IRIS AperTO

UNIVERSITÀ DEGLI STUDI DI TORINO

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Cumulative Occupational Exposures and Lung-Function Decline in Two Large General-Population Cohorts

This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1771156 since 2021-02-03T16:05:24Z

Published version:

DOI:10.1513/AnnalsATS.202002-113OC

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

08 May 2024

Annals of the American Thoracic Society

Cumulative occupational exposures and lung function decline in two large general population cohorts

Journal:	*Annals of the American Thoracic Society*
Manuscript ID	White-202002-113OC.R1
Manuscript Type:	OC - Original Research
Date Submitted by the Author:	n/a
Complete List of Authors:	Lytras, Theodore; Barcelona Institute for Global Health; Universitat Pompeu Fabra, Department of Experimental and Health Sciences Beckmeyer-Borowko, Anna; Swiss Tropical and Public Health Institute, Department of Epidemiology and Public Health; University of Basel Kogevinas , Manolis; Barcelona Institute for Global Health; Universitat Pompeu Fabra; Centro de Investigacion Biomedica en Red de Epidemiologia y Salud Publica; Hospital del Mar Institute for Medical Research Kromhout, Hans; University of Utrecht, Institute for Risk Assessment Sciences, Division of Environmental Epidemiology Carsin, Anne; Barcelona Institute for Global Health; Universitat Pompeu Fabra; Centro de Investigacion Biomedica en Red de Epidemiologia y Salud Publica Anto, Joseph; Barcelona Institute for Global Health; Universitat Pompeu Fabra, Department of Experimental and Health Sciences; Centro de Investigacion Biomedica en Red de Epidemiologia y Salud Publica; Hospital del Mar Institute for Medical Research Bentouhami, Hayat; University of Antwerp Faculty of Medicine and Health Sciences, Social Epidemiology and Health Policy, Department of Epidemiology and Social Medicine (ESOC) Weyler, Joost; University of Antwerp Faculty of Medicine and Health Sciences, Social Epidemiology and Health Policy, Department of Epidemiology and Social Medicine (ESOC) Heinrich, Joachim ; Institute of Occupational, Social, and Environmental Medicine, University Hospital LMU , Institute of Occupational, Social, and Environmental Medicine; Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, ☐, Institute of Epidemiology I Nowak, Dennis; University of Munich, Urrutia, Isabel; Department of Respiratory Medicine, Galdakao Hospital Moratalla, Jesús; Servicio de Salud de Castilla – La Mancha, Servicio de Neumología Gullón, José; Hospital San Agustin de Aviles, Departement of Pneumology Pereira-Vega, Antonio; Hospital Juan Ramon Jimenez, Pneumology Section Raherison, Chantal; Université Bordeaux Segalen, Unité Epidémiologie et Biostatistique Pin, Isabelle; CHU de Grenoble Alpes Hopital Sud, Department of

Pediatrie; INSERM, U1209, IAB, Team of Environmental Epidemiology applied to Reproduction and Respiratory Health; Universite Grenoble Alpes
Demoly, Pascal; University Hospital of Montpellier, Allergy
Leynaert, Bénédicte; INSERM,
Villani, Simona; University of Pavia, Unit of Biostatistics and Clinical Epidemiology, Department of Public Health, Experimental and Forensic Medicine
Gislason, Thorarinn; Landspitali University Hospital,
Svanes, Øistein; University of Bergen, Department of Clinical Science
Holm, Mathias; Sahlgrenska University Hospital, Department of Occupational and Environmental Medicine
Forsberg, Bertil; Division of Occupational and Environmental Medicine, Umeå University
Norbäck, Dan; Uppsala University,
Mehta, Amar; University of Copenhagen, Department of Public Health, Section of Epidemiology
Keidel, Dirk; Swiss Tropical and Public Health Institute, Department of Epidemiology and Public Health; University of Basel
Vernez, David; University of Lausanne, Center for Primary Care and Public Health (Unisante)
Benke, Geza; Monash University, Department of Epidemiology and Preventive Medicine
Jõgi, Rain; Foundation Tartu University Clinics, Lung Clinic
Torén, Kjell; Dept of Occupational Medicine, Sahlgrenska Academy
Sigsgaard, Torben; Aarhus University, Dept. of Public Health
Schlünssen, Vivi; Aarhus University, Department of Public Health
Olivieri, Mario; University Hospital of Verona
Blanc, Paul; University of California, San Francisco,
Watkins, John; Public Health Wales; Cardiff University, School of Medicine
Bono, Roberto; University of Turin, Department of Public Health and Pediatrics
Squillacioti, Giulia; University of Turin, Department of Public Health and Pediatrics
Buist, A. Sonia; Oregon Health Sciences University, Medicine / Pulmonary & Critical Care
Vermeulen, Roel; University of Utrecht, Institute for Risk Assessment Sciences, Division of Environmental Epidemiology
Jarvis, Debbie; Imperial College,
Probst-Hensch, Nicole; Swiss Tropical and Public Health Institute; University of Basel
Zock, Jan-Paul; Barcelona Institute for Global Health; Universitat Pompeu Fabra, Department of Experimental and Health Sciences; Centro de Investigacion Biomedica en Red de Epidemiologia y Salud Publica

Subject Category: 1.25 Occupational and Environmental Airways Disease < ENVIRONMENTAL AND OCCUPATIONAL HEALTH, 6.04 Epidemiology < ENVIRONMENTAL AND OCCUPATIONAL HEALTH, 6.13 Lung Health and the Working Life < ENVIRONMENTAL AND OCCUPATIONAL HEALTH

Key Words: occupational exposures, spirometry, longitudinal studies, occupational disease, chronic obstructive pulmonary disease

SCHOLARONE™
Manuscripts

Cumulative occupational exposures and lung function decline in two large general population cohorts

Theodore Lytras[1,2], Anna Beckmeyer-Borowko[3,4], Manolis Kogevinas[1,2,5,6], Hans Kromhout[7], Anne-Elie Carsin[1,2,5], Josep Maria Antó[1,2,5,6], Hayat Bentouhami[8], Joost Weyler[8], Joachim Heinrich[9], Dennis Nowak[9], Isabel Urrutia[10], Jesús Martínez-Moratalla[11,12], José Antonio Gullón[13], Antonio Pereira Vega[14], Chantal Raherison Semjen[15], Isabelle Pin[16,17,18], Pascal Demoly[19,20], Bénédicte Leynaert[21], Simona Villani[22], Thorarinn Gislason[23,24], Øistein Svanes[25], Mathias Holm[26], Bertil Forsberg[27], Dan Norbäck[28], Amar J Mehta[29], Dirk Keidel[3,4], David Vernez[30], Geza Benke[31], Rain Jõgi[32], Kjell Torén[33], Torben Sigsgaard[34], Vivi Schlünssen[34,35], Mario Olivieri[36], Paul D Blanc[37], John Watkins[38], Roberto Bono[39], Giulia Squillacioti[39], A. Sonia Buist[40], Roel Vermeulen[7], Deborah Jarvis[41,42], Nicole Probst-Hensch[3,4], Jan-Paul Zock[1,2,5]

1. Barcelona Institute of Global Health (ISGlobal), Barcelona, Spain

2. Universitat Pompeu Fabra (UPF), Barcelona, Spain

3. Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland

4. University of Basel, Basel, Switzerland

5. CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

6. Hospital del Mar Medical Research Institute, Barcelona, Spain

7. IRAS, University of Utrecht, The Netherlands

8. Social Epidemiology and Health Policy, Department of Epidemiology and Social Medicine (ESOC), Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

9. Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Ludwig Maximilians University, Munich, Comprehensive Pneumology Centre Munich, German Centre for Lung Research

10. Pulmonology Department, Galdakao Hospital, Spain

11. Servicio de Neumología, Complejo Hospitalario Universitario, Albacete, Spain

12. Facultad de Medicina Albacete, University of Castilla-La Mancha, Ciudad Real, Spain

13. Respiratory Department, Hospital Universitario San Agustín, Avilés, Asturias, Spain

14. Pulmonology and Allergy Clinical Unit, University Hospital Juan Ramón Jiménez, Huelva, Spain

For Review Only

15. Université de Bordeaux, Inserm, Bordeaux Population Health Research Center, team EPICENE, UMR 1219, Bordeaux, France

16. Department of Pédiatrie, CHU de Grenoble Alpes, Grenoble, France

17. Inserm, U1209, IAB, Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Grenoble, France

18. Université Grenoble Alpes, Grenoble, France

19. University Hospital of Montpellier, Montpellier, France

20. INSERM UMR-S 1136 - Sorbonne Université, Paris, France

21. Inserm UMR 1152-Equipe Epidémiologie, Université Paris Diderot, Paris, France

22. Department of Public Health, Experimental and Forensic Medicine, Unit of Biostatistics and Clinical Epidemiology, University of Pavia, Pavia, Italy

23. Dept. of Respiratory Medicine and Sleep, Landspitali University Hospital 108, Reykjavik, Iceland

24. Faculty of Medicine, University of Iceland, Reykjavik, Iceland

25. Department of Clinical Science, University of Bergen, Norway

26. Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden

27. Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, Umeå, Sweden

28. Uppsala University, Department of Medical Sciences, Uppsala, Sweden

29. Department of Public Health, Section of Epidemiology, University of Copenhagen, Denmark

30. Center for Primary Care and Public Health (Unisante), University of Lausanne, Switzerland

31. Monash Centre for Occupation and Environmental Health, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

32. Tartu University Hospital, Lung Clinic, Estonia, Europe

33. Occupational and environmental medicine, School of Public Health and Community Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

34. Department of Public Health, section for Environment, Occupation and Health, Danish Ramazzini center, Aarhus University, Denmark

35. National Research Center for the Working Environment, Copenhagen, Denmark

36. Unit of Occupational Medicine, Department of Diagnostics and Public Health, University of Verona, Verona, Italy

37. University of California San Francisco and the San Francisco Veterans Affairs Health Care System, San Francisco, United States

38. School of Medicine, Cardiff University / Public Health Wales, Cardiff, Wales, United Kingdom

39. Department of Public Health and Pediatrics, University of Turin, Turin, Italy

For Review Only

40. Pulmonary and Critical Care Medicine, Oregon Health & Science University, Portland, Oregon, United States

41. Population Health and Occupational Disease, National Heart and Lung Institute,

Imperial College London, London, United Kingdom

42. MRC-PHE Centre for Environment and Health, Imperial College London, London, United Kingdom

Corresponding author: Theodore Lytras, Barcelona Institute of Global Health (ISGlobal), Barcelona, Spain. Tel: +30 6946 814271

Contributorship statement: Study idea & design: TL, ABB, MK, JPZ, NPH, HK, JMA, KT, DJ. Data collection: MK, HK, AEC, JMA, HB, JW, JH, DN, IU, JMM, JAG, APV, CRS, IP, PD, BL, SV, TG, OS, MH, BF, DN, AJM, DK, DV, GB, RJ, KT, TS, VS, MO, PDB, JW, RB, GS, ASB, RV, DJ, NPH, JPZ. Data analysis: TL, ABB, DK, JPZ. Data interpretation: all authors. Initial manuscript draft: TL, ABB, MK, JPZ. Critical revision of the manuscript for important intellectual content: all authors. Final approval of the manuscript for publication: all authors

Funding: None of the study sponsors/funders had any role on study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had full responsibility for the decision to submit for publication. Full funding statement is provided in the online data supplement.

Running head: Occupational exposures and lung function decline

Descriptor number: 1.25 Occupational and Environmental Airways Disease

Word count: 3,296

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

For Review Only

Abstract

Rationale: Few longitudinal studies have assessed the relationship between occupational exposures and lung function decline in the general population, with sufficiently long follow-up.

Objectives: Our objective was to examine this potential association in two large cohorts (ECRHS and SAPALDIA).

Methods: General population samples aged 18 to 62 were randomly selected in 1991-1993, and followed up approximately 10 and 20 years later. Spirometry (without bronchodilation) was performed at each visit. Coded complete job histories during follow-up visits were linked to a Job-Exposure Matrix, generating cumulative exposure estimates for 12 occupational exposures. FEV_1 and FVC were jointly modelled in linear mixed-effects models, fitted in a Bayesian framework, taking into account age and smoking.

Main results: A total of 40,024 lung function measurements from 17,833 study participants were analyzed. We found accelerated declines in FEV_1 and the FEV_1/FVC ratio for exposure to biological dust, mineral dust and metals (FEV_1 -15.1ml, -14.4ml and -18.7ml respectively, and FEV_1/FVC -0.52%, -0.43% and -0.36% respectively, per 25 intensity-years of exposure). These declines were comparable in magnitude to those associated with long-term smoking. No effect modification by sex or smoking status was identified. Findings were similar between the ECRHS and SAPALDIA cohorts.

Conclusions: Our results greatly strengthen the evidence base implicating occupation, independent of smoking, as a risk factor for lung function decline and by inference for COPD. This highlights the need to prevent or control these exposures in the workplace.

For Review Only

Word count: 223.

Keywords: Spirometry; Chronic Obstructive Pulmonary Disease; Occupational Exposure; Occupational Disease; Longitudinal studies

For Review Only

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). The most well-recognized risk factor is tobacco smoking, which is associated with the majority of COPD cases. Other environmental risk factors are also implicated in the pathogenesis of COPD (2), including occupational exposures (3). The European Community Respiratory Health Survey (ECRHS) has recently shown a higher incidence of COPD in workers exposed to biological dusts, gases, fumes and pesticides, with a combined population attributable fraction of 21% (4).

Lung function declines naturally with age, but an accelerated decline is a primary, though not obligate, cause of COPD (5), as well as a long-term feature of asthma (6). Despite a large number of studies, both population- and industry based, demonstrating an association of asthma and COPD with occupational exposures (3, 7, 8), relatively few population-based longitudinal studies have examined the relationship between lung function decline and occupational exposures as estimated by a Job-Exposure Matrix (JEM) (9–11). 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 (9); the cohort however was fairly young then (30-55 years old at the time), and the follow-up time may have been too short to detect an association.

Therefore our aim was to examine the association between occupational exposures and the rate of lung function decline, given its relevance to COPD risk. To do so, we combined two large prospective cohorts participating in the ALEC project (www.alecstudy.org): the ECRHS (12) and the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) (13). Both cohorts have accumulated two decades of follow-up, with more

For Review Only

participants over 50 years of age, thus allowing better and more precise estimates of the determinants of lung function decline. In addition, we examined whether the association between occupation and lung function decline is different between men and women, and between smokers and non-smokers.

Methods

The ECRHS is a multicentre longitudinal study initiated in 1991–1993 that enrolled random general population samples aged 20 to 44 years in 55 centres from 23 countries (12). 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). SAPALDIA is also a multicentre longitudinal study with objectives, methods and protocols very similar to those of the ECRHS, that was initiated in 1991 (SAPALDIA 1) and enrolled a random general population sample aged 18 to 62 years from eight regions in Switzerland (13). SAPALDIA participants were also followed up in 2001 and 2011 (SAPALDIA 2 and 3). A flowchart of study participants from both cohorts can be found in the online supplement (Supplemental Figure 1).

During both follow-ups, participants in both cohorts were asked to provide a detailed list of their occupations and industries from all 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, who were blind to participant status. Ethical approval for each centre was obtained from their respective competent bodies, and written informed consent was obtained from all participants.

For Review Only

The population for this analysis includes all participants who completed spirometry at baseline (ECRHS I / SAPALDIA 1) and were followed up at least once (at ECRHS II / SAPALDIA 2 and/or ECRHS III / SAPALDIA 3). All spirometries were performed without bronchodilation and according to the ATS/ERS standards for reproducibility, utilizing 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 (10). 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); these intensities reflect the lognormal distribution of occupational exposure concentrations when calculating cumulative exposures.

Covariates used for adjustment included at each visit age, sex, height (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 (14). 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

For Review Only

education, and classified into three categories: high (>19 years), middle (16-19 years), low (<16 years).

Associations between cumulative occupational exposures and lung function (FEV_1, FVC and the FEV_1/FVC ratio) were assessed using linear mixed-effects models, providing the mean change in lung function per intensity-year of exposure. FEV_1 and FVC were jointly modelled, and all models included participant-level random intercepts and slopes, taking account of the correlations both between random intercepts and slopes as well as between FEV_1 and FVC. For each ALOHA(+) exposure agent we fitted two joint models, one using absolute FEV_1 and FVC ("linear model") and one using their logarithms as the outcome ("log-linear model"); from the latter 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). In all instances, the comparison was between exposed and unexposed participants to the particular ALOHA(+) agent, not against participants without any occupational exposure.

The models were fitted in a Bayesian framework with the JAGS software, setting non-informative priors for all parameters, and using 4 chains and 20,000 iterations per chain, discarding the first 2,000 as burn-in, and with a thinning interval of 5. 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 (see online supplement for details). Uncertainty for the fixed effects was expressed with 95% Credible Intervals (95% CrI).

In addition to the unstratified models, we fitted another set of models with added interaction terms for sex, and smoking status (ever/never smoker), thereby calculating stratified estimates for the effect of occupational exposures in men and women, and in ever smokers and never

For Review Only

smokers. As a criterion to determine the presence of interaction (effect modification) we used the posterior probability distribution of the interaction term, at least 95% of which should lie above or below zero. We also fitted all models separately to the data from each cohort (ECRHS and SAPALDIA), as a sensitivity analysis.

All analyses were performed with the R statistical environment, version 3.6.0 (15).

For Review Only

Results

Table 1 highlights the characteristics of the study population. We analyzed a total of 40,024 lung function measurements from 17,833 study participants across 38 ECRHS and SAPALDIA centres who completed at least one follow-up visit after baseline, with a mean follow-up duration of 16.3 years (range 4.3–22.6 years). Of these participants, 10,803 (60.6%) completed both visits over a mean duration of 19.6 years (range 15.7–22.6 years). 5,793 (32.5%) participants completed the initial and first follow-up visits only, while 1,237 (6.9%) completed the initial and second follow-up visits only. Slightly less than half of our sample had never smoked, and about a third were current smokers at baseline, dropping almost by half to 18.3% at the second follow-up. A little less than half of all participants had been occupationally exposed to VGDF at some point during follow-up (39.8%), whereas fewer had been exposed to solvents (24.2%), metals (9.3%) or pesticides (3.3%). Men were overall more likely than women to be occupationally exposed to most agents, with the exception of biological dust (Table 2). In addition, many exposures showed substantial overlap with each other (Figure 1). A list of the most common jobs by exposure category can be found online (Supplemental Table 1).

