphasized though, that the percentage of participants exposed to mineral dust and metals was lower than that for other exposures. On the other hand, both mineral dust and particularly metals were found to be associated with higher incidence of chronic phlegm and chronic bronchitis. This points to a different mechanism of action for these exposures, one involving chronic inflammation and mucus hypersecretion, and linked to a distinct COPD phenotype.

Exposure to solvents has not been extensively studied for its effects on lung function decline and COPD, or has been studied as a composite with other harmful exposures

(Bergdahl *et al.*, 2004; Weinmann *et al.*, 2008). A recent study reported an increased risk of airway obstruction in women exposed to chlorinated solvents, but not in men (Alif *et al.*, 2017), while another recent study found no association at all (de Jong *et al.*, 2014b). In our analyses we found no effect on COPD incidence for any category of solvent exposure (aromatic, chlorinated or other solvents), in neither men nor women. In terms of lung function decline, we found a slightly accelerated FEV1 decline only in male ever smokers exposed to chlorinated solvents. At the same time, however, we found a slower FVC decline in women exposed to aromatic and chlorinated solvents, independent of smoking status. This finding is difficult to explain; it might be the case that these exposed jobs (such as hairdressers, gardeners, decorators, painters, mechanical enginieers, etc) are selected by fitter, healthier women, with naturally slower rates of lung function decline, i.e. a “healthy worker selection” effect. Furthermore, we found a modestly increased incidence in chronic phlegm among men exposed to all three categories of solvents, but not in women, and particularly among ever smokers. Therefore it appears that solvents may interact with smoking, particularly in men, to cause chronic mucus hypersecretion but that in itself may not increase a person's COPD risk by very much – at least in this younger cohort.

In summary, we see that the role of occupational exposures in respiratory health is complex and multi-faceted, with different agents having different effects in such people, and being linked to different COPD phenotypes. These analyses begin to shed a light in this complexity, while adding strong prospective evidence for the associations between occupational exposures and COPD-related outcomes.

5.2 Methodological considerations

A common difficulty for all three analyses is exposure assessment. Although the use of a JEM avoids recall bias to a large extent, it cannot avoid a degree of non-differential misclassification, given that it assigns the same exposure for the same job code, ignoring any heterogeneity of exposure within similar jobs. Using more complex quantitative JEMs that also include a time axis or expert assessment steps may result in less misclassification, but such JEMs require a large amount of data on exposures and may not be easily generalizable in a multi-country study such as the ECRHS. The ALOHA(+) JEM employed in these analyses is a tried and tested semi-quantitative JEM, assigning three intensities of exposure (none/low/high) per job code and favoring specificity over sensitivity. Using “any exposure” or “any high” / “only low exposure” over a follow-up period as the independent variable in analyses is more crude but less

susceptible to misclassification; on the other hand, cumulative exposure in intensity-years is more detailed but potentially more susceptible to non-differential misclassification, thereby blunting potential associations (Pearce *et al.*, 2007). For this reason we avoided using cumulative exposure except in the analysis of lung function decline (Paper III), where the very detailed modelling of lung function over time necessitates having a quantitative measure of exposure. For the other two analyses (COPD incidence, chronic bronchitis incidence) we only used the binary ("any exposure") or categorical ("any high" / "only low") exposure; this also facilitates making comparisons of event rates or proportions between exposure groups, thus making the results more direct and interpretable.

