**TITLE: Lifetime occupational exposures and chronic obstructive pulmonary disease risk in the UK Biobank Cohort.**

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**ABSTRACT**

**Background and Aim** Occupational exposures are important, preventable causes of chronic obstructive pulmonary disease (COPD). We previously found an increased COPD risk among six occupations by analysing lifetime job-histories and lung function data in the population-based UK Biobank cohort. We aimed to build upon these findings and elucidate the underlying potential causal agents to focus preventive strategies.

**Methods** We applied the ALOHA+ job-exposure matrix (JEM) based on ISCO-88 codes in which exposure to 12 selected agents was rated as 0 (no exposure), 1 (low), or 2 (high). COPD was spirometrically-defined as forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) < lower limit of normal (LLN).We calculated semi-quantitative cumulative exposure estimates for each agent by multiplying duration of exposure and squared intensity. Prevalence ratios (PR) and 95% confidence intervals (CI) for COPD were estimated using robust Poisson regression adjusted for centre, sex, age, smoking, and co-exposure to JEM agents. Only associations confirmed among never-smokers and never-asthmatics were considered reliable.

**Results** Out of 116,375 participants with complete job-histories, 94,514 had acceptable/repeatable spirometry data and smoking information and were included in the analysis. Pesticides exposure showed increased COPD risks for ever exposure (PR=1.13;95%CI:1.01-1.28), and for high cumulative exposure (PR=1.32;95%CI:1.12-1.56), with positive exposure-response trends (P-trend=0.004), that were confirmed among never-smokers (P-trend=0.005) and never-asthmatics (P-trend=0.001).

**Conclusion** In a large population-based study, occupational exposure to pesticides was associated with COPD risk. Focussed preventive strategies for workers exposed to pesticides can avoid the associated COPD burden.

**Key words:** Occupational exposure; Pesticides; Lung diseases; Spirometry, COPD.

**Word count:** Abstract: 242; Text: 2,838

**‘Key Messages’**

* **What is the key question?** What are the occupational exposures associated with COPD risk in a general population?
* **What is the bottom line?** In a large population-based study, lifetime cumulative exposure to pesticideswas positively associated with COPD. The results were confirmed among never-smokers and never-asthmatics.
* **Why read on?** In the largest study on lifetime occupational exposures and spirometrically-defined COPD, pesticides increase COPD risk**.** Focussed preventive strategies are warranted.

**Introduction**

Occupational exposures are important, preventable causes of chronic obstructive pulmonary disease (COPD), and it has been recently estimated that about 14% of all cases are work-related[1](#_ENREF_1). Identification of the specific occupations and underlying exposures associated with increased COPD risk is key to prevent the associated public health burden, in terms both of morbidity, and mortality, and to focus preventive strategies. However, there are several challenges: the study sample size should be large enough to cover the broad range of occupations present in a population; the occupational exposure assessment should not rely on self-reported information (subject to recall bias) and take into account the entire individual lifetime job-history; the COPD definition should be based on standard diagnostic tests, and the effect of the major confounder, tobacco smoking, should be ruled out. We managed to overcome these challenges by using the UK Biobank cohort [2](#_ENREF_2), a very large population-based study that allowed us to evaluate a broad range of occupations in relation to spirometrically-defined COPD risk also in analyses restricted to never-smokers. By analysing lifetime job-histories and lung function data in this cohort we previously found that six occupations increased COPD risk, and in particular agriculture-related jobs emerged at higher risk [3](#_ENREF_3). To follow up and progress these findings we applied a job exposure matrix for selected agents, including pesticides, previously reported to be associated with COPD risk in order to identify the potential underlying causal agents, and focus future preventive strategies.

**Methods**

**Study base: the UK Biobank cohort**

The UK Biobank study is a large population-based prospective cohort of over half a million men and women recruited between 2006 and 2010 throughout the UK [2](#_ENREF_2). Briefly, a random sample of adults aged 40–69 years was identified from lists of those registered with the National Health Service in Britain, and who lived within specified distances of 22 health assessment centres. The response rate to the baseline UK Biobank survey was 5.5% (503,325/9.2 million invited). At baseline, personal data (including age, sex, lifetime smoking history, current employment and doctor-diagnosed asthma) were collected through computer-assisted self-administered questionnaire and face-to-face interview, and physical health measurements (including spirometry) were performed.