Lifetime smoking pack-years were missing in 7.8% of all observations, and had to be imputed in our models as described in the "Methods" section; also current smoking status was missing in 2.9%, current asthma in 0.5% and SES in 1.1% of all observations. Lung function in the study population naturally declined with advancing age across both follow-ups, and our Bayesian mixed-effects model was reliable in describing both mean lung function by age as well as the variability around the mean (Figure 2).

Table 3 summarizes the main results from our analysis, i.e. the effect of 25 intensity-years of occupational exposure to each ALOHA(+) agent on the three lung function parameters (FEV_1, FVC and the FEV_1/FVC ratio), both overall and stratified by sex and smoking status. A negative sign indicates reduced lung function compare to no occupational exposure to the respective agent given the same age, sex and other covariates, i.e. an accelerated lung function decline, whereas a positive number indicates a slower lung function decline. As the numbers are very small, the effect per 25 intensity-years is presented rather than per one intensity-year of exposure.

A decreased FEV_1/FVC ratio was observed for biological dust and mineral dust exposure (-0.52% and -0.43% respectively, Table 3), which was purely attributed to a FEV_1 decline (-15.08 ml and -14.42 ml respectively) with no change in FVC. A significant decline in FEV_1 only was also observed for metals exposure (-18.73 ml, 95% CrI -34.41 to -2.60 ml), as well as a lower FEV_1/FVC ratio for the composite VGDF exposure (-0.34%, 95% CrI -0.56 to -0.12%). On the other hand, smaller lung function declines were seen for gases & fumes (-7.35 ml in FEV_1 and -0.24% in FEV_1/FVC), and also for pesticides, especially in terms of FEV_1, although the results were very imprecise, with a wider 95% CrI than other exposures (Table 3). Among solvents, only exposure to chlorinated solvents was weakly associated with both lower FEV_1 and lower FVC (-16.98 ml and -14.59 ml). For comparison, as estimated in the

For Review Only

model, 25 pack-years of smoking reduced FEV1 by an additional -11.07 ml (95% CrI -22.27 to 2.49 ml), FVC by -14.83 ml (95% CrI -32.29 to -0.55 ml) and FEV1/FVC by -0.21% (95% CrI -0.44 to 0.03%). Also, current asthma was associated with a FEV1 that was -80.28 ml lower (95% CrI -92.72 to -67.71 ml), a FVC lower by -13.60 ml (95% CrI -27.44 to -0.05 ml) and a FEV1/FVC -2.16% lower (95% CrI -2.52 to -1.81%).

No effect modification by sex was detected for any occupational exposure and any lung function parameter, with one exception: women exposed to aromatic solvents had a slower FVC decline than unexposed women (+86.87 ml, 95% CrI 13.80 to 161.25 ml), whereas no significant difference was found among men (-7.84 ml, 95% CrI -34.96 to 20.18 ml). In addition, no effect modification by smoking status was detected, although in most cases the effects of occupational exposures in ever smokers tended to be slightly lower than in never smokers (Table 3). In the sensitivity analysis, results were similar between the two cohorts and showed wide overlap; pesticide exposure resulted in greater FEV_1 decline among ECRHS participants, while solvents resulted in slightly greater declines among SAPALDIA participants (Supplemental Table 2).

For Review Only

Discussion

In this pooled analysis from two large longitudinal cohorts we showed that certain groups of occupational exposures, namely biological dust, mineral dust and metals exposure, were prospectively associated with accelerated lung function decline, specifically with respect to FEV1 and the FEV1/FVC ratio. This loss of lung function is comparable to that associated with smoking, highlighting the importance of these occupational exposures in respiratory health. Our study provides significant new evidence on the topic, as few such studies have

examined longitudinal lung function decline and in a general population setting (10, 11, 16–18). 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. Previous analyses from both ECRHS and SAPALDIA have shown an increased asthma risk for certain occupational exposures (19), an increased incidence of COPD in participants occupationally exposed to biological dust and mineral dust (4, 20), as well as an increased incidence of chronic cough and chronic phlegm symptoms in those exposed to mineral dust and metals (21). Our current analysis corroborates previous findings for biological dust in a much larger study population with additional follow-up. It also indicates that mineral dust and metals exposure are associated also with lung function decline and not only with chronic bronchitis symptoms. The latter result is in agreement with recent findings from the smaller Tasmanian longitudinal Health Study (TAHS) cohort (22), as well as with a systematic review of exposure to welding fumes and lung function decline (23).

A striking finding is the very small absolute effect sizes observed, only a few millilitres (or a fraction of a percentage point) of lung function decline after 25 intensity-years of exposure, which for many workers may represent their entire lifetime exposure. At first glance such reductions could not plausibly account for an increased COPD risk as seen in previous analyses (4, 8, 20); however, these are average subject-specific effects over an exposure group, and small average reductions can mask a larger effect for certain individuals inside the group (24), especially if one also considers the sizeable individual variation in lung function (Figure 2). In addition, the comparator is not a fully occupationally unexposed group, but rather participants unexposed to the agent under consideration (who may have other occupational exposures). Furthermore, non-differential misclassification is the main limitation

For Review Only

in using JEMs in population-based occupational epidemiology studies, mostly stemming from the variability in job tasks and actual exposures between workers belonging in the same JEM exposure category (25). Grouping exposures in a JEM does not in itself bias regression coefficients towards the null, but rather results in imprecision due to Berkson-type error (26); nevertheless, regression dilution bias can be introduced if the estimated group mean is different than the true group mean (27). Intra-individual variability in exposure over time is another consideration, which is particularly relevant when calculating a cumulative exposure estimate based on job duration and a JEM classification, in this case over a long period of 20 years (28). All these factors mean that the small average declines observed in our analysis should not be used for prediction, as they are unlikely to represent the actual magnitude of the effect of these exposures on lung function, in any particular individual. For the same reasons, our results cannot definitively rule out an effect of occupational solvent exposure on lung function as recently observed in the TAHS cohort (22), nor an effect of pesticide exposure (4, 10). Especially as regards pesticides, the small percentage of exposed participants (less than 5% – Table 2) has substantially reduced precision, as reflected in the wider credible intervals of the lung function decline estimates.

Smoking is known to induce inflammation and impair the host defense mechanisms of the lung (29, 30), and has been reported to increase the adverse effect of occupational exposures on lung function decline and COPD risk (31–33). However, in our analyses we found little evidence of effect modification by smoking, after tightly adjusting both for current smoking status and cumulative pack-years. This indicates that all workers may be at risk of airway obstruction due to these occupational exposures, even though this may be more clinically significant for smokers, who represent the majority of COPD patients in most countries, and who already have lower levels of lung function and any additional loss or acceleration of

For Review Only

decline may push them over the diagnostic cutoff. Similarly, we found little difference between men and women on the effect of occupational exposures, even though the distribution of jobs per each exposure category was different between men and women. This may partially be explained by the lower proportion of occupationally exposed women in our cohorts, particularly for exposures like metals, pesticides and solvents. Future occupational epidemiology studies should try to recruit more women, in order to investigate effect modification by sex.

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 involved. Lung function was modelled in great detail, using a mixed-effects model with random intercepts and slopes, and accounting for the correlation between FEV1 and FVC; joint modelling of both spirometric parameters is important, as we identified positive correlations not just between the participant-level random intercepts and slopes for FEV1 and for FVC, but also between the intercepts for FEV1 and FVC and the slopes for FEV1 and FVC (data not shown). In addition we controlled for multiple confounders, including socioeconomic status, current asthma and especially lifetime smoking pack-years, in order to minimize confounding by intensity of smoking. The sample size was very large, thanks to the pooling of two large cohorts, facilitating the detection of associations of very small magnitude.

On the other hand, there are certain limitations to our study. Spirometries were performed without bronchodilation, and the results should be interpreted accordingly. Accelerated lung function decline in and of itself does not equate with COPD risk; in particular, occupation can also be a risk factor for asthma, thus it is not possible to distinguish lung function decline due

For Review Only

to new-onset occupational asthma from that contributing to increased COPD incidence. The application of a JEM may ensure more objective exposure estimates, free from exposure-specific recall, but can introduce both imprecision due to Berkson-type error and some bias towards the null; therefore, despite the large sample size, it may not have been always sufficient to detect an association, e.g. for the effects of pesticides or to identify effect modification. For the same reason, we cannot disentangle the effect of multiple overlapping exposures, which would require a large number of small subgroup analyses. We could also not assess heterogeneity of the results across study centres or countries, since the (necessary) inclusion of participant-level random effects left almost no variance to be explained by study centre. Finally, residual confounding cannot be completely ruled out despite the detailed model adjustments, and may have affected the observed associations given their small magnitude. As this is an observational study, some selection and response bias also cannot be definitely ruled out.

In conclusion, long-term occupational exposure to biological dust, mineral dust and metals over two decades of follow-up was associated with an accelerated decline in FEV_1 and the FEV_1/FVC ratio, which would translate to an increased risk of airways obstruction and COPD. This decline was comparable to that associated with smoking, and similar between men and women as well as between smokers and non-smokers. These results strengthen the case for occupation as a modifiable risk factor for asthma and COPD, in agreement with previous studies. And they make the case for avoiding these exposures in the workplace, or controlling them with appropriate protective measures, in order to protect the respiratory health of workers.

For Review Only

Bibliography

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2017 report. 2017;
2. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, Romieu I, Silverman EK, Balmes JR. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;182:693–718.
3. Blanc PD, Annesi-Maesano I, Balmes JR, Cummings KJ, Fishwick D, Miedinger D, Murgia N, Naidoo RN, Reynolds CJ, Sigsgaard T, Torén K, Vinnikov D, Redlich CA. The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement. *Am J Respir Crit Care Med* 2019;199:1312–1334.
4. Lytras T, Kogevinas M, Kromhout H, Carsin A-E, Antó JM, Bentouhami H, Weyler J, Heinrich J, Nowak D, Urrutia I, Martinez-Moratalla J, Gullón JA, Pereira-Vega A, Raherison-Semjen C, Pin I, Demoly P, Leynaert B, Villani S, Gislason T, Svanes C, Holm M, Forsberg B, Norbäck D, Mehta AJ, Probst-Hensch N, Benke G, Jogi R, Torén K, Sigsgaard T, *et al.* Occupational exposures and 20-year incidence of COPD: the European Community Respiratory Health Survey. *Thorax* 2018;73:1008–1015.
5. Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, Guerra S, Marott JL, Martinez FD, Martinez-Camblor P, Meek P, Owen CA, Petersen H, Pinto-Plata V, Schnohr P, Sood A, Soriano JB, Tesfaigzi Y, Vestbo J. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2015;373:111–122.
6. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194–1200.
7. Omland O, Würtz ET, Aasen TB, Blanc P, Brisman JB, Miller MR, Pedersen OF, Schlünssen V, Sigsgaard T, Ulrik CS, Viskum S. Occupational chronic obstructive pulmonary disease: a systematic literature review. *Scand J Work Environ Health* 2014;40:19–35.
8. De Matteis S, Jarvis D, Darnton A, Hutchings S, Sadhra S, Fishwick D, Rushton L, Cullinan P.

For Review Only

The occupations at increased risk of COPD: analysis of lifetime job-histories in the population-based UK Biobank Cohort. *Eur Respir J* 2019;54:.

9. Sunyer J, Zock JP, Kromhout H, Garcia-Esteban R, Radon K, Jarvis D, Toren K, Künzli N, Norbäck D, d'Errico A, Urrutia I, Payo F, Olivieri M, Villani S, Van Sprundel M, Antó JM, Kogevinas M, Occupational Group of the European Community Respiratory Health Survey. Lung function decline, chronic bronchitis, and occupational exposures in young adults. *Am J Respir Crit Care Med* 2005;172:1139–1145.
10. de Jong K, Boezen HM, Kromhout H, Vermeulen R, Postma DS, Vonk JM. Association of occupational pesticide exposure with accelerated longitudinal decline in lung function. *Am J Epidemiol* 2014;179:1323–1330.
11. Liao S-Y, Lin X, Christiani DC. Occupational exposures and longitudinal lung function decline. *Am J Ind Med* 2015;58:14–20.
12. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954–960.
13. Martin BW, Ackermann-Liebrich U, Leuenberger P, Künzli N, Stutz EZ, Keller R, Zellweger JP, Wüthrich B, Monn C, Blaser K, Bolognini G, Bongard JP, Brändli O, Braun P, Defila C, Domenighetti G, Grize L, Karrer W, Keller-Wossidlo H, Medici TC, Peeters A, Perruchoud AP, Schindler C, Schoeni MH, Villiger B. SAPALDIA: methods and participation in the cross-sectional part of the Swiss Study on Air Pollution and Lung Diseases in Adults. *Soz Praventivmed* 1997;42:67–84.
14. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, de Marco R, Norbäck D, Raherison C, Villani S, Wjst M, Svanes K, Antó JM. Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010;65:14–20.
15. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2019. at <http://www.R-project.org/>.
16. Kauffmann F, Drouet D, Lellouch J, Brille D. Occupational exposure and 12-year spirometric changes among Paris area workers. *Br J Ind Med* 1982;39:221–232.
17. Krzyzanowski M, Jedrychowski W, Wysocki M. Factors associated with the change in ventilatory

For Review Only

function and the development of chronic obstructive pulmonary disease in a 13-year follow-up of the Cracow Study. Risk of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;134:1011–1019.

18. Harber P, Tashkin DP, Simmons M, Crawford L, Hnizdo E, Connett J, Lung Health Study Group. Effect of occupational exposures on decline of lung function in early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;176:994–1000.
19. Kogevinas M, Zock J-P, Jarvis D, Kromhout H, Lillienberg L, Plana E, Radon K, Torén K, Alliksoo A, Benke G, Blanc PD, Dahlman-Hoglund A, D'Errico A, Héry M, Kennedy S, Kunzli N, Leynaert B, Mirabelli MC, Muniozguren N, Norbäck D, Olivieri M, Payo F, Villani S, van Sprundel M, Urrutia I, Wieslander G, Sunyer J, Antó JM. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet* 2007;370:336–341.
20. Mehta AJ, Miedinger D, Keidel D, Bettschart R, Bircher A, Bridevaux P-O, Curjuric I, Kromhout H, Rochat T, Rothe T, Russi EW, Schikowski T, Schindler C, Schwartz J, Turk A, Vermeulen R, Probst-Hensch N, Künzli N, SAPALDIA Team. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. *Am J Respir Crit Care Med* 2012;185:1292–1300.
21. Lytras T, Kogevinas M, Kromhout H, Carsin A-E, Antó JM, Bentouhami H, Weyler J, Heinrich J, Nowak D, Urrutia I, Martínez-Moratalla J, Gullón JA, Vega AP, Raherison Semjen C, Pin I, Demoly P, Leynaert B, Villani S, Gíslason T, Svanes Ø, Holm M, Forsberg B, Norbäck D, Mehta AJ, Probst-Hensch N, Benke G, Jogi R, Torén K, Sigsgaard T, *et al.* Occupational exposures and incidence of chronic bronchitis and related symptoms over two decades: the European Community Respiratory Health Survey. *Occup Environ Med* 2019;76:222–229.
22. Alif SM, Dharmage S, Benke G, Dennekamp M, Burgess J, Perret JL, Lodge C, Morrison S, Johns DP, Giles G, Gurrin L, Thomas PS, Hopper JL, Wood-Baker R, Thompson B, Feather I, Vermeulen R, Kromhout H, Jarvis D, Garcia Aymerich J, Walters EH, Abramson MJ, Matheson MC. Occupational exposure to solvents and lung function decline: A population based study.

For Review Only

Thorax 2019;doi:10.1136/thoraxjnl-2018-212267.

23. Szram J, Schofield SJ, Cosgrove MP, Cullinan P. Welding, longitudinal lung function decline and chronic respiratory symptoms: a systematic review of cohort studies. *Eur Respir J* 2013;42:1186–1193.
24. Petersen H, Sood A, Meek PM, Shen X, Cheng Y, Belinsky SA, Owen CA, Washko G, Pinto-Plata V, Kelly E, Celli B, Tesfaigzi Y. Rapid lung function decline in smokers is a risk factor for COPD and is attenuated by angiotensin-converting enzyme inhibitor use. *Chest* 2014;145:695–703.
25. Kauppinen TP. Assessment of exposure in occupational epidemiology. *Scand J Work Environ Health* 1994;20 Spec No:19–29.
26. Tielemans E, Kupper LL, Kromhout H, Heederik D, Houba R. Individual-based and group-based occupational exposure assessment: some equations to evaluate different strategies. *Ann Occup Hyg* 1998;42:115–119.
27. Armstrong BG. The effects of measurement errors on relative risk regressions. *Am J Epidemiol* 1990;132:1176–1184.
28. Preller L, Kromhout H, Heederik D, Tielen MJ. Modeling long-term average exposure in occupational exposure-response analysis. *Scand J Work Environ Health* 1995;21:504–512.
29. Herr C, Beisswenger C, Hess C, Kandler K, Suttorp N, Welte T, Schroeder J-M, Vogelmeier C, R Bals for the CAPNETZ Study Group. Suppression of pulmonary innate host defence in smokers. *Thorax* 2009;64:144–149.
30. Lugade AA, Bogner PN, Thatcher TH, Sime PJ, Phipps RP, Thanavala Y. Cigarette smoke exposure exacerbates lung inflammation and compromises immunity to bacterial infection. *J Immunol* 2014;192:5226–5235.
31. Boggia B, Farinaro E, Grieco L, Lucariello A, Carbone U. Burden of smoking and occupational exposure on etiology of chronic obstructive pulmonary disease in workers of Southern Italy. *J Occup Environ Med* 2008;50:366–370.
32. Blanc PD, Iribarren C, Trupin L, Earnest G, Katz PP, Balmes J, Sidney S, Eisner MD. Occupational exposures and the risk of COPD: dusty trades revisited. *Thorax* 2009;64:6–12.