A second common difficulty is how to take account of the effect of Socioeconomic Status (SES) on the outcomes. Depending on the context, SES can act both as a confounder and as a mediator of the effect of occupation on disease (Lahelma *et al.*, 2004; Richiardi *et al.*, 2008). Our preference was to adjust for SES in all analyses, and do a sensitivity analysis without this adjustment where applicable. We used education level (years of formal education) as a surrogate variable for SES, and we found that omitting it in the models did not meaningfully affect the results (Papers I and II). A third issue common to all analyses was how to disentangle the effect of multiple occupational exposures, given that there was substantial correlation between many of them. Adding all ten individual exposures of the ALOHA(+) JEM in the same model was not an option given the available sample size. Instead we opted for univariate-type comparisons between study participants exposed to each agent and participants not exposed to the same agent; this has the drawback of mixing other occupational exposures to the "unexposed" group, but in this way results in more conservative effect estimates. An alternative would be to use a uniform comparison group consisting of only those participants fully unexposed to all ALOHA(+) agents, which in practice would mean all white-collar workers; such an option, however, would discard part of the sample and also increase the potential for residual confounding especially by socioeconomic status. For this reason it was attempted only as a sensitivity analysis for COPD incidence, where it did not result in substantially different associations (Paper I). In terms of assessing multiple occupational exposures adjusted for the effects of each other, we only attempted it for few exposures (two or three) in order to conserve statistical power, when univariate-type analyses showed an effect and there were substantial correlations between these exposures (for example, between VGDF and pesticides).

Lung function decline is affected by many factors, including gender, height and lifetime smoking pack-years, that need to be carefully modelled, otherwise there is a large margin for substantial residual confounding. Importantly, the rate of lung function decline is characterized by substantial heterogeneity among individuals; in addition, correlations between baseline lung function and subsequent rate of decline, as well as between different spirometric parameters (FEV1 and FVC), need to be taken into account in any model. This was highlighted by our findings; although most occupational exposures resulted in consistently steeper declines in the FEV1/FVC ratio, in some cases this was caused by a steeper decline in FEV1 with normal FVC decline (e.g. biological dust), in other cases both parameters has accelerated declines but FEV1 more so (e.g. pesticides), and in others it was caused by normal FEV1 decline and shallower FVC decline (e.g. gases/fumes, VGDF). All these issues necessitate a complex model for lung function, that includes both FEV1 and FVC and their associations, as well as participant-level random effects to capture inter-person variability. Such a detailed model requires similarly detailed exposure and covariate information; as a result lifetime pack-years of smoking (and not just smoking status as a binary variable or intensity of smoking as a categorical variable) need to be included, as well as occupational cumulative exposure expressed in intensity-years. Again, though, it should be emphasized that non-differential misclassification in the cumulative exposure estimates is expected to bias the results for lung function decline towards the null; this should be taken into consideration when interpreting the magnitude of the observed effects on lung function decline.

When studying respiratory symptoms, an issue arises from their relapsing and remitting nature, as well as their specificity for COPD. The latter is especially true for chronic cough, which can also be a feature of asthma or other respiratory conditions. Also chronic bronchitis (CB – chronic cough *and* chronic phlegm) was much less sensitive than chronic phlegm alone, and as a result only metals and mineral dust showed an effect on CB incidence, whereas more types of exposures appeared to affect the incidence of chronic phlegm. At the same time, patients may or may not report a symptom at different time points; study participants who reported a symptom at a previous visit may not report it at a subsequent visit, and may do again later. There are various analytical approaches that can account for this. Using Generalized Estimating Equations (GEE) allows for analyzing all observations made on each participant in the course of a longitudinal study. In addition, we studied symptom incidence as outcome, by focusing on a cohort with neither chronic cough nor chronic phlegm at baseline; using a stricter criterion guards against baseline disease misclassification, which can bias relative risk estimates away from the null (Pekkanen *et al.*, 2006).

In the analyses for COPD incidence, we adjusted for the baseline %predicted FEV1/FVC ratio, which was found to be a strong predictor of subsequent COPD incidence. COPD is not a stochastic but a progressive event, occuring when FEV1/FVC falls below a certain threshold. As such, the FEV1/FVC ratio at the start of follow-up is an expression of the "distance to be covered" until that threshold, and therefore predicts the outcome, i.e. COPD incidence. Whether it is also a confounder depends on whether it is also associated with the exposure, i.e. occupation. For example, if healthier workers (with higher baseline FEV1/FVC) are more likely to be hired on more exposed jobs, then this will blunt any association between occupation and COPD incidence. As a result we adjusted for baseline FEV1/FVC in all models and also undertook a sensitivity analysis, in which the unadjusted estimates were not substantially different (more than 10% off) than the adjusted ones.