**COPD definition**

Among the 502,649 UK Biobank participants who completed the baseline questionnaire, 457,282 subjects (91%) underwent lung function testing at recruitment as detailed in the spirometry protocol [2](#_ENREF_2). All spirometry tests were performed according to the ATS/ERS guidelines [4](#_ENREF_4), but only up to three attempts to provide two reproducible manoeuvres were required. Bronchial reversibility was not tested. For our work, we included acceptable spirometry data based on a quality appraisal of the flow curves as previously described [3](#_ENREF_3)[5](#_ENREF_5). We used the spirometry threshold FEV1/FVC<LLN (i.e. the 5% lower tail of the normal distribution of the average predicted FEV1/FVC in a reference healthy never-smoking population) as a *proxy* for COPD based on the age range of our study population [6](#_ENREF_6). We used the Hankinson equation to calculate the individual predicted values for FEV1/FVC [6-8](#_ENREF_6). About 95% of the study participants reported a ‘White’ ethnic origin.

**Lifetime occupational exposure: application of the ALOHA+ JEM to coded job-histories**

The lifetime job-histories for all the UK Biobank participants were collected and coded using OSCAR (Occupations Self-Coding Automatic Recording), a validated web-based tool developed for this project as previously described [9](#_ENREF_9). Briefly, OSCAR is a categorical decision tree, based on the hierarchical structure of the UK Standard Occupational Classification (SOC),v.2000 [10](#_ENREF_10). OSCAR uses a three-level job grouping tree to enable participants to quickly and easily find each job (paid and ≥6 months) held in their life. On each final job-title selection, a hidden 4-digit SOC code is automatically linked and saved in the database. The start/end year for each job and any job gap were recorded in an editable ‘career timeline’. To assess the individual lifetime exposure to occupational respiratory agents we applied the ALOHA+ job-exposure matrix (JEM), an extension of the ALOHA-JEM that was developed by using industrial hygienists’ expert assessment to evaluate in community-based studies the occupational hazards for COPD. [11](#_ENREF_11) This semi-quantitative JEM assigns, for every job coded using the four-digit codes of the International Standard Classification of Occupations v.1988 (ISCO-88) [12](#_ENREF_12), three levels of exposure (0=none, 1=low, 2=high), based on rated workers’ intensity and prevalence of exposure in each job, to 10 categories of agents (biological dusts, mineral dusts, gases and fumes, herbicides, insecticides, fungicides, aromatic solvents, chlorinated solvents, other solvents, and metals) plus two composites of the above (all pesticides and vapours/gases/dusts/fumes – VGDF). Cross-mapping between the SOC v.2000 and the ISCO-88 classification was performed using the official UK Office for National Statistics files available at https://www.ons.gov.uk/.

**Statistical analysis**

To evaluate the association between lifetime occupational exposures and COPD risk, individual job-histories and exposure to potential confounders were truncated to the time of spirometry.

Given the potential overlap of exposure to each JEM agent, we assessed between-agent correlation using Spearman’s coefficient. In case of strong correlation (≥85%) agents were combined to avoid collinearity in the statistical models.

For each agent, we used a Poisson regression model with a robust error variance [13](#_ENREF_13) to estimate prevalence ratios (PRs) and 95% confidence intervals (CIs) for: ever exposure; intensity of exposure (never, only low, ever high); duration of exposure (years), either continuous or categorized (never exposed, 0.5 to <10 years, 10+ years); cumulative exposure (in exposure-unit-years, EU-years, either continuous or categorized (never exposed, 0.5 to <10 EU-years, 10+ EU-years). Since exposure levels were log-normally distributed, cumulative exposure was calculated as the sum of products of exposure duration and squared intensity covering all lifetime job periods. [14](#_ENREF_14)

The final statistical models included, as adjustment covariates, recruitment centre (22 categories), sex, age (5-year categories), and three variables for lifetime tobacco smoking (ever/never, pack-years and years since quitting). Addition of education had negligible effects on exposure estimates and was not included in the final models.

We fitted two types of models: PR1 models, in which the PR for each category of agents was adjusted by the covariates listed above; and PR2 models, additionally adjusted for co-exposures to categories of the JEM agents. To visualise the relationship between cumulative exposure and duration of exposure to pesticides and PR2, we fitted linear and restricted cubic spline models with knots at 25th, 50th, 75th, and 90th percentiles. The two covariates were entered in the models after natural log-transformation, for the reason given above.