For Review Only

33. Hu Y, Chen B, Yin Z, Jia L, Zhou Y, Jin T. Increased risk of chronic obstructive pulmonary diseases in coke oven workers: interaction between occupational exposure and smoking. *Thorax* 2006;61:290–295.

For Review Only

Figure Legends

Figure 1: Correlation matrix (Spearman's rho) between cumulative occupational exposures (intensity-years) in the study population, as estimated by the ALOHA(+) JEM. (N=17,833 ECRHS and SAPALDIA participants)

Figure 2: Lung function by age and sex in the study population, observed and model-predicted. (N=40,024 measurements in 17,833 ECRHS and SAPALDIA participants)

Footnote for Figure 2:

Height set to cohort mean by sex; smoking pack-years and cumulative VGDF exposure set to cohort mean by age and sex.

For Review Only

Table 1: Characteristics of study participants, by study wave. (N=17,833 ECRHS and SAPALDIA participants followed-up at least once)*

	ECRHS I / SAPALDIA 1	ECRHS II / SAPALDIA 2	ECRHS III / SAPALDIA 3
Number of participants	17833 (9765 / 8068)	16596 (8725 / 7871)	12040 (6013 / 6027)
% men	48.0 (48.0 / 47.9)	48.1 (48.1 / 48.0)	47.7 (47.9 / 47.5)
Mean age	37.2 (34.0 / 41.0)	47.2 (42.8 / 52.0)	56.9 (54.1 / 59.7)
% current asthma	6.4 (7.9 / 4.7)	7.9 (9.9 / 5.6)	7.6 (11.2 / 4.1)
% never smokers	46.0 (44.8 / 47.4)	45.9 (45.5 / 46.4)	48.5 (49.0 / 48.1)
% current smokers	33.3 (34.5 / 31.9)	27.7 (29.0 / 26.3)	18.3 (18.1 / 18.5)
Mean cumulative smoking pack-years	8.4 (7.2 / 10.0)	11.1 (9.7 / 12.7)	11.7 (10.9 / 12.3)
% of participants exposed			
Biological dust	-	22.0 (26.6 / 17.0)	26.7 (30.7 / 22.6)
Mineral Dust	-	17.6 (21.1 / 13.8)	20.9 (23.9 / 18.0)
Gases & fumes	-	31.7 (37.4 / 25.4)	37.4 (41.3 / 33.5)
Vapors, Gases, Dusts & Fumes	-	35.8 (41.9 / 29.2)	42.0 (46.1 / 37.9)
Herbicides	-	1.7 (1.5 / 1.9)	2.2 (1.8 / 2.6)
Insecticides	-	2.1 (2.3 / 1.9)	2.8 (2.9 / 2.6)
Fungicides	-	2.2 (2.4 / 2.0)	3.1 (3.4 / 2.8)
All pesticides	-	2.7 (3.2 / 2.1)	3.6 (4.3 / 3.0)
Aromatic solvents	-	11.4 (13.1 / 9.6)	13.5 (14.9 / 12.1)
Chlorinated solvents	-	9.1 (10.3 / 7.7)	10.9 (12.2 / 9.6)
Other solvents	-	19.4 (23.0 / 15.3)	23.6 (26.9 / 20.4)
Metals	-	7.9 (9.5 / 6.1)	9.7 (11.4 / 8.0)
Mean cumulative exposures since previous follow-up (intensity-years)			
Biological dust	-	2.2 (2.2 / 2.1)	4.1 (4.7 / 3.6)
Mineral Dust	-	2.3 (2.4 / 2.2)	4.1 (4.7 / 3.5)
Gases & fumes	-	3.6 (3.9 / 3.3)	6.6 (7.7 / 5.4)
Vapors, Gases, Dusts & Fumes	-	5.1 (5.3 / 4.8)	9.2 (10.6 / 7.9)
Herbicides	-	0.2 (0.1 / 0.3)	0.4 (0.3 / 0.6)
Insecticides	-	0.4 (0.3 / 0.6)	0.8 (0.6 / 1.1)
Fungicides	-	0.3 (0.3 / 0.4)	0.6 (0.6 / 0.6)
All pesticides	-	0.5 (0.4 / 0.6)	0.9 (0.7 / 1.1)
Aromatic solvents	-	1.0 (1.0 / 1.0)	1.7 (1.9 / 1.6)
Chlorinated solvents	-	1.2 (1.2 / 1.2)	1.9 (2.1 / 1.7)
Other solvents	-	1.7 (1.8 / 1.6)	3.2 (3.7 / 2.7)
Metals	-	1.2 (1.3 / 1.1)	2.0 (2.3 / 1.7)

* Data for the entire cohort (data for ECRHS / data for SAPALDIA)

For Review Only

Table 2: Proportion of participants with any occupational exposure during follow-up, stratified by sex. (N=17,833 ECRHS and SAPALDIA participants followed-up at least once)*

	% of men exposed	% of women exposed
Biological dust	22.2 (25.5 / 18.2)	27.7 (32.5 / 22.0)
Mineral Dust	28.8 (33.6 / 23.1)	11.8 (13.4 / 10.0)
Gases & fumes	42.7 (47.9 / 36.4)	29.0 (33.2 / 23.8)
Vapors, Gases, Dusts & Fumes	46.3 (51.8 / 39.7)	33.8 (38.2 / 28.4)
Herbicides	2.8 (2.5 / 3.1)	1.2 (1.0 / 1.5)
Insecticides	3.5 (3.8 / 3.1)	1.6 (1.6 / 1.5)
Fungicides	4.1 (4.7 / 3.4)	1.5 (1.4 / 1.6)
All pesticides	4.9 (5.9 / 3.7)	1.7 (1.8 / 1.6)
Aromatic solvents	21.5 (23.6 / 18.8)	5.0 (5.9 / 3.8)
Chlorinated solvents	16.8 (18.7 / 14.5)	4.5 (5.2 / 3.7)
Other solvents	25.5 (28.4 / 22.0)	18.9 (22.7 / 14.4)
Metals	17.3 (20.1 / 13.9)	1.8 (2.4 / 1.0)

* Data for the entire cohort (data for ECRHS / data for SAPALDIA)

For Review Only

Table 3: Effect of occupational exposures on lung function decline, per 25 intensity-years of exposure, compared to unexposed to the respective agent, overall and stratified by sex and smoking status. (N=17,833 ECRHS and SAPALDIA participants followed-up at least once)*

	FEV1 (ml)		FVC (ml)		FEV1FVC (%)	
Biological dust	**-15.08 (-28.66, -0.88)**		2.68 (-12.68, 18.28)		**-0.52 (-0.88, -0.16)**	
Never smokers, men / women	-3.23 (-26.67, 20.22)	-14.38 (-45.32, 15.59)	13.44 (-12.79, 39.41)	8.35 (-25.83, 43.27)	-0.28 (-0.95, 0.41)	-0.52 (-1.35, 0.36)
Ever smokers, men / women	-15.86 (-33.93, 2.09)	**-27.11 (-53.91, -1.19)**	-0.47 (-20.80, 19.98)	-5.59 (-35.49, 24.14)	**-0.52 (-1.02, -0.02)**	**-0.76 (-1.46, -0.04)**
Mineral Dust	**-14.42 (-26.41, -2.50)**		0.12 (-12.99, 13.10)		**-0.43 (-0.75, -0.10)**	
Never smokers, men / women	-9.38 (-28.04, 9.65)	5.55 (-29.53, 39.95)	10.96 (-10.24, 31.96)	15.54 (-22.24, 53.37)	**-0.56 (-1.10, -0.02)**	-0.31 (-1.23, 0.61)
Ever smokers, men / women	**-20.83 (-35.33, -6.25)**	-6.15 (-37.68, 24.57)	-7.12 (-23.55, 9.48)	-2.42 (-37.19, 33.52)	**-0.44 (-0.84, -0.03)**	-0.18 (-1.01, 0.65)
Gases & fumes	-7.35 (-17.99, 3.15)		3.46 (-8.66, 15.25)		-0.24 (-0.53, 0.04)	
Never smokers, men / women	4.22 (-12.83, 21.44)	-10.01 (-39.00, 19.03)	14.43 (-4.90, 33.41)	11.31 (-22.02, 43.81)	-0.14 (-0.64, 0.35)	-0.38 (-1.16, 0.43)
Ever smokers, men / women	-10.22 (-23.34, 3.14)	-24.37 (-51.63, 3.81)	-2.14 (-16.77, 12.32)	-5.52 (-36.24, 25.02)	-0.24 (-0.59, 0.11)	-0.48 (-1.24, 0.24)
Vapors, Gases, Dusts & Fumes	-7.42 (-15.93, 1.03)		6.02 (-3.04, 15.42)		**-0.34 (-0.56, -0.12)**	
Never smokers, men / women	-1.44 (-14.83, 11.91)	-6.21 (-28.65, 16.31)	11.89 (-2.73, 26.67)	14.92 (-10.55, 39.96)	-0.27 (-0.65, 0.11)	-0.47 (-1.06, 0.13)
Ever smokers, men / women	-9.45 (-19.62, 0.97)	-14.20 (-35.47, 7.03)	1.76 (-9.68, 13.41)	5.14 (-18.42, 28.40)	**-0.33 (-0.61, -0.06)**	-0.52 (-1.06, 0.01)
Herbicides	-14.69 (-49.54, 20.57)		-8.57 (-47.42, 29.56)		-0.34 (-1.28, 0.59)	
Never smokers, men / women	-19.16 (-85.70, 43.26)	35.35 (-51.37, 122.19)	-23.73 (-96.58, 48.69)	22.63 (-73.97, 120.70)	-0.28 (-2.17, 1.65)	0.55 (-1.85, 3.00)
Ever smokers, men / women	-33.13 (-77.76, 11.56)	21.78 (-46.93, 91.26)	-20.84 (-72.01, 28.90)	26.82 (-50.71, 104.30)	-0.67 (-1.88, 0.55)	0.12 (-1.71, 2.05)
Insecticides	-7.24 (-29.73, 15.04)		-2.43 (-27.68, 23.16)		-0.23 (-0.83, 0.38)	
Never smokers, men / women	-7.72 (-47.54, 32.36)	22.94 (-28.06, 74.16)	3.48 (-40.41, 46.91)	35.24 (-22.53, 92.33)	-0.50 (-1.60, 0.65)	-0.21 (-1.64, 1.20)
Ever smokers, men / women	-20.10 (-51.00, 10.02)	10.06 (-31.78, 52.25)	-18.67 (-53.26, 15.24)	12.87 (-34.21, 58.71)	-0.24 (-1.06, 0.60)	0.04 (-1.07, 1.17)
Fungicides	-13.68 (-41.81, 14.97)		-11.45 (-43.33, 20.68)		-0.17 (-0.97, 0.61)	
Never smokers, men / women	-22.51 (-72.85, 28.73)	28.10 (-41.07, 98.08)	-12.06 (-67.76, 43.25)	38.65 (-39.70, 114.70)	-0.46 (-1.98, 1.03)	0.03 (-1.88, 1.96)
Ever smokers, men / women	-28.92 (-66.48, 8.72)	21.69 (-36.93, 79.10)	-29.25 (-69.81, 12.87)	21.37 (-45.18, 87.03)	-0.26 (-1.31, 0.77)	0.23 (-1.37, 1.85)
All pesticides	-10.74 (-32.37, 10.90)		-6.60 (-31.35, 18.95)		-0.20 (-0.78, 0.39)	

For Review Only

	FEV1 (ml)		FVC (ml)		FEV1FVC (%)	
Never smokers, men / women	-16.23 (-55.54, 22.68)	17.02 (-34.02, 66.51)	-7.92 (-52.14, 36.53)	27.85 (-26.88, 84.30)	-0.42 (-1.50, 0.69)	-0.18 (-1.58, 1.25)
Ever smokers, men / women	-22.87 (-52.79, 7.68)	10.42 (-30.63, 51.27)	-21.70 (-55.53, 11.46)	14.28 (-32.80, 59.60)	-0.23 (-1.00, 0.58)	0.01 (-1.05, 1.12)
Aromatic solvents	0.28 (-22.53, 23.42)		3.90 (-21.95, 29.65)		0.01 (-0.61, 0.63)	
Never smokers, men / women	-12.82 (-49.46, 24.15)	40.35 (-32.52, 113.02)	-13.70 (-53.99, 25.40)	79.39 (-1.55, 159.07)	-0.08 (-1.18, 1.02)	-0.17 (-2.14, 1.82)
Ever smokers, men / women	-2.34 (-30.95, 26.43)	51.06 (-15.10, 117.27)	-3.31 (-36.96, 28.35)	**89.92 (14.99, 162.53)**	0.07 (-0.71, 0.84)	-0.02 (-1.77, 1.81)
Chlorinated solvents	-16.98 (-34.20, 0.43)		-14.59 (-33.52, 4.42)		-0.18 (-0.64, 0.29)	
Never smokers, men / women	-13.31 (-42.06, 14.73)	5.43 (-61.00, 72.39)	-10.47 (-40.24, 21.30)	31.80 (-42.25, 106.20)	-0.19 (-1.01, 0.64)	-0.14 (-2.00, 1.79)
Ever smokers, men / women	-20.45 (-40.67, 0.17)	-1.38 (-67.59, 65.47)	-20.98 (-43.51, 1.47)	21.02 (-51.04, 93.25)	-0.19 (-0.73, 0.37)	-0.14 (-1.89, 1.67)
Other solvents	-6.05 (-23.61, 11.37)		7.65 (-11.39, 27.28)		-0.24 (-0.70, 0.24)	
Never smokers, men / women	3.67 (-28.12, 36.60)	-11.05 (-46.12, 24.35)	22.33 (-14.03, 58.55)	17.37 (-22.07, 55.83)	-0.32 (-1.25, 0.61)	-0.56 (-1.53, 0.39)
Ever smokers, men / women	-0.76 (-26.90, 26.20)	-15.35 (-43.67, 12.26)	5.32 (-23.18, 36.10)	-0.01 (-32.23, 32.14)	-0.06 (-0.73, 0.63)	-0.29 (-1.04, 0.44)
Metals	**-18.73 (-34.41, -2.60)**		-10.17 (-27.46, 7.85)		-0.36 (-0.79, 0.07)	
Never smokers, men / women	-11.75 (-37.20, 14.07)	-30.34 (-110.04, 48.64)	0.82 (-27.55, 29.57)	-36.03 (-123.98, 50.88)	-0.47 (-1.20, 0.26)	-0.43 (-2.59, 1.81)
Ever smokers, men / women	**-21.37 (-40.42, -2.68)**	-39.73 (-118.34, 35.47)	-13.01 (-34.08, 8.36)	-49.46 (-135.45, 35.93)	-0.30 (-0.84, 0.21)	-0.24 (-2.38, 1.91)

*Results are posterior medians and 95% CrI in parentheses. Numbers represent absolute change in ml for FEV1 and FVC, and relative %change for FEV1/FVC. A negative sign indicates a lower value compared to fully unexposed to the respective agent. Adjusted for age, sex, current smoking, cumulative smoking pack-years, socioeconomic status and early life disadvantage score. All lung function measurements are without bronchodilation.

For Review Only

MARKED-UP VERSION FOR REVISION

Cumulative occupational exposures and lung function decline in two large general population cohorts

Theodore Lytras[1,2], Anna Beckmeyer-Borowko[3,4], Manolis Kogevinas[1,2,5,6], Hans Kromhout[7], Anne-Elie Carsin[1,2,5], Josep Maria Antó[1,2,5,6], Hayat Bentouhami[8], Joost Weyler[8], Joachim Heinrich[9], Dennis Nowak[9], Isabel Urrutia[10], Jesús Martínez-Moratalla[11,12], José Antonio Gullón[13], Antonio Pereira Vega[14], Chantal Raherison Semjen[15], Isabelle Pin[16,17,18], Pascal Demoly[19,20], Bénédicte Leynaert[21], Simona Villani[22], Thorarinn Gislason[23,24], Øistein Svanes[25], Mathias Holm[26], Bertil Forsberg[27], Dan Norbäck[28], Amar J Mehta[29], Dirk Keidel[3,4], David Vernez[30], Geza Benke[31], Rain Jõgi[32], Kjell Torén[33], Torben Sigsgaard[34], Vivi Schlünssen[34,35], Mario Olivieri[36], Paul D Blanc[37], John Watkins[38], Roberto Bono[39], Giulia Squillacioti[39], A. Sonia Buist[40], Roel Vermeulen[7], Deborah Jarvis[41,42], Nicole Probst-Hensch[3,4], Jan-Paul Zock[1,2,5]

1. Barcelona Institute of Global Health (ISGlobal), Barcelona, Spain

2. Universitat Pompeu Fabra (UPF), Barcelona, Spain

3. Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland

4. University of Basel, Basel, Switzerland

5. CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

6. Hospital del Mar Medical Research Institute, Barcelona, Spain

7. IRAS, University of Utrecht, The Netherlands

8. Social Epidemiology and Health Policy, Department of Epidemiology and Social Medicine (ESOC), Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

9. Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Ludwig Maximilians University, Munich, Comprehensive Pneumology Centre Munich, German Centre for Lung Research

For Review Only

10. Pulmonology Department, Galdakao Hospital, Spain

11. Servicio de Neumología, Complejo Hospitalario Universitario, Albacete, Spain

12. Facultad de Medicina Albacete, University of Castilla-La Mancha, Ciudad Real, Spain

13. Respiratory Department, Hospital Universitario San Agustín, Avilés, Asturias, Spain

14. Pulmonology and Allergy Clinical Unit, University Hospital Juan Ramón Jiménez, Huelva, Spain

15. Université de Bordeaux, Inserm, Bordeaux Population Health Research Center, team EPICENE, UMR 1219, Bordeaux, France

16. Department of Pédiatrie, CHU de Grenoble Alpes, Grenoble, France

17. Inserm, U1209, IAB, Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Grenoble, France

18. Université Grenoble Alpes, Grenoble, France

19. University Hospital of Montpellier, Montpellier, France

20. INSERM UMR-S 1136 - Sorbonne Université, Paris, France

21. Inserm UMR 1152-Equipe Epidémiologie, Université Paris Diderot, Paris, France

22. Department of Public Health, Experimental and Forensic Medicine, Unit of Biostatistics and Clinical Epidemiology, University of Pavia, Pavia, Italy

23. Dept. of Respiratory Medicine and Sleep, Landspitali University Hospital 108, Reykjavik, Iceland

24. Faculty of Medicine, University of Iceland, Reykjavik, Iceland

25. Department of Clinical Science, University of Bergen, Norway

26. Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden

27. Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, Umeå, Sweden

28. Uppsala University, Department of Medical Sciences, Uppsala, Sweden

29. Department of Public Health, Section of Epidemiology, University of Copenhagen, Denmark

30. Center for Primary Care and Public Health (Unisante), University of Lausanne, Switzerland

31. Monash Centre for Occupation and Environmental Health, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

32. Tartu University Hospital, Lung Clinic, Estonia, Europe

33. Occupational and environmental medicine, School of Public Health and Community Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

34. Department of Public Health, section for Environment, Occupation and Health, Danish Ramazzini center, Aarhus University, Denmark

35. National Research Center for the Working Environment, Copenhagen, Denmark

36. Unit of Occupational Medicine, Department of Diagnostics and Public Health, University of Verona, Verona,

For Review Only

Italy

37. University of California San Francisco and the San Francisco Veterans Affairs Health Care System~~Medical Center~~, San Francisco, United States

38. School of Medicine, Cardiff University / Public Health Wales, Cardiff, Wales, United Kingdom

39. Department of Public Health and Pediatrics, University of Turin, Turin, Italy

40. Pulmonary and Critical Care Medicine, Oregon Health & Science University, Portland, Oregon, United States

41. Population Health and Occupational Disease, National Heart and Lung Institute,

Imperial College London, London, United Kingdom

42. MRC-PHE Centre for Environment and Health, Imperial College London, London, United Kingdom

Corresponding author: Theodore Lytras, Barcelona Institute of Global Health (ISGlobal), Barcelona, Spain. Tel: +30 6946 814271

For Review Only

Contributorship statement: Study idea & design: TL, ABB, MK, JPZ, NPH, HK, JMA, KT, DJ. Data collection: MK, HK, AEC, JMA, HB, JW, JH, DN, IU, JMM, JAG, APV, CRS, IP, PD, BL, SV, TG, OS, MH, BF, DN, AJM, DK, DV, GB, RJ, KT, TS, VS, MO, PDB, JW, RB, GS, ASB, RV, DJ, NPH, JPZ. Data analysis: TL, ABB, DK, JPZ. Data interpretation: all authors. Initial manuscript draft: TL, ABB, MK, JPZ. Critical revision of the manuscript for important intellectual content: all authors. Final approval of the manuscript for publication: all authors

Funding: None of the study sponsors/funders had any role on study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had full responsibility for the decision to submit for publication. Full funding statement is provided in the online data supplement.