In both the COPD incidence and the lung function analysis, we fitted regression models under a Bayesian framework using Markov Chain Monte Carlo (MCMC) methods. This has a number of critical advantages. First, Bayesian MCMC can accomodate the very complex mixed model employed to analyze lung function decline (two correlated continuous outcomes, individual-level random intercepts and slopes, and data with only up to three observations per participant), which is practically nearly impossible to do in a likelihood-based frequentist mixed modelling framework. It also allows estimating any number of stratified effects or model-based predictions, including their associated uncertainty. For the COPD incidence analysis, Bayesian MCMC allows fitting a log-binomial model, which is a more natural choice to model Relative Risks but very often has convergence problems in a frequentist setting (Zou, 2004). At the same time, the Bayesian framework significantly facilitates the handling of missing covariates, while maintaining the required level of uncertainty in the effect estimates, by including appropriate priors for every partially observed variable in the same analysis model (Erler *et al.*, 2016); this is a very flexible approach that avoids the use of multiple imputation, which can become inconvenient when multiple analyses have to be performed on many imputed datasets. Furthermore, Bayesian statistics provide 95% Credible Intervals as a measure of effect estimate precision, which have a more natural interpretation than Confidence Intervals (i.e. an interval that contains the population parameter with 95% probability). The use of non-informative priors for all model parameters maintains objective inference, and in the most common cases the results of the Bayesian analysis (point estimate and credible interval) will conicide with those from an equivalent frequentist analysis (Jaynes & Kempthorne, 1976); in any event, the choice of prior will usually have negligible influence on the results when the amount of data available is large, as is the case here.

Strengths of the present study include the population-based design, large sample size, long follow-up of 20 years, and full job histories collected, allowing comprehensive and unbiased exposure assessment using a JEM. As a result, the analyses presented here provide substantially stronger evidence for the observed associations compared to the previous literature, which mostly consists of smaller studies and/or cross-sectional in design, as well as studies with occupational exposures assessed via self-report. An additional strength is the international nature of the study, with study centres in multiple developed countries, which increases the generalizability and applicability of the findings.

On the other hand, however, there are certain limitations. As already mentioned, the use of a JEM cannot avoid a degree of non-differential exposure misclassification, which is expected to decrease the magnitude of any observed association; this particularly applies to the lung function decline analyses. There is substantial overlap between occupational exposures in particular jobs, making it hard to disentangle the effects of each exposure despite the large sample size. With ten individual exposures in the ALOHA(+) JEM, and with significant correlations between each other, estimating the effect of each one adjusted for the presence of all the others would require many times the available sample size. For similar reasons we did not attempt to assess heterogeneity between study centres or countries for any of our findings, as the sample size – although large – was clearly insufficient to do such subgroup analyses. In addition, although women made up approximately half of the study population, they worked much less frequently than men to occupationally exposed jobs; this was particularly true for mineral dust, metals, solvents and pesticides exposure. As a result, there was substantially less statistical power to detect associations in women for these exposures, or to detect effect modification by sex. Future population-based occupational epidemiology studies should aim to recruit more women in order to compensate for this difference. Finally, the study was undertaken in developed countries only, therefore it is not known to what extent the findings can be generalized in less developed countries, where occupations, working conditions, population characteristics and other details are different.