As sensitivity analyses, we ran the PR1 and PR2 models restricted to: 1) never-smokers (to rule out residual confounding by tobacco smoking); and 2) never-asthmatics (to decrease the chance of disease misclassification given that only pre-bronchodilator spirometry measures were available). Finally, all analyses were repeated using a common reference category of those never-exposed to any agent.

## Analyses were performed using Stata version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP).

**Results**

All UK Biobank participants who consented to provide an email address (n=324,653) were invited to complete OSCAR. Out of 116,375 participants who provided complete job-histories, 94,551 had acceptable/repeatable spirometry data and smoking information and were included in the analysis (Figure 1).

*[Figure 1 here]*

Since our last publication 37 Biobank participants had withdrawn from the study, so 94,514 were included in the analysis (Table 1). About 56% were women; the average age was 56 years (SD: 7.6). Most were never-smokers (n= 55,574; 58.8%); only a minority were current smokers (n=5,298; 5.6%). About 11% of participants reported a diagnosis of asthma. The prevalence of spirometry-defined COPD was 8.0% (corresponding to 7,603 cases). As expected, the frequency of COPD was higher among current smokers (16.8%) than in former (8.6%) and never-smokers (6.9%).

These results were similar in women and men.

*[Table 1 here]*

Based on the Spearman correlation matrix there was significant overlap between exposures (see table S1 in the online supplementary material), particularly between pesticide subgroups and solvents. Moreover, there were sparse data for pesticide subgroups, making it impossible to disentangle their specific effects. For these reasons, we combined for the analyses subgroups of pesticides (i.e. herbicides, insecticides, fungicides), and aromatic and chlorinated solvents.

The percentage of participants exposed varied considerably across the occupational agents (table 2): a relative small percentages of cohort members was exposed to pesticides (4.2% among COPD cases, and 3.5% among non-COPD subjects), and exposure to VGDF was the most prevalent (47.6%, and 46.9%, respectively). Of note, most subjects had been exposed to only low levels of exposure in their lifetime job career. In multivariable analyses adjusted for the core covariates, ever exposure to pesticides was associated with increased COPD risk. This was confirmed after adjustment also for co-exposure to the other JEM agents, and in sensitivity analyses restricted to never-asthmatics and never-smokers. In addition, positive exposure-response trends for level of intensity (ever high vs. only low) were found.

*[Table 2 here]*

When considering categories of lifetime cumulative exposures in EU-years (table 3), the positive association of pesticides with increased COPD risk was confirmed in all analyses. Of note, the shape of the positive exposure-response trends appeared substantially linear both for cumulative exposure (Figure 2) and duration (Figure 3), with fully adjusted PRs of 1.08 (95% CI: 1.03-1.14) and 1.09 (95% CI: 1.03-1.15), respectively).

We did not find a significant increased COPD risk for any of the other agents included in the JEM.

*[Table 3 here]*

*[Figure 2 and 3 here]*

Results remained unchanged when using a common reference category of subjects never-exposed to any of the JEM agents (results not shown).

**Discussion**

In a large UK population-based prospective cohort, we found that lifetime cumulative occupational exposure to pesticides increased COPD risk, with positive exposure-response trends. This result was confirmed also among never smokers, and never asthmatics.

These findings are consistent with our previous study [3](#_ENREF_3), the largest to refer to on occupational COPD, where using a job-title approach we analysed the lifetime job-histories of the UK Biobank participants and we identified ‘gardener, groundsman, park keeper’ and ‘agriculture, and fishing occupations not elsewhere classified’ among six occupations at increased COPD risk.