Running head: Occupational exposures and lung function decline

Descriptor number: 1.25 Occupational and Environmental Airways Disease

Word count: 3,~~155~~296

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

For Review Only

Abstract

Rationale: Few longitudinal studies have assessed the relationship between occupational exposures and lung function decline in the general population, with sufficiently long follow-up.

Objectives: Our objective was to examine this potential association in two large cohorts (ECRHS and SAPALDIA).

Methods: General population samples aged 18 to 62 were randomly selected in 1991-1993, and followed up approximately 10 and 20 years later. Spirometry (without bronchodilation) was performed at each visit. Coded complete job histories during follow-up visits were linked to a Job-Exposure Matrix, generating cumulative exposure estimates for 12 occupational exposures. FEV_1 and FVC were jointly modelled in linear mixed-effects models, fitted in a Bayesian framework, taking into account age and smoking.

Main results: A total of 40,024 lung function measurements from 17,833 study participants were analyzed. We found accelerated declines in FEV_1 and the FEV_1/FVC ratio for exposure to biological dust, mineral dust and metals (FEV_1 -15.1ml, -14.4ml and -18.7ml respectively, and FEV_1/FVC -0.52%, -0.43% and -0.36% respectively, per 25 intensity-years of exposure). These declines were comparable in magnitude to those associated with long-term smoking. No effect modification by sex or smoking status was identified. Findings were similar between the ECRHS and SAPALDIA cohorts.

Conclusions: Our results greatly strengthen the evidence base implicating occupation, independent of smoking, as a risk factor for lung function decline and by inference for COPD.~~, which is independent from smoking, and~~ This highlights the need to prevent or control these exposures in the workplace.

For Review Only

Word count: 221~~1~~3.

Keywords: Spirometry; Chronic Obstructive Pulmonary Disease; Occupational Exposure; Occupational Disease; Longitudinal studies

For Review Only

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). The most ~~important~~well-recognized risk factor is tobacco smoking, which is associated with the ~~vast~~ majority of COPD cases. Other environmental risk factors are also implicated in the pathogenesis of COPD (2), including occupational exposures (3). The European Community Respiratory Health Survey (ECRHS) has recently shown a higher incidence of COPD in workers exposed to biological dusts, gases, fumes and pesticides, with a combined population attributable fraction of 21% (4).

Lung function declines naturally with age, but an accelerated decline is a primary, though not obligate, cause of COPD (5), as well as a long-term feature of asthma (6). Despite a large number of studies, both population- and industry based, demonstrating an association of asthma and COPD with occupational exposures (3, 7, 8), relatively few population-based longitudinal studies have examined the relationship between lung function decline and occupational exposures as estimated by a Job-Exposure Matrix (JEM) (9–11). 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 (9); the cohort however was fairly young then (30-55 years old at the time), and the follow-up time may have been too short to detect an association.

Therefore our aim was to examine the association between occupational exposures and the rate of lung function decline, given its relevance to COPD risk. To do so, we combined ~~in~~ two large prospective cohorts participating in the ALEC project (www.alecstudy.org): the ECRHS (12) and the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) (13). Both cohorts have accumulated two decades of follow-up, with more

For Review Only

participants over 50 years of age, thus allowing better and more precise estimates of the determinants of lung function decline. In addition, we examined whether the association between occupation and lung function decline is different between men and women, and between smokers and non-smokers.

Methods

The ECRHS is a multicentre longitudinal study initiated in 1991–1993 that enrolled random general population samples aged 20 to 44 years in 55 centres from 23 countries (12). 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). SAPALDIA is also a multicentre longitudinal study with objectives, methods and protocols very similar to those of the ECRHS, that was initiated in 1991 (SAPALDIA 1) and enrolled a random general population sample aged 18 to 62 years from eight regions in Switzerland (13). SAPALDIA participants were also followed up in 2001 and 2011 (SAPALDIA 2 and 3). A flowchart of study participants from both cohorts can be found in the online supplement (Supplemental Figure 1).

During both follow-ups, participants in both cohorts were asked to provide a detailed list of their occupations and industries from all 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, who were blind to participant status. Ethical approval for each centre was obtained from their respective competent bodies, and written informed consent was obtained from all participants.

For Review Only

The population for this analysis includes all participants who completed spirometry at baseline (ECRHS I / SAPALDIA 1) and were followed up at least once (at ECRHS II / SAPALDIA 2 and/or ECRHS III / SAPALDIA 3). All spirometries were performed without bronchodilation and according to the ATS/ERS standards for reproducibility, utilizing 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 (10). 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); these intensities reflect the lognormal distribution of occupational exposure concentrations when calculating cumulative exposures.

Covariates used for adjustment included at each visit age, sex, height (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 (14). 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

For Review Only

education, and classified into three categories: high (>19 years), middle (16-19 years), low (<16 years).

Associations between cumulative occupational exposures and lung function (FEV_1, FVC and the FEV_1/FVC ratio) were assessed using linear mixed-effects models, providing the mean change in lung function per intensity-year of exposure. FEV_1 and FVC were jointly modelled, and all models included participant-level random intercepts and slopes, taking account of the correlations both between random intercepts and slopes as well as between FEV_1 and FVC. For each ALOHA(+) exposure agent we fitted two joint models, one using absolute FEV_1 and FVC ("linear model") and one using their logarithms as the outcome ("log-linear model"); from the latter 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). In all instances, the comparison was between exposed and unexposed participants to the particular ALOHA(+) agent, not against participants without any occupational exposure.

The models were fitted in a Bayesian framework with the JAGS software, setting non-informative priors for all parameters, and using 4 chains and 20,000 iterations per chain, discarding the first 2,000 as burn-in, and with a thinning interval of 5. 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 (see online supplement for details). Uncertainty for the fixed effects was expressed with 95% Credible Intervals (95% CrI).

In addition to the unstratified models, we fitted another set of models with added interaction terms for sex, and smoking status (ever/never smoker), thereby calculating stratified estimates for the effect of occupational exposures in men and women, and in ever smokers and never

For Review Only

smokers. As a criterion to determine the presence of interaction (effect modification) we used the posterior probability distribution of the interaction term, at least 95% of which should lie above or below zero. We also fitted all models separately to the data from each cohort (ECRHS and SAPALDIA), as a sensitivity analysis.

All analyses were performed with the R statistical environment, version 3.6.0 (15).

For Review Only

Results

Table 1 highlights the characteristics of the study population. We analyzed a total of 40,024 lung function measurements from 17,833 study participants across 38 ECRHS and SAPALDIA centres who completed at least one follow-up visit after baseline, with a mean follow-up duration of 16.3 years (range 4.3–22.6 years). Of these participants, 10,803 (60.6%) completed both visits over a mean duration of 19.6 years (range 15.7–22.6 years). 5,793 (32.5%) participants completed the initial and first follow-up visits only, while 1,237 (6.9%) completed the initial and second follow-up visits only. Slightly less than half of our sample had never smoked, and about a third were current smokers at baseline, dropping almost by half to 18.3% at the second follow-up. A little less than half of all participants had been occupationally exposed to VGDF at some point during follow-up (39.8%), whereas fewer had been exposed to solvents (24.2%), metals (9.3%) or pesticides (3.3%). Men were overall more likely than women to be occupationally exposed to most agents, with the exception of biological dust (Table 2). In addition, many exposures showed substantial overlap with each other (Figure 1). A list of the most common jobs by exposure category can be found online (Supplemental Table 1).

Lifetime smoking pack-years were missing in 7.8% of all observations, and had to be imputed in our models as described in the "Methods" section; also current smoking status was missing in 2.9%, current asthma in 0.5% and SES in 1.1% of all observations. Lung function in the study population naturally declined with advancing age across both follow-ups, and our Bayesian mixed-effects model was reliable in describing both mean lung function by age as well as the variability around the mean (Figure 2).

Table 3 summarizes the main results from our analysis, i.e. the effect of 25 intensity-years of occupational exposure to each ALOHA(+) agent on the three lung function parameters (FEV_1, FVC and the FEV_1/FVC ratio), both overall and stratified by sex and smoking status. A negative sign indicates reduced lung function compare to no occupational exposure to the respective agent given the same age, sex and other covariates, i.e. an accelerated lung function decline, whereas a positive number indicates a slower lung function decline. As the numbers are very small, the effect per 25 intensity-years is presented rather than per one intensity-year of exposure.

A decreased FEV_1/FVC ratio was observed for biological dust and mineral dust exposure (-0.52% and -0.43% respectively, Table 3), which was purely attributed to a FEV_1 decline (-15.08 ml and -14.42 ml respectively) with no change in FVC. A significant decline in FEV_1 only was also observed for metals exposure (-18.73 ml, 95% CrI -34.41 to -2.60 ml), as well as a lower FEV_1/FVC ratio for the composite VGDF exposure (-0.34%, 95% CrI -0.56 to -0.12%). On the other hand, smaller lung function declines were seen for gases & fumes (-7.35 ml in FEV_1 and -0.24% in FEV_1/FVC), and also for pesticides, especially in terms of FEV_1, although the results were very imprecise, with a wider 95% CrI than other exposures (Table 3). Among solvents, only exposure to chlorinated solvents was weakly associated with both lower FEV_1 and lower FVC (-16.98 ml and -14.59 ml). For comparison, as estimated in the

For Review Only

model, 25 pack-years of smoking reduced FEV1 by an additional -11.07 ml (95% CrI -22.27 to 2.49 ml), FVC by -14.83 ml (95% CrI -32.29 to -0.55 ml) and FEV1/FVC by -0.21% (95% CrI -0.44 to 0.03%). Also, current asthma was associated with a FEV1 that was -80.28 ml lower (95% CrI -92.72 to -67.71 ml), a FVC lower by -13.60 ml (95% CrI -27.44 to -0.05 ml) and a FEV1/FVC -2.16% lower (95% CrI -2.52 to -1.81%).

No effect modification by sex was detected for any occupational exposure and any lung function parameter, with one exception: women exposed to aromatic solvents had a slower FVC decline than unexposed women (+86.87 ml, 95% CrI 13.80 to 161.25 ml), whereas no significant difference was found among men (-7.84 ml, 95% CrI -34.96 to 20.18 ml). In addition, no effect modification by smoking status was detected, although in most cases the effects of occupational exposures in ever smokers tended to be slightly lower than in never smokers (Table 3). In the sensitivity analysis, results were similar between the two cohorts and showed wide overlap; pesticide exposure resulted in greater FEV_1 decline among ECRHS participants, while solvents resulted in slightly greater declines among SAPALDIA participants (Supplemental~~ry~~ Table ~~1~~2).

For Review Only

Discussion

In this pooled analysis from two large longitudinal cohorts we showed that certain groups of occupational exposures, namely biological dust, mineral dust and metals exposure, were prospectively associated with accelerated lung function decline, specifically with respect to FEV1 and the FEV1/FVC ratio. This loss of lung function is comparable to that associated with smoking, highlighting the importance of these occupational exposures in respiratory health. Our study provides significant new evidence on the topic, as few such studies have

examined longitudinal lung function decline and in a general population setting (10, 11, 16–18). 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. Previous analyses from both ECRHS and SAPALDIA have shown an increased asthma risk for certain occupational exposures (19), an increased incidence of COPD in participants occupationally exposed to biological dust and mineral dust (4, 20), as well as an increased incidence of chronic cough and chronic phlegm symptoms in those exposed to mineral dust and metals (21). Our current analysis corroborates previous findings for biological dust in a much larger study population with additional follow-up. It also indicates that mineral dust and metals exposure are associated also with lung function decline and not only with chronic bronchitis symptoms. The latter result is in agreement with recent findings from the smaller Tasmanian longitudinal Health Study (TAHS) cohort (22), as well as with a systematic review of exposure to welding fumes and lung function decline (23).

A striking finding is the very small absolute effect sizes observed, only a few millilitres (or a fraction of a percentage point) of lung function decline after 25 intensity-years of exposure, which for many workers may represent their entire lifetime exposure. At first glance such reductions could not plausibly account for an increased COPD risk as seen in previous analyses (4, 8, 20); however, these are average subject-specific effects over an exposure group, and small average reductions can mask a larger effect for certain individuals inside the group (24), especially if one also considers the sizeable individual variation in lung function (Figure 2). In addition, the comparator is not a fully occupationally unexposed group, but rather participants unexposed to the agent under consideration (who may have other occupational exposures). Furthermore, non-differential misclassification is the main limitation

For Review Only

in using JEMs in population-based occupational epidemiology studies, mostly stemming from the variability in job tasks and actual exposures between workers belonging in the same JEM exposure category (25). Grouping exposures in a JEM does not in itself bias regression coefficients towards the null, but rather results in imprecision due to Berkson-type error (26); nevertheless, regression dilution bias can be introduced if the estimated group mean is different than the true group mean (27). Intra-individual variability in exposure over time is another consideration, which is particularly relevant when calculating a cumulative exposure estimate based on job duration and a JEM classification, in this case over a long period of 20 years (28). All these factors mean that the small average declines observed in our analysis should not be used for prediction, as they are unlikely to represent the actual magnitude of the effect of these exposures on lung function, in any particular individual. For the same reasons, our results cannot definitively rule out an effect of occupational solvent exposure on lung function as recently observed in the TAHS cohort (22), nor an effect of pesticide exposure (4, 10). Especially as regards pesticides, the small percentage of exposed participants (less than 5% – Table 2) has substantially reduced precision, as reflected in the wider credible intervals of the lung function decline estimates.

Smoking is known to induce inflammation and impair the host defense mechanisms of the lung (29, 30), and has been reported to increase the adverse effect of occupational exposures on lung function decline and COPD risk (31–33). However, in our analyses we found little evidence of effect modification by smoking, after tightly adjusting both for current smoking status and cumulative pack-years. This indicates that all workers may be at risk of airway obstruction due to these occupational exposures, even though this may be more clinically significant for smokers, who represent the majority of COPD patients in most countries, and who already have lower levels of lung function and any additional loss or acceleration of

For Review Only

decline may push them over the diagnostic cutoff. Similarly, we found little difference between men and women on the effect of occupational exposures, even though the distribution of jobs per each exposure category was different between men and women. This may partially be explained by the lower proportion of occupationally exposed women in our cohorts, particularly for exposures like metals, pesticides and solvents. Future occupational epidemiology studies should try to recruit more women, in order to investigate effect modification by sex.

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 involved. Lung function was modelled in great detail, using a mixed-effects model with random intercepts and slopes, and accounting for the correlation between FEV1 and FVC; joint modelling of both spirometric parameters is important, as we identified positive correlations not just between the participant-level random intercepts and slopes for FEV1 and for FVC, but also between the intercepts for FEV1 and FVC and the slopes for FEV1 and FVC (data not shown). In addition we controlled for multiple confounders, including socioeconomic status, current asthma and especially lifetime smoking pack-years, in order to minimize confounding by intensity of smoking. The sample size was very large, thanks to the pooling of two large cohorts, facilitating the detection of associations of very small magnitude.

On the other hand, there are certain limitations to our study. Spirometries were performed without bronchodilation, and the results should be interpreted accordingly. Accelerated lung function decline in and of itself does not equate with COPD risk; in particular, ~~As~~ occupation ~~is~~can also be a risk factor for asthma, thus it is not possible to distinguish lung function

For Review Only

decline due to new-onset occupational asthma from that contributing to increased COPD incidence. The application of a JEM may ensure more objective exposure estimates, free from exposure-specific recall, but can introduce both imprecision due to Berkson-type error and some bias towards the null; therefore, despite the large sample size, it may not have been always sufficient to detect an association, e.g. for the effects of pesticides or to identify effect modification. For the same reason, we cannot disentangle the effect of multiple overlapping exposures, which would require a large number of small subgroup analyses. We could also not assess heterogeneity of the results across study centres or countries, since the (necessary) inclusion of participant-level random effects left almost no variance to be explained by study centre. Finally, residual confounding cannot be completely ruled out despite the detailed model adjustments, and may have affected the observed associations given their small magnitude. As this is an observational study, some selection and response bias also cannot be definitely ruled out.