Can we be confident that the associations reported in this thesis between occupational exposures and COPD-related outcomes (or at least most of them) are causal? One can apply several criteria to assess this question, even though almost all of them come with caveats or are open to criticism (Ioannidis, 2016). The most striking feature of these results is their internal consistency; for example, those occupational exposures that were associated with increased COPD incidence (biological dust, gases/fumes and pesticides)

were also associated with accelerated FEV1/FVC decline. The criterion of temporality is also largely fulfilled; we examined incidence as outcome, carefully defining a group of participants without the outcome at baseline, and exposures were assessed prospectively. The observed associations are coherent with respect to the previous literature, strengthening and expanding on past findings, and biologically plausible according to current basic science knowledge. The strength of the associations appear reasonable, not to small as to be clinically insignificant or potentially accounted for by residual confounding, and not too large as to be implausible. Finally, in some cases we were able to demonstrate dose-response relationships to a certain extent. For example those ever exposed to high levels of biological dust appeared to have higher COPD incidence than those only exposed to low levels, and exposure to high levels of VGDF increased chronic phlegm incidence even more than only low exposure to VGDF. Also the analyses of lung function decline related two quantitative variables with each other (lung function and cumulative occupational exposure in intensity-years), thus by definition showing a dose-response relationship. As a result, one can place a reasonable amount of confidence in the findings of this thesis and speak of causal associations between occupation and these COPD-related outcomes, in line with previous knowledge.

5.3 Public health implications and future research

The findings presented in this thesis significantly expand the evidence base on the role of occupation in lung function decline and COPD, and are particularly important from a public health point of view. Occupation is a defining feature in the life of every adult person in the world; almost everyone has this "risk factor". Current worldwide economic and social trends mean that people stay in their jobs longer, and work not in one but in multiple jobs during their working lives. Economic considerations, especially in less developed countries, imply that the prevalence of harmful occupational exposures is likely to continue in the future. In our study population, 20% of COPD cases were attributable to occupational exposures, which is a substantial proportion, and in line with previous estimates (Balmes *et al.*, 2003). As the prevalence of tobacco smoking gradually decreases in Western countries (Bilano *et al.*, 2015), risk factors such as occupational exposures are set to rise further as causes of COPD.

As a result, it is necessary to develop prevention strategies to mitigate the risks involved. Such strategies involve exposure avoidance or control, by modifying work processes, ventilation and extraction measures, or using personal protective measures.

In addition, overall COPD risk reduction by highlighting smoking prevention for occupationally exposed workers is warranted.

However, more detailed data about occupational risk assessment are still needed; there are multiple jobs with varying types and intensities of exposures, and the magnitude of their association with COPD outcomes is not well defined. Also it is not fully known whether men and women are equally affected. Men and women often work in different jobs, therefore their occupational exposures have different sources. In addition, it is possible that biological differences modify the effects of particular exposures. Furthermore, the effect of occupational exposures may also be modified by smoking; the magnitude of such an interaction, and which particular exposures it concerns, is very important from both a clinical and a public health standpoint. The analyses presented in this thesis only begin to provide some much needed answers to the above questions and further research is needed.

First of all, the current literature is full of small-scale, cross-sectional and workforce-based studies, which are good for generating interesting hypotheses but much less for confirmation; also their heterogeneity in definitions and methods precludes any meaningful meta-analysis in order to answer specific questions (Omland *et al.*, 2014). Therefore more large prospective population-based epidemiological studies are urgently required in order to provide good-quality evidence on the various open issues. The sample size for these studies needs to be sufficiently large to allow multiple subgroup analyses, and to begin to disentangle the effects of multiple correlated occupational exposures. Such future studies need to thoroughly collect a multitude of information: (a) complete data on jobs and occupational exposures, potentially supplemented by objective enviromental measurements, in order to have good exposure assessment, (b) detailed data on smoking, which is the most important confounder in any COPD-related study, and other covariates such as socioeconomic status and comorbidities, (c) information on various patient-related outcomes, such as quality of life, hospitalization and healthcare use, respiratory symptom history, post-bronchodilator spirometry, among others. Pooling already available and ongoing cohorts can go a long way towards providing the evidence necessary to detail the role of occupation in COPD.

Investigating differences between men and women should be a primary objective in any future research on occupation and COPD; this will probably require enrolling more women at the start of a study, in order to have a sufficient number of occupationally exposed women to maintain statistical power. In addition, it is important to assess multiple job-related exposures and not just the “classics” such as dusts and fumes; new agents such as pesticides can also be associated with lung function decline and COPD

and might even be more amenable to prevention efforts. Ethnic differences are of particular interest for future studies, especially in light of increased globalisation and population migration. It is also important to have more occupational epidemiology studies in less developed countries, where exposures may be less well controlled and the burden of occupational-related and preventable disease potentially higher. Furthermore, studies on occupation and COPD should not only aim to establish a causal association, but also to elucidate particular COPD phenotypes with respect to clinical, physiological, radiological and other characteristics such as quality of life and healthcare use (Han *et al.*, 2010). Such future research will allow more detailed and individualized occupational risk assessment and better targeting of workplace prevention efforts to those workers at higher risk for poor outcomes.

6.CONCLUSIONS

- Exposure to biological dust, gases/fumes and pesticides was associated with increased incidence of COPD over two decades of follow up. A combined 21% of all COPD cases in the study population was attributable to these exposures.

- Exposure to gases, dusts, fumes, pesticides and metals was associated with accelerated decline in the FEV1/FVC ratio, and therefore with increased COPD prevalence, particularly in male smokers.

- Mineral dust exposure and particularly metals exposure were associated with increased incidence of chronic bronchitis.

- Besides the increased incidence of COPD and accelerated FEV1/FVC decline, pesticides were associated with accelerated FVC decline in smokers only, as well as increased incidence of chronic phlegm in women only. Thus the effect of pesticides on respiratory health is complex.

- Exposure to solvents was associated with increased incidence of chronic phlegm in men only, and was not associated with accelerated lung function decline or increased COPD incidence.

- Smoking and sex appear to be important effect modifiers of the effect of occupational exposures on COPD outcomes. Studies should always aim to provide effect estimates stratified by smoking status and sex.

ANNEX

About the author

Theodore Lytras received a medical degree from the University of Ioannina, Greece in 2004 and a Master of Public Health from the National School of Public Health in Athens, Greece in 2010. He completed a medical residency in occupational medicine in 2014, and has since been working as an epidemiologist at the Hellenic Centre for Disease Control and Prevention. He carried out his PhD thesis while affiliated with the Centre for Research in Environmental Epidemiology (CREAL – now Barcelona Institute of Global Health, ISGlobal) from 2013 to the present.

Abstracts in conferences

1. Chronic cough and phlegm in relation to occupational exposures in a prospective cohort study (ECRHS III)

Theodore Lytras, Hans Kromhout, Josep Maria Antó, Per Bakke, Geza Benke, Paul Blanc, Sandra Dorado, Johan Hellgren, Mathias Holm, Deborah Jarvis, Amar Jayant Mehta, David Miedinger, Maria C Mirabelli, Dan Norbäck, Mario Olivieri, Vivi Schlünssen, Isabel Urrutia, Simona Villani, Manolis Kogevinas, Jan-Paul Zock

A causal relationship between occupational exposures and the development of chronic bronchitis and COPD has been recognized, but there is limited evidence from prospective population-based studies. The ECRHS is a multicentre cohort study that has recently completed a second follow-up after a mean of 19 years. We examined the relationship between occupational exposures and group-level changes in chronic bronchitis symptoms using 3 time points. We used repeated questionnaire data from 9175 ECRHS participants in 29 study centres, 6754 (74%) of whom completed the second follow-up. Occupational exposures were assessed from job histories up to the first follow-up using the ALOHA Job-Exposure Matrix. Absolute annual change in prevalence of chronic cough and/or chronic phlegm was assessed using Generalized Estimating Equation models, fitted separately for each study centre and pooled using multivariate meta-analysis. Any high exposure to dusts, gases or fumes (14% of participants) was associated with increasing prevalence of cough or phlegm in men

(0.087%/year, p=0.002), and decreasing prevalence of cough with phlegm in women (-0.039%/year, p<0.001). Heterogeneity between centre-level estimates was moderate (men: I2=46%, women: I2=26%). Smoking was a strong predictor of cough and phlegm, but did not modify the observed associations. Certain occupations were associated with increased, but others with decreased prevalence of symptoms, e.g. nurses (-0.039%/year, p=0.001). We conclude that occupational exposures may affect the prevalence of chronic bronchitis during two decades of follow-up. The direction of this effect depends on gender and specific occupation.