In conclusion, long-term occupational exposure to biological dust, mineral dust and metals over two decades of follow-up was associated with an accelerated decline in FEV_1 and the FEV_1/FVC ratio, which would translate to an increased risk of airways obstruction and COPD. This decline was comparable to that associated with smoking, and similar between men and women as well as between smokers and non-smokers. These results strengthen the case for occupation as a modifiable risk factor for asthma and COPD, in agreement with previous studies. And they make the case for avoiding these exposures in the workplace, or controlling them with appropriate protective measures, in order to protect the respiratory health of workers.

For Review Only

Bibliography

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2017 report. 2017;
2. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, Romieu I, Silverman EK, Balmes JR. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;182:693–718.
3. Blanc PD, Annesi-Maesano I, Balmes JR, Cummings KJ, Fishwick D, Miedinger D, Murgia N, Naidoo RN, Reynolds CJ, Sigsgaard T, Torén K, Vinnikov D, Redlich CA. The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement. *Am J Respir Crit Care Med* 2019;199:1312–1334.
4. Lytras T, Kogevinas M, Kromhout H, Carsin A-E, Antó JM, Bentouhami H, Weyler J, Heinrich J, Nowak D, Urrutia I, Martinez-Moratalla J, Gullón JA, Pereira-Vega A, Raherison-Semjen C, Pin I, Demoly P, Leynaert B, Villani S, Gislason T, Svanes C, Holm M, Forsberg B, Norbäck D, Mehta AJ, Probst-Hensch N, Benke G, Jogi R, Torén K, Sigsgaard T, *et al.* Occupational exposures and 20-year incidence of COPD: the European Community Respiratory Health Survey. *Thorax* 2018;73:1008–1015.
5. Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, Guerra S, Marott JL, Martinez FD, Martinez-Camblor P, Meek P, Owen CA, Petersen H, Pinto-Plata V, Schnohr P, Sood A, Soriano JB, Tesfaigzi Y, Vestbo J. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2015;373:111–122.
6. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194–1200.
7. Omland O, Würtz ET, Aasen TB, Blanc P, Brisman JB, Miller MR, Pedersen OF, Schlünssen V, Sigsgaard T, Ulrik CS, Viskum S. Occupational chronic obstructive pulmonary disease: a systematic literature review. *Scand J Work Environ Health* 2014;40:19–35.
8. De Matteis S, Jarvis D, Darnton A, Hutchings S, Sadhra S, Fishwick D, Rushton L, Cullinan P.

For Review Only

The occupations at increased risk of COPD: analysis of lifetime job-histories in the population-based UK Biobank Cohort. *Eur Respir J* 2019;54:.

9. Sunyer J, Zock JP, Kromhout H, Garcia-Esteban R, Radon K, Jarvis D, Toren K, Künzli N, Norbäck D, d'Errico A, Urrutia I, Payo F, Olivieri M, Villani S, Van Sprundel M, Antó JM, Kogevinas M, Occupational Group of the European Community Respiratory Health Survey. Lung function decline, chronic bronchitis, and occupational exposures in young adults. *Am J Respir Crit Care Med* 2005;172:1139–1145.
10. de Jong K, Boezen HM, Kromhout H, Vermeulen R, Postma DS, Vonk JM. Association of occupational pesticide exposure with accelerated longitudinal decline in lung function. *Am J Epidemiol* 2014;179:1323–1330.
11. Liao S-Y, Lin X, Christiani DC. Occupational exposures and longitudinal lung function decline. *Am J Ind Med* 2015;58:14–20.
12. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954–960.
13. Martin BW, Ackermann-Liebrich U, Leuenberger P, Künzli N, Stutz EZ, Keller R, Zellweger JP, Wüthrich B, Monn C, Blaser K, Bolognini G, Bongard JP, Brändli O, Braun P, Defila C, Domenighetti G, Grize L, Karrer W, Keller-Wossidlo H, Medici TC, Peeters A, Perruchoud AP, Schindler C, Schoeni MH, Villiger B. SAPALDIA: methods and participation in the cross-sectional part of the Swiss Study on Air Pollution and Lung Diseases in Adults. *Soz Praventivmed* 1997;42:67–84.
14. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, de Marco R, Norbäck D, Raherison C, Villani S, Wjst M, Svanes K, Antó JM. Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010;65:14–20.
15. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2019. at <http://www.R-project.org/>.
16. Kauffmann F, Drouet D, Lellouch J, Brille D. Occupational exposure and 12-year spirometric changes among Paris area workers. *Br J Ind Med* 1982;39:221–232.
17. Krzyzanowski M, Jedrychowski W, Wysocki M. Factors associated with the change in ventilatory

For Review Only

function and the development of chronic obstructive pulmonary disease in a 13-year follow-up of the Cracow Study. Risk of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;134:1011–1019.

18. Harber P, Tashkin DP, Simmons M, Crawford L, Hnizdo E, Connett J, Lung Health Study Group. Effect of occupational exposures on decline of lung function in early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;176:994–1000.
19. Kogevinas M, Zock J-P, Jarvis D, Kromhout H, Lillienberg L, Plana E, Radon K, Torén K, Alliksoo A, Benke G, Blanc PD, Dahlman-Hoglund A, D'Errico A, Héry M, Kennedy S, Kunzli N, Leynaert B, Mirabelli MC, Muniozguren N, Norbäck D, Olivieri M, Payo F, Villani S, van Sprundel M, Urrutia I, Wieslander G, Sunyer J, Antó JM. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet* 2007;370:336–341.
20. Mehta AJ, Miedinger D, Keidel D, Bettschart R, Bircher A, Bridevaux P-O, Curjuric I, Kromhout H, Rochat T, Rothe T, Russi EW, Schikowski T, Schindler C, Schwartz J, Turk A, Vermeulen R, Probst-Hensch N, Künzli N, SAPALDIA Team. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. *Am J Respir Crit Care Med* 2012;185:1292–1300.
21. Lytras T, Kogevinas M, Kromhout H, Carsin A-E, Antó JM, Bentouhami H, Weyler J, Heinrich J, Nowak D, Urrutia I, Martínez-Moratalla J, Gullón JA, Vega AP, Raherison Semjen C, Pin I, Demoly P, Leynaert B, Villani S, Gíslason T, Svanes Ø, Holm M, Forsberg B, Norbäck D, Mehta AJ, Probst-Hensch N, Benke G, Jogi R, Torén K, Sigsgaard T, *et al.* Occupational exposures and incidence of chronic bronchitis and related symptoms over two decades: the European Community Respiratory Health Survey. *Occup Environ Med* 2019;76:222–229.
22. Alif SM, Dharmage S, Benke G, Dennekamp M, Burgess J, Perret JL, Lodge C, Morrison S, Johns DP, Giles G, Gurrin L, Thomas PS, Hopper JL, Wood-Baker R, Thompson B, Feather I, Vermeulen R, Kromhout H, Jarvis D, Garcia Aymerich J, Walters EH, Abramson MJ, Matheson MC. Occupational exposure to solvents and lung function decline: A population based study.

For Review Only

Thorax 2019;doi:10.1136/thoraxjnl-2018-212267.

23. Szram J, Schofield SJ, Cosgrove MP, Cullinan P. Welding, longitudinal lung function decline and chronic respiratory symptoms: a systematic review of cohort studies. *Eur Respir J* 2013;42:1186–1193.
24. Petersen H, Sood A, Meek PM, Shen X, Cheng Y, Belinsky SA, Owen CA, Washko G, Pinto-Plata V, Kelly E, Celli B, Tesfaigzi Y. Rapid lung function decline in smokers is a risk factor for COPD and is attenuated by angiotensin-converting enzyme inhibitor use. *Chest* 2014;145:695–703.
25. Kauppinen TP. Assessment of exposure in occupational epidemiology. *Scand J Work Environ Health* 1994;20 Spec No:19–29.
26. Tielemans E, Kupper LL, Kromhout H, Heederik D, Houba R. Individual-based and group-based occupational exposure assessment: some equations to evaluate different strategies. *Ann Occup Hyg* 1998;42:115–119.
27. Armstrong BG. The effects of measurement errors on relative risk regressions. *Am J Epidemiol* 1990;132:1176–1184.
28. Preller L, Kromhout H, Heederik D, Tielen MJ. Modeling long-term average exposure in occupational exposure-response analysis. *Scand J Work Environ Health* 1995;21:504–512.
29. Herr C, Beisswenger C, Hess C, Kandler K, Suttorp N, Welte T, Schroeder J-M, Vogelmeier C, R Bals for the CAPNETZ Study Group. Suppression of pulmonary innate host defence in smokers. *Thorax* 2009;64:144–149.
30. Lugade AA, Bogner PN, Thatcher TH, Sime PJ, Phipps RP, Thanavala Y. Cigarette smoke exposure exacerbates lung inflammation and compromises immunity to bacterial infection. *J Immunol* 2014;192:5226–5235.
31. Boggia B, Farinaro E, Grieco L, Lucariello A, Carbone U. Burden of smoking and occupational exposure on etiology of chronic obstructive pulmonary disease in workers of Southern Italy. *J Occup Environ Med* 2008;50:366–370.
32. Blanc PD, Iribarren C, Trupin L, Earnest G, Katz PP, Balmes J, Sidney S, Eisner MD. Occupational exposures and the risk of COPD: dusty trades revisited. *Thorax* 2009;64:6–12.

For Review Only

33. Hu Y, Chen B, Yin Z, Jia L, Zhou Y, Jin T. Increased risk of chronic obstructive pulmonary diseases in coke oven workers: interaction between occupational exposure and smoking. *Thorax* 2006;61:290–295.

For Review Only

Figure Legends

Figure 1: Correlation matrix (Spearman's rho) between cumulative occupational exposures (intensity-years) in the study population, as estimated by the ALOHA(+) JEM. (N=17,833 ECRHS and SAPALDIA participants)

Figure 2: Lung function by age and sex in the study population, observed and model-predicted. (N=40,024 measurements in 17,833 ECRHS and SAPALDIA participants)

Footnote for Figure 2:

Height set to cohort mean by sex; smoking pack-years and cumulative VGDF exposure set to cohort mean by age and sex.

For Review Only

Table 1: Characteristics of study participants, by study wave. (N=17,833 ECRHS and SAPALDIA participants followed-up at least once)*

	ECRHS I / SAPALDIA 1	ECRHS II / SAPALDIA 2	ECRHS III / SAPALDIA 3
Number of participants	17833 (9765 / 8068)	16596 (8725 / 7871)	12040 (6013 / 6027)
% men	48.0 (48.0 / 47.9)	48.1 (48.1 / 48.0)	47.7 (47.9 / 47.5)
Mean age	37.2 (34.0 / 41.0)	47.2 (42.8 / 52.0)	56.9 (54.1 / 59.7)
% current asthma	6.4 (7.9 / 4.7)	7.9 (9.9 / 5.6)	7.6 (11.2 / 4.1)
% never smokers	46.0 (44.8 / 47.4)	45.9 (45.5 / 46.4)	48.5 (49.0 / 48.1)
% current smokers	33.3 (34.5 / 31.9)	27.7 (29.0 / 26.3)	18.3 (18.1 / 18.5)
Mean cumulative smoking pack-years	8.4 (7.2 / 10.0)	11.1 (9.7 / 12.7)	11.7 (10.9 / 12.3)
% of participants exposed			
Biological dust	-	22.0 (26.6 / 17.0)	26.7 (30.7 / 22.6)
Mineral Dust	-	17.6 (21.1 / 13.8)	20.9 (23.9 / 18.0)
Gases & fumes	-	31.7 (37.4 / 25.4)	37.4 (41.3 / 33.5)
Vapors, Gases, Dusts & Fumes	-	35.8 (41.9 / 29.2)	42.0 (46.1 / 37.9)
Herbicides	-	1.7 (1.5 / 1.9)	2.2 (1.8 / 2.6)
Insecticides	-	2.1 (2.3 / 1.9)	2.8 (2.9 / 2.6)
Fungicides	-	2.2 (2.4 / 2.0)	3.1 (3.4 / 2.8)
All pesticides	-	2.7 (3.2 / 2.1)	3.6 (4.3 / 3.0)
Aromatic solvents	-	11.4 (13.1 / 9.6)	13.5 (14.9 / 12.1)
Chlorinated solvents	-	9.1 (10.3 / 7.7)	10.9 (12.2 / 9.6)
Other solvents	-	19.4 (23.0 / 15.3)	23.6 (26.9 / 20.4)
Metals	-	7.9 (9.5 / 6.1)	9.7 (11.4 / 8.0)
Mean cumulative exposures since previous follow-up (intensity-years)			
Biological dust	-	2.2 (2.2 / 2.1)	4.1 (4.7 / 3.6)
Mineral Dust	-	2.3 (2.4 / 2.2)	4.1 (4.7 / 3.5)
Gases & fumes	-	3.6 (3.9 / 3.3)	6.6 (7.7 / 5.4)
Vapors, Gases, Dusts & Fumes	-	5.1 (5.3 / 4.8)	9.2 (10.6 / 7.9)
Herbicides	-	0.2 (0.1 / 0.3)	0.4 (0.3 / 0.6)
Insecticides	-	0.4 (0.3 / 0.6)	0.8 (0.6 / 1.1)
Fungicides	-	0.3 (0.3 / 0.4)	0.6 (0.6 / 0.6)
All pesticides	-	0.5 (0.4 / 0.6)	0.9 (0.7 / 1.1)
Aromatic solvents	-	1.0 (1.0 / 1.0)	1.7 (1.9 / 1.6)
Chlorinated solvents	-	1.2 (1.2 / 1.2)	1.9 (2.1 / 1.7)
Other solvents	-	1.7 (1.8 / 1.6)	3.2 (3.7 / 2.7)
Metals	-	1.2 (1.3 / 1.1)	2.0 (2.3 / 1.7)

* Data for the entire cohort (data for ECRHS / data for SAPALDIA)

For Review Only

Table 2: Proportion of participants with any occupational exposure during follow-up, stratified by sex. (N=17,833 ECRHS and SAPALDIA participants followed-up at least once)*

	% of men exposed	% of women exposed
Biological dust	22.2 (25.5 / 18.2)	27.7 (32.5 / 22.0)
Mineral Dust	28.8 (33.6 / 23.1)	11.8 (13.4 / 10.0)
Gases & fumes	42.7 (47.9 / 36.4)	29.0 (33.2 / 23.8)
Vapors, Gases, Dusts & Fumes	46.3 (51.8 / 39.7)	33.8 (38.2 / 28.4)
Herbicides	2.8 (2.5 / 3.1)	1.2 (1.0 / 1.5)
Insecticides	3.5 (3.8 / 3.1)	1.6 (1.6 / 1.5)
Fungicides	4.1 (4.7 / 3.4)	1.5 (1.4 / 1.6)
All pesticides	4.9 (5.9 / 3.7)	1.7 (1.8 / 1.6)
Aromatic solvents	21.5 (23.6 / 18.8)	5.0 (5.9 / 3.8)
Chlorinated solvents	16.8 (18.7 / 14.5)	4.5 (5.2 / 3.7)
Other solvents	25.5 (28.4 / 22.0)	18.9 (22.7 / 14.4)
Metals	17.3 (20.1 / 13.9)	1.8 (2.4 / 1.0)

* Data for the entire cohort (data for ECRHS / data for SAPALDIA)

For Review Only

Table 3: Effect of occupational exposures on lung function decline, per 25 intensity-years of exposure, compared to unexposed to the respective agent, overall and stratified by sex and smoking status. (N=17,833 ECRHS and SAPALDIA participants followed-up at least once)*

	FEV1 (ml)		FVC (ml)		FEV1FVC (%)	
Biological dust	**-15.08 (-28.66, -0.88)**		2.68 (-12.68, 18.28)		**-0.52 (-0.88, -0.16)**	
Never smokers, men / women	-3.23 (-26.67, 20.22)	-14.38 (-45.32, 15.59)	13.44 (-12.79, 39.41)	8.35 (-25.83, 43.27)	-0.28 (-0.95, 0.41)	-0.52 (-1.35, 0.36)
Ever smokers, men / women	-15.86 (-33.93, 2.09)	**-27.11 (-53.91, -1.19)**	-0.47 (-20.80, 19.98)	-5.59 (-35.49, 24.14)	**-0.52 (-1.02, -0.02)**	**-0.76 (-1.46, -0.04)**
Mineral Dust	**-14.42 (-26.41, -2.50)**		0.12 (-12.99, 13.10)		**-0.43 (-0.75, -0.10)**	
Never smokers, men / women	-9.38 (-28.04, 9.65)	5.55 (-29.53, 39.95)	10.96 (-10.24, 31.96)	15.54 (-22.24, 53.37)	**-0.56 (-1.10, -0.02)**	-0.31 (-1.23, 0.61)
Ever smokers, men / women	**-20.83 (-35.33, -6.25)**	-6.15 (-37.68, 24.57)	-7.12 (-23.55, 9.48)	-2.42 (-37.19, 33.52)	**-0.44 (-0.84, -0.03)**	-0.18 (-1.01, 0.65)
Gases & fumes	-7.35 (-17.99, 3.15)		3.46 (-8.66, 15.25)		-0.24 (-0.53, 0.04)	
Never smokers, men / women	4.22 (-12.83, 21.44)	-10.01 (-39.00, 19.03)	14.43 (-4.90, 33.41)	11.31 (-22.02, 43.81)	-0.14 (-0.64, 0.35)	-0.38 (-1.16, 0.43)
Ever smokers, men / women	-10.22 (-23.34, 3.14)	-24.37 (-51.63, 3.81)	-2.14 (-16.77, 12.32)	-5.52 (-36.24, 25.02)	-0.24 (-0.59, 0.11)	-0.48 (-1.24, 0.24)
Vapors, Gases, Dusts & Fumes	-7.42 (-15.93, 1.03)		6.02 (-3.04, 15.42)		**-0.34 (-0.56, -0.12)**	
Never smokers, men / women	-1.44 (-14.83, 11.91)	-6.21 (-28.65, 16.31)	11.89 (-2.73, 26.67)	14.92 (-10.55, 39.96)	-0.27 (-0.65, 0.11)	-0.47 (-1.06, 0.13)
Ever smokers, men / women	-9.45 (-19.62, 0.97)	-14.20 (-35.47, 7.03)	1.76 (-9.68, 13.41)	5.14 (-18.42, 28.40)	**-0.33 (-0.61, -0.06)**	-0.52 (-1.06, 0.01)
Herbicides	-14.69 (-49.54, 20.57)		-8.57 (-47.42, 29.56)		-0.34 (-1.28, 0.59)	
Never smokers, men / women	-19.16 (-85.70, 43.26)	35.35 (-51.37, 122.19)	-23.73 (-96.58, 48.69)	22.63 (-73.97, 120.70)	-0.28 (-2.17, 1.65)	0.55 (-1.85, 3.00)
Ever smokers, men / women	-33.13 (-77.76, 11.56)	21.78 (-46.93, 91.26)	-20.84 (-72.01, 28.90)	26.82 (-50.71, 104.30)	-0.67 (-1.88, 0.55)	0.12 (-1.71, 2.05)
Insecticides	-7.24 (-29.73, 15.04)		-2.43 (-27.68, 23.16)		-0.23 (-0.83, 0.38)	
Never smokers, men / women	-7.72 (-47.54, 32.36)	22.94 (-28.06, 74.16)	3.48 (-40.41, 46.91)	35.24 (-22.53, 92.33)	-0.50 (-1.60, 0.65)	-0.21 (-1.64, 1.20)
Ever smokers, men / women	-20.10 (-51.00, 10.02)	10.06 (-31.78, 52.25)	-18.67 (-53.26, 15.24)	12.87 (-34.21, 58.71)	-0.24 (-1.06, 0.60)	0.04 (-1.07, 1.17)
Fungicides	-13.68 (-41.81, 14.97)		-11.45 (-43.33, 20.68)		-0.17 (-0.97, 0.61)	
Never smokers, men / women	-22.51 (-72.85, 28.73)	28.10 (-41.07, 98.08)	-12.06 (-67.76, 43.25)	38.65 (-39.70, 114.70)	-0.46 (-1.98, 1.03)	0.03 (-1.88, 1.96)
Ever smokers, men / women	-28.92 (-66.48, 8.72)	21.69 (-36.93, 79.10)	-29.25 (-69.81, 12.87)	21.37 (-45.18, 87.03)	-0.26 (-1.31, 0.77)	0.23 (-1.37, 1.85)
All pesticides	-10.74 (-32.37, 10.90)		-6.60 (-31.35, 18.95)		-0.20 (-0.78, 0.39)	

For Review Only

	FEV1 (ml)		FVC (ml)		FEV1FVC (%)	
Never smokers, men / women	-16.23 (-55.54, 22.68)	17.02 (-34.02, 66.51)	-7.92 (-52.14, 36.53)	27.85 (-26.88, 84.30)	-0.42 (-1.50, 0.69)	-0.18 (-1.58, 1.25)
Ever smokers, men / women	-22.87 (-52.79, 7.68)	10.42 (-30.63, 51.27)	-21.70 (-55.53, 11.46)	14.28 (-32.80, 59.60)	-0.23 (-1.00, 0.58)	0.01 (-1.05, 1.12)
Aromatic solvents	0.28 (-22.53, 23.42)		3.90 (-21.95, 29.65)		0.01 (-0.61, 0.63)	
Never smokers, men / women	-12.82 (-49.46, 24.15)	40.35 (-32.52, 113.02)	-13.70 (-53.99, 25.40)	79.39 (-1.55, 159.07)	-0.08 (-1.18, 1.02)	-0.17 (-2.14, 1.82)
Ever smokers, men / women	-2.34 (-30.95, 26.43)	51.06 (-15.10, 117.27)	-3.31 (-36.96, 28.35)	**89.92 (14.99, 162.53)**	0.07 (-0.71, 0.84)	-0.02 (-1.77, 1.81)
Chlorinated solvents	-16.98 (-34.20, 0.43)		-14.59 (-33.52, 4.42)		-0.18 (-0.64, 0.29)	
Never smokers, men / women	-13.31 (-42.06, 14.73)	5.43 (-61.00, 72.39)	-10.47 (-40.24, 21.30)	31.80 (-42.25, 106.20)	-0.19 (-1.01, 0.64)	-0.14 (-2.00, 1.79)
Ever smokers, men / women	-20.45 (-40.67, 0.17)	-1.38 (-67.59, 65.47)	-20.98 (-43.51, 1.47)	21.02 (-51.04, 93.25)	-0.19 (-0.73, 0.37)	-0.14 (-1.89, 1.67)
Other solvents	-6.05 (-23.61, 11.37)		7.65 (-11.39, 27.28)		-0.24 (-0.70, 0.24)	
Never smokers, men / women	3.67 (-28.12, 36.60)	-11.05 (-46.12, 24.35)	22.33 (-14.03, 58.55)	17.37 (-22.07, 55.83)	-0.32 (-1.25, 0.61)	-0.56 (-1.53, 0.39)
Ever smokers, men / women	-0.76 (-26.90, 26.20)	-15.35 (-43.67, 12.26)	5.32 (-23.18, 36.10)	-0.01 (-32.23, 32.14)	-0.06 (-0.73, 0.63)	-0.29 (-1.04, 0.44)
Metals	**-18.73 (-34.41, -2.60)**		-10.17 (-27.46, 7.85)		-0.36 (-0.79, 0.07)	
Never smokers, men / women	-11.75 (-37.20, 14.07)	-30.34 (-110.04, 48.64)	0.82 (-27.55, 29.57)	-36.03 (-123.98, 50.88)	-0.47 (-1.20, 0.26)	-0.43 (-2.59, 1.81)
Ever smokers, men / women	**-21.37 (-40.42, -2.68)**	-39.73 (-118.34, 35.47)	-13.01 (-34.08, 8.36)	-49.46 (-135.45, 35.93)	-0.30 (-0.84, 0.21)	-0.24 (-2.38, 1.91)

*Results are posterior medians and 95% CrI in parentheses. Numbers represent absolute change in ml for FEV1 and FVC, and relative %change for FEV1/FVC. A negative sign indicates a lower value compared to fully unexposed to the respective agent. Adjusted for age, sex, current smoking, cumulative smoking pack-years, socioeconomic status and early life disadvantage score. All lung function measurements are without bronchodilation.

For Review Only

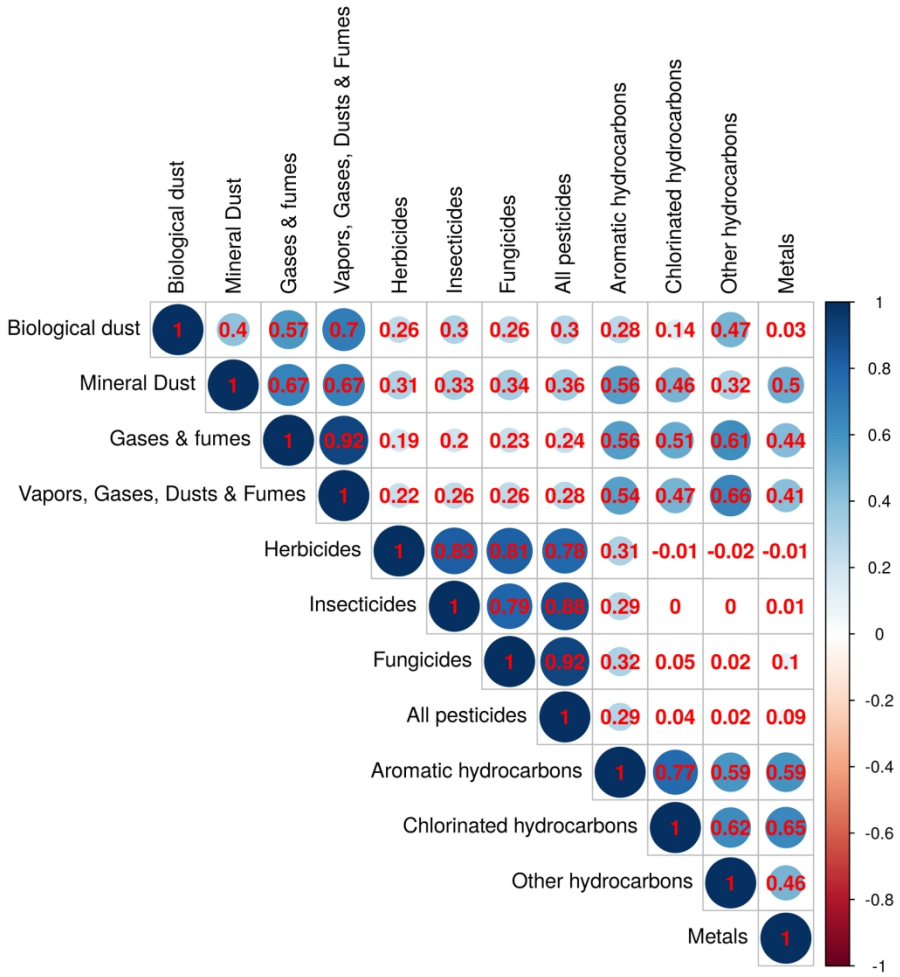


Figure 1: Correlation matrix (Spearman's rho) between cumulative occupational exposures (intensity-years) in the study population, as estimated by the ALOHA(+) JEM. (N=17,833 ECRHS and SAPALDIA participants)

203x203mm (300 x 300 DPI)

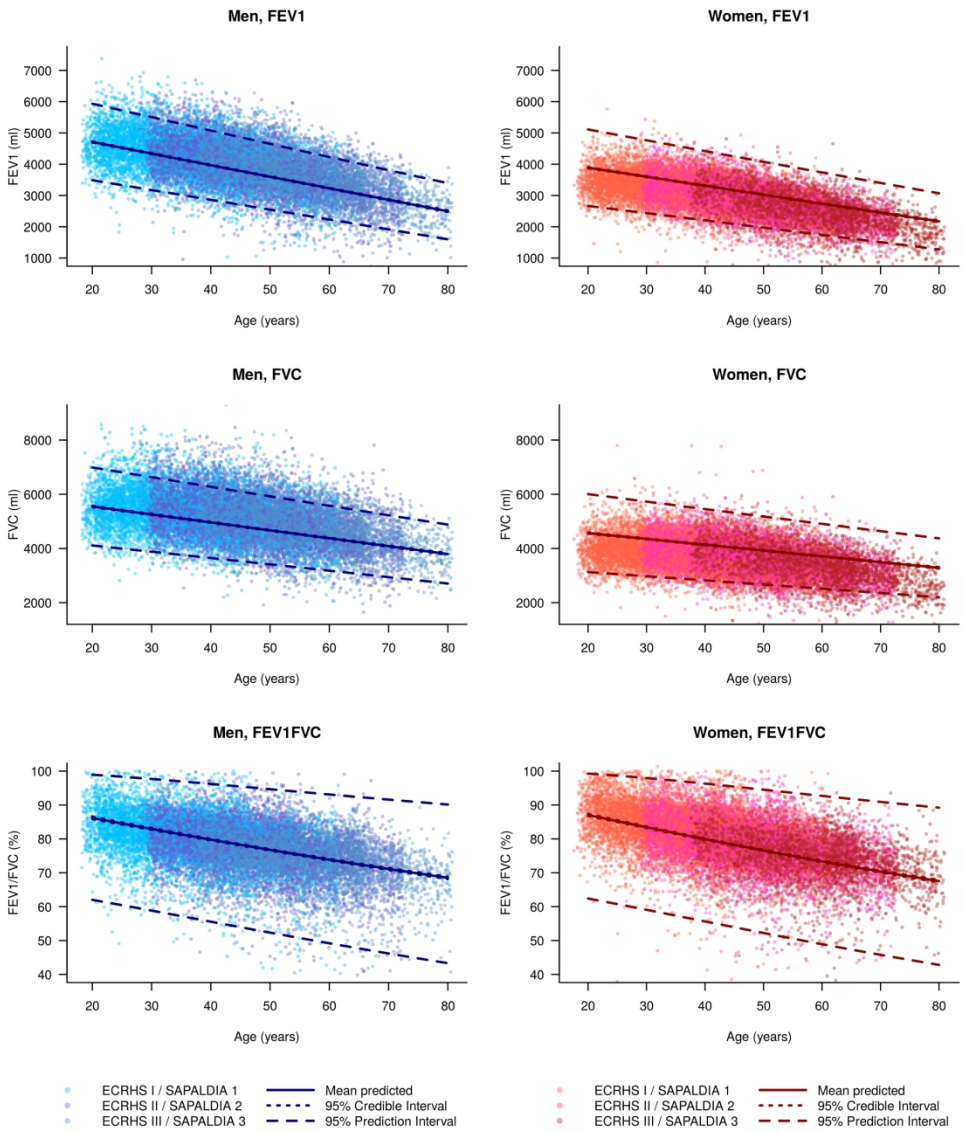


Figure 2: Lung function by age and sex in the study population, observed and model-predicted. (N=40,024 measurements in 17,833 ECRHS and SAPALDIA participants)

Footnote for Figure 2: Height set to cohort mean by sex; smoking pack-years and cumulative VGDF exposure set to cohort mean by age and sex.

217x254mm (300 x 300 DPI)

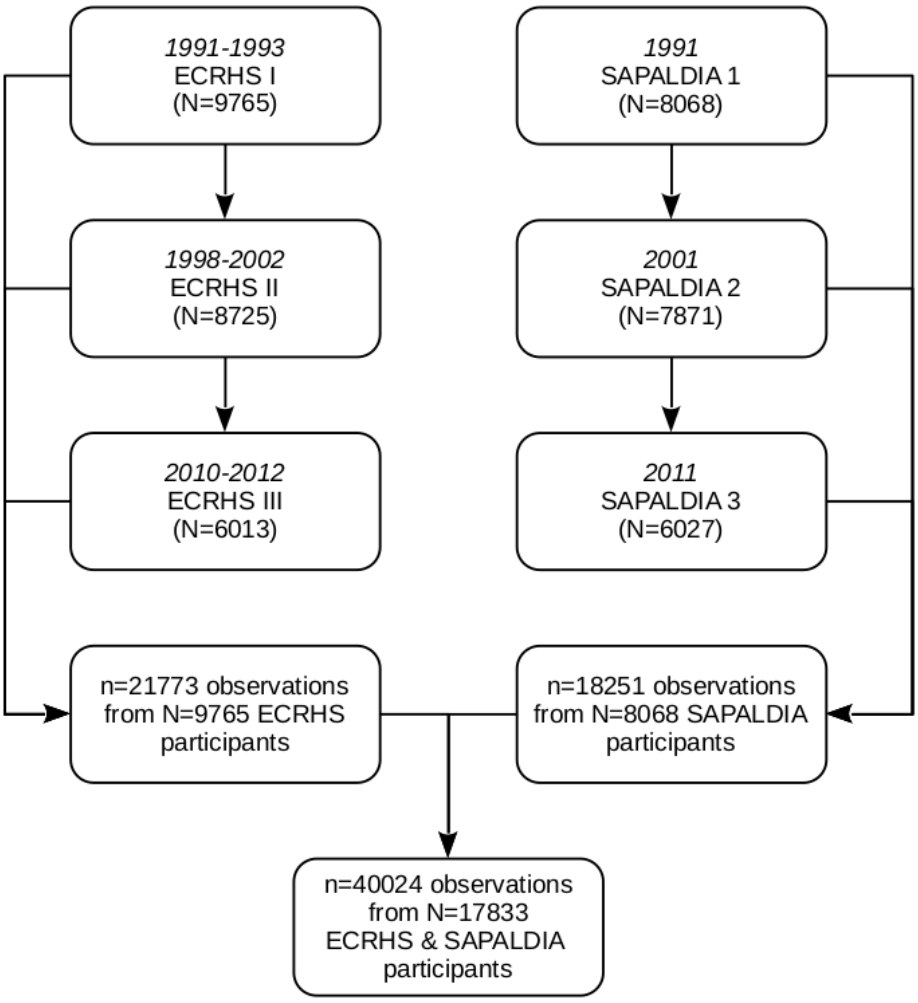
ONLINE DATA SUPPLEMENT

Cumulative occupational exposures and lung function decline in two large general population cohorts

Theodore Lytras, Anna Beckmeyer-Borowko, Manolis Kogevinas, Hans Kromhout, Anne-Elie Carsin, Josep Maria Antó, Hayat Bentouhami, Joost Weyler, Joachim Heinrich, Dennis Nowak, Isabel Urrutia, Jesús Martínez-Moratalla, José Antonio Gullón, Antonio Pereira Vega, Chantal Raherison Semjen, Isabelle Pin, Pascal Demoly, Bénédicte Leynaert, Simona Villani, Thorarinn Gislason, Øistein Svanes, Mathias Holm, Bertil Forsberg, Dan Norbäck, Amar J Mehta, Dirk Keidel, David Vernez, Geza Benke, Rain Jõgi, Kjell Torén, Torben Sigsgaard, Vivi Schlünssen, Mario Olivieri, Paul D Blanc, John Watkins, Roberto Bono, Giulia Squillacioti, A. Sonia Buist, Roel Vermeulen, Deborah Jarvis, Nicole Probst-Hensch, Jan-Paul Zock

For Review Only

Supplemental Figure 1: Flowchart of study participants from ECRHS and SAPALDIA



Details about the modelling of lung function

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 a 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)

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

As the participant-level random effect already explains a large part of the overall variance, and participants are nested within centres, a centre-level random effect was not needed and not included in the models.

We set priors on three fixed covariates that included some missing values, namely current asthma, SES, current smoking and total smoking pack-years, in order to do Bayesian imputation of their 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 same specification was used for both the linear (absolute FEV_1 and FVC as outcome) and 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 model 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 (although the practical difference is very small).

For Review Only

The full JAGS code of the model was as follows (interaction terms for gender and smoking status are included):

```
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 +
```

For Review Only

```
                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])

}
```

For Review Only

Supplemental Table 1: Ten most frequent occupations by exposure category, across both cohorts (ECRHS and SAPALDIA), with number and percentage of exposed participants.