(Presented as poster discussion at the 2015 ERS congress in Amsterdam, The Netherlands)

2. Lung function decline and COPD prevalence in relation to occupational exposures in a prospective cohort study: the ECRHS III

Theodore Lytras, Anne-Elie Carsin, Hans Kromhout, Roel Vermeulen, Josep Maria Antó, Per Bakke, Geza Benke , Paul Blanc, Sandra Dorado, Johan Hellgren, Mathias Holm, Deborah Jarvis, Amar Jayant Mehta, David Miedinger, Maria C Mirabelli, Dan Norbäck, Mario Olivieri, Vivi Schlünssen, Isabel Urrutia, Simona Villani, Manolis Kogevinas, Jan-Paul Zock

INTRODUCTION: Few prospective population-based studies have demonstrated a relationship between occupational exposures and the rate of lung function decline. We examined the effect of occupational exposures on lung function decline (FEV1 and FVC) and COPD prevalence in the ECRHS, a multicentre cohort study that has completed its second follow-up after a mean of 19 years.

METHODS: We used repeated questionnaire and pre-bronchodilator spirometric data from 9175 ECRHS participants in 29 study centres who completed the first follow-up; 4549 (50%) of them completed the second follow-up. COPD was defined using a lower limit of normal criterion for FEV1/FVC. Occupational exposures were assessed from job histories up to the first follow-up using the ALOHA Job-Exposure Matrix. Decline in FEV1 and FVC was analyzed using mixed-effects linear models, and change in COPD prevalence using marginal (GEE) logistic regression. All models were adjusted for age, gender, height, BMI, smoking status, passive smoking, current asthma, socioeconomic status, and early-life disadvantage score. To account for differential loss

to follow-up and item non-response we used multiple imputation with chained equations (100 imputed datasets).

RESULTS: In women, exposure to low levels of dusts, gases or fumes resulted in accelerated declines in FEV1 (-1.4 ml/yr; 95% CI -2.8 to 0.0) and FVC (-1.7 ml/yr; -3.4 to -0.1); FEV1 decline was higher in female smokers (-3.1 ml/yr; -4.8 to -1.3). In men, the same exposures had a statistically significant effect only in smokers, with accelerated declines in FEV1 (-3.2 ml/yr; -5.1 to -1.2) and the FEV1/FVC ratio (-0.6% / 10 years; -1.1% to -0.2%), as well as an increased prevalence of COPD (OR = 1.21; 1.03 – 1.43). Higher exposures produced similar effects, in both genders.

CONCLUSIONS: Occupational exposures appear to affect lung function decline and COPD prevalence, and the magnitude of this effect depends on gender and smoking status.

(Presented as oral presentation at the 25th EPICOH conference in Barcelona, Spain)

Other work related to the thesis

Participated in the team of experts that performed the update of the Asthma JEM, a JEM evaluating exposure to 22 risk factors for asthma (Kennedy *et al.*, 2000):

Nicole Le Moual, Jan-Paul Zock, Orianne Dumas, Theodore Lytras, Eva Andersson, Linnéa Lillienberg, Vivi Schlünssen, Geza Benke, Hans Kromhout. “Update of an Occupational Asthma-specific Job-Exposure Matrix to assess exposure to 30 specific agents.” *(Paper submitted to Occupational & Environmental Medicine)*

Training seminars

Participated at the EEPE (European Educational Programme in Epidemiology) 28th Residential Summer Course in Epidemiology, Florence, Italy, 23 June – 11 July 2015.

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