Biological dust

ISCO code	Occupation	N (%)
9132	Helpers and cleaners in offices, hotels and other establishments	426 (7.0%)
5132	Institution-based personal care workers	413 (6.8%)
2230	Nursing and midwifery professionals	360 (5.9%)
3231	Nursing associate professionals	355 (5.8%)
9141	Building caretakers	289 (4.7%)
5122	Cooks	228 (3.7%)
2221	Medical doctors	179 (2.9%)
5133	Home-based personal care workers	167 (2.7%)
9131	Domestic helpers and cleaners	162 (2.6%)
9130	Domestic and related helpers, cleaners and launderers	156 (2.6%)

Mineral Dust

ISCO code	Occupation	N (%)
9132	Helpers and cleaners in offices, hotels and other establishments	426 (8.5%)
9141	Building caretakers	289 (5.8%)
7231	Motor vehicle mechanics and fitters	171 (3.4%)
9131	Domestic helpers and cleaners	162 (3.2%)
9130	Domestic and related helpers, cleaners and launderers	156 (3.1%)
3471	Decorators and commercial designers	154 (3.1%)
8324	Heavy truck and lorry drivers	153 (3.1%)
7137	Building and related electricians	152 (3.0%)
7136	Plumbers and pipe fitters	142 (2.8%)
6130	Market-oriented crop and animal producers	129 (2.6%)

Gases & fumes

ISCO code	Occupation	N (%)
9132	Helpers and cleaners in offices, hotels and other establishments	426 (4.6%)
5132	Institution-based personal care workers	413 (4.4%)
2230	Nursing and midwifery professionals	360 (3.9%)
9141	Building caretakers	289 (3.1%)
5123	Waiters, waitresses and bartenders	284 (3.1%)
5122	Cooks	228 (2.4%)
3340	Other teaching associate professionals	191 (2.1%)
7231	Motor vehicle mechanics and fitters	171 (1.8%)
5133	Home-based personal care workers	167 (1.8%)
9131	Domestic helpers and cleaners	162 (1.7%)

Vapors, Gases, Dusts & Fumes

For Review Only

ISCO code	Occupation	N (%)
9132	Helpers and cleaners in offices, hotels and other establishments	426 (4.0%)
5132	Institution-based personal care workers	413 (3.9%)
2230	Nursing and midwifery professionals	360 (3.4%)
3231	Nursing associate professionals	355 (3.3%)
9141	Building caretakers	289 (2.7%)
5123	Waiters, waitresses and bartenders	284 (2.7%)
5122	Cooks	228 (2.1%)
3340	Other teaching associate professionals	191 (1.8%)
2221	Medical doctors	179 (1.7%)
7231	Motor vehicle mechanics and fitters	171 (1.6%)

Herbicides

ISCO code	Occupation	N (%)
6130	Market-oriented crop and animal producers	129 (27.7%)
6112	Tree and shrub crop growers	102 (21.9%)
6113	Gardeners, horticultural and nursery growers	82 (17.6%)
6111	Field crop and vegetable growers	61 (13.1%)
6141	Forestry workers and loggers	23 (4.9%)
9211	Farm-hands and labourers	16 (3.4%)
6114	Mixed-crop growers	13 (2.8%)
8331	Motorised farm and forestry plant operators	12 (2.6%)
3212	Agronomy and forestry technicians	10 (2.1%)
6100	Market-oriented skilled agricultural and fishery workers	9 (1.9%)

Insecticides

ISCO code	Occupation	N (%)
6130	Market-oriented crop and animal producers	129 (22.3%)
6112	Tree and shrub crop growers	102 (17.6%)
6113	Gardeners, horticultural and nursery growers	82 (14.2%)
9333	Freight handlers	63 (10.9%)
6111	Field crop and vegetable growers	61 (10.5%)
6121	Dairy and livestock producers	30 (5.2%)
6129	Market-oriented animal producers and related workers not elsewhere classified	20 (3.5%)
9211	Farm-hands and labourers	16 (2.8%)
6114	Mixed-crop growers	13 (2.2%)
2223	Veterinarians	12 (2.1%)

Fungicides

ISCO code	Occupation	N (%)
6130	Market-oriented crop and animal producers	129 (20.2%)
6112	Tree and shrub crop growers	102 (15.9%)
8211	Machine-tool operators	100 (15.6%)

For Review Only

ISCO code	Occupation	N (%)
6113	Gardeners, horticultural and nursery growers	82 (12.8%)
6111	Field crop and vegetable growers	61 (9.5%)
6121	Dairy and livestock producers	30 (4.7%)
6129	Market-oriented animal producers and related workers not elsewhere classified	20 (3.1%)
8141	Wood-processing-plant operators	18 (2.8%)
9211	Farm-hands and labourers	16 (2.5%)
6114	Mixed-crop growers	13 (2.0%)

All pesticides

ISCO code	Occupation	N (%)
6130	Market-oriented crop and animal producers	129 (17.2%)
6112	Tree and shrub crop growers	102 (13.6%)
8211	Machine-tool operators	100 (13.3%)
6113	Gardeners, horticultural and nursery growers	82 (10.9%)
9333	Freight handlers	63 (8.4%)
6111	Field crop and vegetable growers	61 (8.1%)
6121	Dairy and livestock producers	30 (4.0%)
6141	Forestry workers and loggers	23 (3.1%)
6129	Market-oriented animal producers and related workers not elsewhere classified	20 (2.7%)
8141	Wood-processing-plant operators	18 (2.4%)

Aromatic solvents

ISCO code	Occupation	N (%)
7231	Motor vehicle mechanics and fitters	171 (5.8%)
3471	Decorators and commercial designers	154 (5.2%)
7136	Plumbers and pipe fitters	142 (4.8%)
6130	Market-oriented crop and animal producers	129 (4.4%)
7241	Electrical mechanics and fitters	125 (4.2%)
7124	Carpenters and joiners	123 (4.2%)
6112	Tree and shrub crop growers	102 (3.5%)
3211	Life science technicians	95 (3.2%)
7233	Agricultural- or industrial-machinery mechanics and fitters	92 (3.1%)
7222	Tool-makers and related workers	88 (3.0%)

Chlorinated solvents

ISCO code	Occupation	N (%)
7231	Motor vehicle mechanics and fitters	171 (7.5%)
3471	Decorators and commercial designers	154 (6.7%)
5141	Hairdressers, barbers, beauticians and related workers	145 (6.3%)
7136	Plumbers and pipe fitters	142 (6.2%)
7241	Electrical mechanics and fitters	125 (5.5%)
7233	Agricultural- or industrial-machinery mechanics and fitters	92 (4.0%)
7222	Tool-makers and related workers	88 (3.9%)

For Review Only

ISCO code	Occupation	N (%)
3111	Chemical and physical science technicians	87 (3.8%)
7422	Cabinet makers and related workers	87 (3.8%)
7141	Painters and related workers	83 (3.6%)

Other solvents

ISCO code	Occupation	N (%)
5132	Institution-based personal care workers	413 (8.1%)
2230	Nursing and midwifery professionals	360 (7.0%)
3231	Nursing associate professionals	355 (6.9%)
2221	Medical doctors	179 (3.5%)
7231	Motor vehicle mechanics and fitters	171 (3.3%)
5133	Home-based personal care workers	167 (3.3%)
3471	Decorators and commercial designers	154 (3.0%)
5141	Hairdressers, barbers, beauticians and related workers	145 (2.8%)
7136	Plumbers and pipe fitters	142 (2.8%)
5130	Personal care and related workers	126 (2.5%)

Metals

ISCO code	Occupation	N (%)
7231	Motor vehicle mechanics and fitters	171 (8.0%)
7136	Plumbers and pipe fitters	142 (6.6%)
7241	Electrical mechanics and fitters	125 (5.8%)
8211	Machine-tool operators	100 (4.7%)
7233	Agricultural- or industrial-machinery mechanics and fitters	92 (4.3%)
7222	Tool-makers and related workers	88 (4.1%)
3114	Electronics and telecommunications engineering technicians	87 (4.1%)
7141	Painters and related workers	83 (3.9%)
2144	Electronics and telecommunications engineers	76 (3.6%)
2145	Mechanical engineers	76 (3.6%)

For Review Only

Supplemental Table 2: Effect of occupational exposures on lung function decline after 25 intensity-years of exposure, compared to unexposed to the respective agent, overall and stratified by sex and smoking status (ever / never smokers), separately for the two participating cohorts (ECRHS and SAPALDIA)

(a) ECRHS

	FEV1		FVC		FEV1FVC	
Biological dust	-9.76 (-28.22 – 7.83)		11.72 (-10.27 – 32.62)		**-0.62 (-1.05 – -0.19)**	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	-0.49 (-1.27 – 0.30)	-0.46 (-1.38 – 0.48)
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	**-0.71 (-1.29 – -0.13)**	-0.68 (-1.56 – 0.21)
Mineral Dust	-9.68 (-23.90 – 5.10)		**22.41 (5.17 – 39.73)**		**-0.88 (-1.22 – -0.53)**	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	-0.57 (-1.23 – 0.11)	0.09 (-1.05 – 1.23)
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	**-1.10 (-1.52 – -0.69)**	-0.45 (-1.57 – 0.66)
Gases & fumes	-2.48 (-15.51 – 10.75)		**24.43 (9.30 – 39.56)**		**-0.60 (-0.90 – -0.28)**	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	-0.27 (-0.83 – 0.28)	-0.25 (-1.12 – 0.64)
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	**-0.75 (-1.14 – -0.36)**	-0.72 (-1.54 – 0.08)
Vapors, Gases, Dusts & Fumes	-2.58 (-12.75 – 8.01)		**23.72 (11.43 – 36.07)**		**-0.63 (-0.88 – -0.39)**	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	-0.35 (-0.80 – 0.11)	-0.21 (-0.89 – 0.49)
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	**-0.79 (-1.09 – -0.48)**	-0.65 (-1.27 – 0.02)
Herbicides	**-68.51 (-120.61 – -13.48)**		**-73.44 (-136.76 – -9.54)**		-0.58 (-1.84 – 0.72)	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	-0.46 (-3.20 – 2.40)	1.31 (-2.22 – 4.97)
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	-1.06 (-2.55 – 0.43)	0.69 (-2.34 – 3.79)
Insecticides	**-39.07 (-75.81 – -2.82)**		-24.81 (-69.02 – 18.45)		-0.72 (-1.58 – 0.13)	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	0.33 (-1.38 – 2.18)	1.13 (-1.27 – 3.59)
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	**-1.31 (-2.37 – -0.22)**	-0.55 (-2.56 – 1.48)
Fungicides	**-40.48 (-77.31 – -3.47)**		-30.32 (-75.21 – 14.96)		-0.60 (-1.48 – 0.28)	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	0.25 (-1.60 – 2.26)	1.49 (-1.09 – 4.10)
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	**-1.17 (-2.21 – -0.11)**	0.01 (-2.03 – 2.09)
All pesticides	**-44.45 (-79.01 – -9.33)**		-29.94 (-69.64 – 11.85)		-0.76 (-1.57 – 0.07)	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	0.30 (-1.42 – 2.03)	1.01 (-1.24 – 3.43)

For Review Only

	FEV1		FVC		FEV1FVC	
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	**-1.27 (-2.25 – -0.26)**	-0.56 (-2.50 – 1.47)
Aromatic solvents	14.20 (-13.96 – 42.54)		**38.00 (3.67 – 71.52)**		-0.48 (-1.19 – 0.22)	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	-0.44 (-1.67 – 0.83)	-0.00 (-2.28 – 2.29)
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	-0.58 (-1.48 – 0.29)	-0.16 (-2.28 – 1.95)
Chlorinated solvents	-12.04 (-33.56 – 9.22)		4.85 (-20.73 – 29.91)		-0.51 (-1.04 – 0.04)	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	-0.45 (-1.44 – 0.51)	-0.17 (-2.50 – 2.35)
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	-0.55 (-1.18 – 0.06)	-0.25 (-2.43 – 2.09)
Other solvents	7.47 (-14.80 – 29.29)		22.81 (-3.15 – 48.32)		-0.39 (-0.92 – 0.14)	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	-0.66 (-1.70 – 0.37)	-0.57 (-1.64 – 0.60)
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	-0.36 (-1.13 – 0.43)	-0.24 (-1.11 – 0.62)
Metals	-12.87 (-32.03 – 6.81)		12.14 (-11.49 – 35.27)		**-0.70 (-1.18 – -0.23)**	
Never smokers, men / women	1.27 (-4.40 – 7.33)	-4.91 (-14.65 – 4.71)	4.85 (-0.98 – 10.35)	-2.82 (-11.49 – 5.98)	-0.43 (-1.29 – 0.44)	0.94 (-1.34 – 3.32)
Ever smokers, men / women	-1.52 (-5.73 – 2.56)	-7.74 (-16.88 – 1.23)	**6.33 (2.55 – 10.09)**	-1.35 (-9.53 – 6.98)	**-0.92 (-1.48 – -0.36)**	0.45 (-1.76 – 2.77)

Results are posterior medians and 95% CrI in parentheses. Numbers represent absolute change in ml for FEV1 and FVC, and relative %change for FEV1/FVC. A negative sign indicates a lower value compared to fully unexposed to the respective agent. Adjusted for age, sex, current smoking, cumulative smoking pack-years, socioeconomic status and early life disadvantage score. All lung function measurements are without bronchodilation.

(b) SAPALDIA

	FEV1		FVC		FEV1FVC	
Biological dust	**-20.33 (-39.79 – -1.15)**		15.28 (-5.70 – 35.96)		**-1.04 (-1.56 – -0.52)**	
Never smokers, men / women	-25.61 (-53.97 – 4.43)	5.27 (-32.33 – 44.40)	5.48 (-25.42 – 36.66)	**66.72 (26.09 – 108.18)**	-0.70 (-1.48 – 0.08)	**-1.36 (-2.43 – -0.32)**
Ever smokers, men / women	**-34.82 (-64.82 – -3.57)**	-3.47 (-47.72 – 39.11)	-13.37 (-45.83 – 19.90)	48.00 (-0.24 – 94.72)	**-1.05 (-1.92 – -0.19)**	**-1.71 (-2.88 – -0.56)**
Mineral Dust	-12.45 (-30.54 – 5.27)		10.55 (-9.43 – 30.02)		**-0.57 (-1.06 – -0.07)**	
Never smokers, men / women	-11.52 (-40.80 – 17.45)	11.72 (-29.79 – 51.91)	14.26 (-18.31 – 45.85)	33.85 (-12.26 – 78.95)	-0.45 (-1.25 – 0.37)	-0.41 (-1.56 – 0.74)
Ever smokers, men / women	-22.18 (-46.39 – 2.37)	0.82 (-44.05 – 45.43)	-0.89 (-27.38 – 26.32)	19.16 (-29.29 – 67.30)	**-0.68 (-1.35 – -0.01)**	-0.64 (-1.86 – 0.61)
Gases & fumes	-5.81 (-22.33 – 10.62)		**22.59 (4.13 – 40.68)**		**-0.64 (-1.08 – -0.19)**	
Never smokers, men / women	-13.35 (-40.04 – 11.98)	-2.53 (-48.16 – 42.93)	19.57 (-8.49 – 47.04)	**58.72 (10.18 – 108.28)**	-0.60 (-1.32 – 0.13)	-1.25 (-2.51 – 0.00)
Ever smokers, men / women	-3.64 (-25.43 – 18.23)	7.53 (-36.29 – 51.53)	14.07 (-9.51 – 37.74)	**53.60 (6.39 – 102.21)**	-0.50 (-1.10 – 0.10)	-1.14 (-2.35 – 0.08)

For Review Only

	FEV1		FVC		FEV1FVC	
Vapors, Gases, Dusts & Fumes	-9.58 (-21.87 – 3.01)		**18.02 (4.44 – 31.96)**		**-0.67 (-1.01 – -0.32)**	
Never smokers, men / women	-17.12 (-36.41 – 2.13)	-5.57 (-35.59 – 23.53)	12.67 (-8.75 – 33.19)	**43.10 (10.98 – 75.71)**	**-0.60 (-1.11 – -0.07)**	**-1.15 (-1.96 – -0.33)**
Ever smokers, men / women	-6.73 (-23.78 – 10.54)	4.86 (-26.17 – 34.98)	12.23 (-6.54 – 31.17)	**42.94 (9.10 – 76.75)**	**-0.53 (-1.00 – -0.08)**	**-1.08 (-1.94 – -0.23)**
Herbicides	5.65 (-36.36 – 47.10)		14.23 (-31.26 – 58.31)		-0.14 (-1.31 – 1.02)	
Never smokers, men / women	-9.95 (-72.21 – 57.68)	31.91 (-51.93 – 117.07)	4.04 (-64.10 – 73.82)	51.94 (-39.70 – 143.97)	-0.35 (-2.11 – 1.42)	0.21 (-2.14 – 2.56)
Ever smokers, men / women	-5.16 (-71.98 – 63.89)	36.54 (-49.93 – 119.46)	-5.78 (-80.47 – 66.90)	41.19 (-51.62 – 132.75)	-0.26 (-2.16 – 1.71)	0.27 (-2.04 – 2.70)
Insecticides	1.01 (-25.85 – 27.58)		5.73 (-24.17 – 34.81)		-0.07 (-0.79 – 0.68)	
Never smokers, men / women	-2.94 (-41.46 – 38.06)	17.76 (-30.20 – 63.96)	4.43 (-38.15 – 48.13)	32.06 (-19.92 – 83.38)	-0.12 (-1.18 – 0.97)	0.01 (-1.30 – 1.34)
Ever smokers, men / women	-13.13 (-61.58 – 37.11)	7.36 (-50.67 – 65.00)	-21.87 (-74.58 – 31.50)	5.99 (-57.71 – 68.63)	-0.07 (-1.42 – 1.30)	0.05 (-1.57 – 1.71)
Fungicides	4.34 (-36.26 – 43.67)		13.95 (-29.23 – 56.33)		-0.18 (-1.34 – 0.92)	
Never smokers, men / women	-13.56 (-76.90 – 49.60)	28.09 (-54.83 – 110.07)	0.39 (-68.34 – 68.18)	48.77 (-42.41 – 139.81)	-0.36 (-2.07 – 1.33)	0.15 (-2.15 – 2.48)
Ever smokers, men / women	-5.43 (-69.28 – 55.62)	34.80 (-42.94 – 116.26)	-4.59 (-72.76 – 63.91)	44.28 (-40.55 – 130.40)	-0.33 (-2.13 – 1.48)	0.20 (-2.02 – 2.48)
All pesticides	0.53 (-26.06 – 27.38)		6.45 (-22.99 – 36.02)		-0.08 (-0.82 – 0.64)	
Never smokers, men / women	-3.68 (-42.31 – 34.60)	18.11 (-29.77 – 66.47)	3.96 (-39.31 – 46.27)	31.71 (-19.57 – 84.72)	-0.14 (-1.20 – 0.94)	0.07 (-1.21 – 1.39)
Ever smokers, men / women	-13.46 (-62.36 – 33.92)	8.07 (-49.25 – 65.47)	-18.34 (-70.69 – 33.74)	9.95 (-54.47 – 71.99)	-0.18 (-1.52 – 1.19)	0.02 (-1.57 – 1.64)
Aromatic solvents	-14.66 (-49.14 – 19.40)		5.11 (-31.27 – 41.31)		-0.46 (-1.37 – 0.50)	
Never smokers, men / women	-42.72 (-94.34 – 9.07)	28.85 (-76.78 – 131.54)	-27.33 (-85.58 – 28.83)	74.84 (-33.79 – 185.12)	-0.46 (-1.84 – 1.01)	-0.50 (-3.27 – 2.44)
Ever smokers, men / women	-7.81 (-53.28 – 37.77)	64.70 (-35.33 – 163.51)	8.68 (-41.38 – 57.93)	**111.39 (4.27 – 217.92)**	-0.45 (-1.72 – 0.87)	-0.51 (-3.16 – 2.32)
Chlorinated solvents	-12.40 (-37.69 – 12.63)		-4.38 (-32.08 – 22.70)		-0.27 (-0.98 – 0.43)	
Never smokers, men / women	-12.50 (-55.02 – 30.36)	-41.86 (-130.82 – 46.18)	-12.46 (-60.29 – 33.73)	-28.22 (-125.07 – 72.43)	0.04 (-1.16 – 1.25)	-0.43 (-2.91 – 2.08)
Ever smokers, men / women	-8.32 (-40.35 – 24.35)	-38.49 (-128.73 – 54.74)	2.29 (-31.81 – 36.44)	-13.14 (-110.89 – 87.01)	-0.38 (-1.27 – 0.52)	-0.88 (-3.38 – 1.68)
Other solvents	-24.04 (-49.73 – 1.11)		17.83 (-10.08 – 45.36)		**-0.99 (-1.69 – -0.29)**	
Never smokers, men / women	-36.95 (-82.40 – 7.04)	-36.36 (-85.03 – 12.21)	30.10 (-18.73 – 80.38)	16.65 (-35.12 – 69.27)	**-1.38 (-2.59 – -0.13)**	-1.24 (-2.55 – 0.12)
Ever smokers, men / women	-14.64 (-55.94 – 27.47)	-14.06 (-53.77 – 28.00)	21.99 (-24.13 – 67.10)	8.00 (-35.61 – 53.53)	-0.84 (-1.95 – 0.30)	-0.70 (-1.78 – 0.39)
Metals	-18.74 (-42.78 – 5.34)		-3.28 (-28.85 – 22.32)		-0.46 (-1.14 – 0.19)	
Never smokers, men / women	-27.93 (-69.89 – 13.38)	**-147.12 (-281.53 – -8.72)**	-18.45 (-63.93 – 27.62)	-88.76 (-238.04 – 54.05)	-0.24 (-1.36 – 0.91)	-3.28 (-7.04 – 0.75)
Ever smokers, men / women	-8.22 (-37.98 – 20.44)	-128.01 (-254.97 – 5.40)	8.09 (-24.69 – 38.98)	-62.51 (-206.22 – 74.48)	-0.43 (-1.24 – 0.41)	-3.44 (-7.18 – 0.27)

Results are posterior medians and 95% CrI in parentheses. Numbers represent absolute change in ml for FEV1 and FVC, and relative

For Review Only

%change for FEV1/FVC. A negative sign indicates a lower value compared to fully unexposed to the respective agent. Adjusted for age, sex, current smoking, cumulative smoking pack-years, socioeconomic status and early life disadvantage score. All lung function measurements are without bronchodilation.

For Review Only

Current SAPALDIA Team

Study directorate: NM Probst-Hensch (PI; e/g); D Stolz (p), C Schindler (s), N Künzli (e/exp)

Scientific team: JC Barthélémy (c), W Berger (g), R Bettschart (p), A Bircher (a), C Brombach (n), PO Bridevaux (p), L Burdet (p), Felber Dietrich D (e), T Sigrist (p), U Frey (pd), MW Gerbase (p), D Gold (e), E de Groot (c), W Karrer (p), F Kronenberg (g), B Martin (pa), A Mehta (e), D Miedinger (o), M Pons (p), F Roche (c), T Rothe (p), P Schmid-Grendelmeyer (a), A Schmidt-Trucksäss (pa), J Schwartz (e), A Turk (p), A von Eckardstein (cc), E Zemp Stutz (e).

Scientific team at coordinating centers: M Adam (e), I Aguilera (exp), A Beckmeyer-Borowko (e), S Brunner (s), D Carballo (c), S Caviezel (pa), I Curjuric (e), A Di Pascale (s), J Dratva (e), R Ducret (s), E Dupuis Lozeron (s), M Eeftens (exp), I Eze (e), E Fischer (g), M Foraster (e), M Germond (s), L Grize (s), S Hansen (e), A Hensel (s), M Imboden (g), A Ineichen (exp), A Jeong (g), D Keidel (s), A Kumar (g), N Maire (s), A Mehta (e), R Meier (exp), E Schaffner (s), T Schikowski (e), M Tsai (exp)

(a) allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (n) nutrition, (o) occupational health, (p) pneumology, (pa) physical activity, (pd) pediatrics, (s) statistics

Research support:
The Swiss National Science Foundation (grants no 33CS30-177506/1, 33CS30-148470/1&2, 33CSCO-134276/1, 33CSCO-108796, , 324730_135673, 3247BO-104283, 3247BO-104288, 3247BO-104284, 3247-065896, 3100-059302, 3200-052720, 3200-042532, 4026-028099, PMPDP3_129021/1, PMPDP3_141671/1), the Federal Office for the Environment, the Federal Office of Public Health, the Federal Office of Roads and Transport, the canton's government of Aargau, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino, Valais, and Zürich, the Swiss Lung League, the canton's Lung League of Basel Stadt/ Basel Landschaft, Geneva, Ticino, Valais, Graubünden and Zurich, Stiftung ehemals Bündner Heilstätten, SUVA, Freiwillige Akademische Gesellschaft, UBS Wealth Foundation, Talecris Biotherapeutics GmbH, Abbott Diagnostics, Klinik Barmelweid, Hirslanden Klinik Aarau, European Commission 018996 (GABRIEL), Wellcome Trust WT 084703MA, Exposomics EC FP7 grant(Grant agreement No: 308610).

Acknowledgements
The study could not have been done without the help of the study participants, technical and administrative support and the medical teams and field workers at the local study sites.

Local fieldworkers S3 : Aarau: S Brun, G Giger, M Sperisen, M Stahel. Basel: C Bürli, C Dahler, N Oertli, I Harreh, F Karrer, G Novicic, N Wyttenbacher. Davos: A Saner, P Senn, R Winzeler, Geneva: F Bonfils, B Blicharz, C Landolt, J Rochat. Lugano: S Boccia, E Gehrig, MT Mandia, G Solari, B Viscardi. Montana: AP Bieri, C Darioly, M Maire., Payerne: F Ding, P Danieli A Vonnez. Wald: D Bodmer, E Hochstrasser, R Kunz, C Meier, J Rakic, U Schafroth, A Walder.

Local fieldworkers S4 : Aarau: A Heichel, E Isenring, C Marti, C Schuler, M Witzig. Basel: N Aebi, R Armbruster, S Nussbaumer, M Rutschi, M Witzig. Davos: S Derfler, M Dinic, L Esghani-Oswald, A Landauf. Geneva: N Ballot, B Ducry, M Plutino. Lugano: C Ferrari, I Paravac, P Parolini, T Vermes. Montana: P Friedrich, M Gérard, L Kristen, T Masserey, D Walther. Payerne: M Bertschy, C Bonzon, B Ducry, F Gainon, H Rodrigues. Wald: D Bodmer, C Kuntze, U Treder, A Lawson, S Mettler, D Studer, B Wigger.

Administrative staff: N Bauer Ott

For Review Only

Funding statement

SAPALDIA is mainly funded by the Swiss National Science Foundation (running grant: 33CS30_177506).

Financial support for ECRHS I, for the local centres included in this study:

Australia: Asthma Foundation of Victoria, Allen and Hanbury's, Belgium: Belgian Science Policy Office, National Fund for Scientific Research, Estonia: Estonian Science Foundation, grant no 1088, France: Ministère de la Santé, Glaxo France, Insitut Pneumologique d'Aquitaine, Contrat de Plan Etat-Région Languedoc-Rousillon, CNMATS, CNMRT (90MR/10, 91AF/6), Ministre delegué de la santé, RNSP, France; GSF, Germany: Bundesminister für Forschung und Technologie, Italy: Ministero dell'Università e della Ricerca Scientifica e Tecnologica, CNR, Regione Veneto grant RSF n. 381/05.93, Norway: Norwegian Research Council project no. 101422/310, Spain: Fondo de Investigación Sanitaria (#91/0016-060-05/E, 92/0319 and #93/0393), Hospital General de Albacete, Hospital General Juan Ramón Jiménez, Dirección Regional de Salud Pública (Consejería de Sanidad del Principado de Asturias), CIRIT (1997 SGR 00079) and Servicio Andaluz de Salud; Sweden: The Swedish Medical Research Council, the Swedish Heart Lung Foundation, the Swedish Association against Asthma and Allergy; Switzerland: Swiss national Science Foundation grant 4026-28099; UK: National Asthma Campaign, British Lung Foundation, Department of Health, South Thames Regional Health Authority, USA: United States Department of Health, Education and Welfare Public Health Service (grant #2 S07 RR05521-28).

Financial Support for ECRHS II, for the local centres included in this study:

Australia: National Health and Medical Research Council, Belgium: Antwerp: Fund for Scientific Research (grant code, G.0402.00), University of Antwerp, Flemish Health Ministry; Estonia: Tartu Estonian Science Foundation grant no 4350, France: (All) Programme Hospitalier de Recherche Clinique—Direction de la Recherche Clinique (DRC) de Grenoble 2000 number 2610, Ministry of Health, Ministère de l'Emploi et de la Solidarité, Direction Génerale de la Santé, Centre Hospitalier Universitaire (CHU) de Grenoble, Bordeaux: Institut Pneumologique d'Aquitaine; Grenoble: Comite des Maladies Respiratoires de l'Isere Montpellier: Aventis (France), Direction Regionale des Affaires Sanitaires et Sociales Languedoc-Roussillon; Paris: Union Chimique Belge- Pharma (France),Aventis (France), Glaxo France, Germany: Erfurt GSF—National Research Centre for Environment and Health, Deutsche Forschungsgemeinschaft (grant code, FR1526/1-1) Hamburg: GSF—National Research Centre for Environment and Health, Deutsche Forschungsgemeinschaft (grant code, MA 711/4-1) Iceland: Reykjavik, Icelandic Research Council, Icelandic University Hospital Fund; Italy: Pavia GlaxoSmithKline Italy, Italian Ministry of University and Scientific and Technological Research (MURST),Local University Funding for Research 1998 and

For Review Only

1999;Turin: Azienda Sanitaria Locale 4 Regione Piemonte (Italy), Azienda Ospedaliera Centro Traumatologico Ospedaliero/Centro Traumatologico Ortopedico—Istituto Clinico Ortopedico Regina Maria Adelaide Regione Piemonte Verona: Ministero dell'Universita´ e della Ricerca Scientifica (MURST), Glaxo Wellcome spa, Norway: Bergen: Norwegian Research Council, Norwegian Asthma and Allergy Association, Glaxo Wellcome AS, Norway Research Fund; Spain: Fondo de Investigacion Santarias (grant codes, 97/0035-01,99/0034-01 and 99/0034 02), HospitalUniversitario de Albacete, Consejeria de Sanidad; Barcelona: Sociedad Espanola de Neumologı´a y Cirugı´a Toracica, Public Health Service(grant code, R01 HL62633-01), Fondo de Investigaciones Santarias (grant codes, 97/0035-01, 99/0034-01, and 99/0034-02), Consell Interdepartamentalde Recerca i Innovacio´ Tecnolo`gica (grant code, 1999SGR 00241) Instituto de Salud Carlos III; Red deCentros de Epidemiologı´a y Salud Pu´blica, C03/09,Redde Basesmoleculares y fisiolo´gicas de lasEnfermedadesRespiratorias,C03/011and Red de Grupos Infancia y Medio Ambiente G03/176; Huelva: Fondo de Investigaciones Santarias (grant codes, 97/0035-01, 99/0034-01, and 99/0034-02); Galdakao: Basque Health Department Oviedo: Fondo de Investigaciones Sanitaria (97/0035-02, 97/0035, 99/0034-01, 99/0034-02, 99/0034-04, 99/0034-06, 99/350, 99/0034--07), European Commission (EU-PEAL PL01237), Generalitat de Catalunya (CIRIT 1999 SGR 00214), Hospital Universitario de Albacete, Sociedad Española de Neumología y Cirugía Torácica (SEPAR R01 HL62633-01) Red de Centros de Epidemiología y Salud Pública (C03/09), Red de Bases moleculares y fisiológicas de las Enfermedades Respiratorias (C03/011) and Red de Grupos Infancia y Medio Ambiente (G03/176);97/0035-01, 99/0034-01, and99/0034-02); Sweden: Göteborg , Umea, Uppsala: Swedish Heart Lung Foundation, Swedish Foundation for Health Care Sciences and Allergy Research, Swedish Asthma and Allergy Foundation, Swedish Cancer and Allergy Foundation, Swedish Council for Working Life and Social Research (FAS),Switzerland: Basel Swiss National Science Foundation, Swiss Federal Office for Education and Science, Swiss National Accident Insurance Fund; UK: Ipswich and Norwich: Asthma UK (formerly known as National Asthma Campaign) USA: Portland: American Lung Association of Oregon, Northwest Health Foundation, Collins Foundation, Merck Pharmaceutical.

Financial Support for ECRHS III, for the local centres included in this study:

Australia: National Health & Medical Research Council, Belgium: Antwerp South, Antwerp City: Research Foundation Flanders (FWO), grant code G.0.410.08.N.10 (both sites), Estonia: Tartu- SF0180060s09 from the Estonian Ministry of Education. France: (All) Ministère de la Santé. Programme Hospitalier de Recherche Clinique (PHRC) national 2010. Bordeaux: INSERM U897 Université Bordeaux segalen, Grenoble: Comite Scientifique AGIRadom 2011. Paris: Agence Nationale de la Santé, Région Ile de France, domaine d'intérêt majeur (DIM) Germany : Erfurt: German Research Foundation HE 3294/10-1 Hamburg: German Research Foundation MA 711/6-1, NO 262/7-1 Iceland: Reykjavik, The Landspitali University Hospital Research Fund, University of Iceland Research Fund, ResMed Foundation, California, USA, Orkuveita Reykjavikur (Geothermal plant), Vegagerðin (The Icelandic Road Administration (ICERA). Italy: All Italian centres were funded by the Italian Ministry of Health, Chiesi Farmaceutici SpA, in addition

For Review Only

Verona was funded by Cariverona foundation, Education Ministry (MIUR). Norway: Norwegian Research council grant no 214123, Western Norway Regional Health Authorities grant no 911631, Bergen Medical Research Foundation. Spain: Fondo de Investigación Sanitaria (PS09/02457, PS09/00716 09/01511) PS09/02185 PS09/03190), Servicio Andaluz de Salud , Sociedad Española de Neumología y Cirurgía Torácica (SEPAR 1001/2010); Sweden: All centres were funded by The Swedish Heart and Lung Foundation, The Swedish Asthma and Allergy Association, The Swedish Association against Lung and Heart Disease.Fondo de Investigación Sanitaria (PS09/02457 Barcelona:Fondo de Investigación Sanitaria (FIS PS09/00716) Galdakao: Fondo de Investigación Sanitaria (FIS 09/01511) Huelva: Fondo de Investigación Sanitaria (FIS PS09/02185) and Servicio Andaluz de Salud Oviedo: Fondo de Investigación Sanitaria (FIS PS09/03190) Sweden: All centres were funded by The Swedish Heart and Lung Foundation, The Swedish Asthma and Allergy Association, The Swedish Association against Lung and Heart Disease. Swedish Research Council for health, working life and welfare (FORTE) Göteborg : Also received further funding from the Swedish Council for Working life and Social Research. Umea also received funding from Vasterbotten Country Council ALF grant. Switzerland: The Swiss National Science Foundation (grants no 33CSCO-134276/1, 33CSCO-108796, 3247BO-104283, 3247BO-104288, 3247BO-104284, 3247-065896, 3100-059302, 3200-052720, 3200-042532, 4026-028099) The Federal office for forest, environment and landscape, The Federal Office of Public Health, The Federal Office of Roads and Transport, the canton's government of Aargan, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino, Valais and Zürich, the Swiss Lung League, the canton's Lung League of Basel Stadt/ Basel, Landschaft, Geneva, Ticino, Valais and Zurich, SUVA, Freiwillige Akademische Gesellschaft, UBS Wealth Foundation, Talecris Biotherapeutics GmbH, Abbott Diagnostics, European Commission 018996 (GABRIEL), Wellcome Trust WT 084703MA, UK: Medical Research Council (Grant Number 92091). Support also provided by the National Institute for Health Research through the Primary Care Research Network

The coordination of the ECRHS 3 was funded through the Medical Research Council (Grant Number 92091).

ISGlobal is a member of the CERCA Programme / Generalitat de Catalunya.

For Review Only