Agriculture has been consistently reported as an high-risk COPD sector, and several occupational hazards including organic and inorganic dusts, pesticides, and diesel exhaust fumes have been proposed as potential causal factors [15](#_ENREF_15) [16](#_ENREF_16) [17](#_ENREF_17) [18](#_ENREF_18) [19](#_ENREF_19) [20](#_ENREF_20). Of note, ‘gardeners/groundsmen’ emerged at increased COPD risk for the first time in our previous study [3](#_ENREF_3), and we hypothesised that pesticides exposure could be one of the potential causal factors. Moreover, we found elevated COPD prevalence in ‘agriculture, and fishing occupations not elsewhere classified’. We hypothesised that pesticides exposure could be one of the potential causal factors in these jobs. The findings of this study (elevated risk associated with pesticides, but not with other agents) reinforce our previous job-title analyses and support the hypothesis that pesticides may affect COPD risk. We tried to disentangle the possible independent effects of pesticide exposure and those two occupations, but the high overlap between them (the JEM assigns ‘high pesticide exposure’ to both jobs) prevented us to discriminate their relative role.

An association between pesticides exposure and COPD risk has been previously reported by two similar studies using the same ALOHA+JEM [21](#_ENREF_21)[22](#_ENREF_22), but both had less power than ours and so were unable to adjust for co-exposure to all other JEM agents; in addition, they did not evaluate the association among never smokers and never asthmatics in order to rule out any potential residual confounding effect of tobacco smoking and disease misclassification with asthma, respectively. A recent meta-analysis evaluating pesticides exposure and lung function metrics found tentative evidence that exposure to cholinesterase (ChE) inhibiting pesticides is associated with a decreased FEV1/FVC [23](#_ENREF_23). In relation to biological plausibility, ChE-inhibiting pesticides such as organophosphate have cholinergic effects resulting in increased bronchial secretion and bronchoconstriction [24](#_ENREF_24). Also, neutrophilic and oxidative stress-mediated inflammation have been hypothesized for pesticide-related chronic respiratory diseases pathogenesis [25](#_ENREF_25) [26](#_ENREF_26) and a recent mechanistic study found that stimulation of alveolar macrophages and increase of NF-kB activation, resulting in TNF-α protein release, could be an additional underlying biological mechanism. [27](#_ENREF_27)

We did not find a positive association with traditional ‘dusty’ exposures, in particular ‘VGDF’, and ‘mineral dusts’ previously reported to be associated with COPD risk, even if mostly based on self-reported exposures [1](#_ENREF_1). We note that neither of the two previous studies that used ALOHA+ JEM in relation to spirometrically-defined COPD risk found an association with dusty exposures [21](#_ENREF_21)[22](#_ENREF_22). A potential explanation is that in our study sample, even if all 353 SOC-coded jobs were covered, some *a priori* high-risk COPD jobs were underrepresented (e.g. coal miners) as reported in our previous job-title analysis [3](#_ENREF_3). Consequently, the related underlying exposures (e.g. mineral dusts) are less prevalent in the current occupational agent-based analysis. In support of this hypothesis, among the six occupations that we previously found at increased COPD risk, only ‘“sculptor, painter, engraver, art restorer” could be clearly associated with underlying mineral dust exposures.

This negative finding for ‘dusty’ job exposures is therefore expected in a general population sample of a ‘developed’ country where manual and non-skilled workers exposed to specific hazardous agents are underrepresented [28](#_ENREF_28), and even more in a voluntary cohort that is internally valid, but may not be representative of the entire UK population and so limiting the generalizability of Biobank study findings [29](#_ENREF_29).

Also, we did not find a positive association for metal exposure; this result confirms and supports our previous job-title analysis [3](#_ENREF_3). This could be due to the low prevalence of metal-related occupations in our study setting, or to limits of the applied JEM in detecting risks specifically for this agent. In fact, other studies using the same JEM found similar results [21](#_ENREF_21)[30](#_ENREF_30)[31](#_ENREF_31), with just one reporting a positive association [32](#_ENREF_32). Also, the presence of a negative exposure trend for ‘ever’ metal exposure, but not for cumulative lifetime exposure could be due to a ‘healthy worker effect’ bias caused by the de-selection of workers with respiratory symptoms before and during employment in metal-exposed jobs.

Our study has several strengths. First, its sample size which, to the best of our knowledge, is larger than any previous study conducted on lifetime occupations and COPD risk (spirometrically-defined) in a general population. Second, the good quality of the spirometry definition of the COPD outcome, based on acceptable, and repeatable manoeuvres according to almost all ATS/ERS criteria [4](#_ENREF_4). Third, the valid job coding, based on a validated automatic online tool, OSCAR [9](#_ENREF_9), which coded each lifetime job collected using standard occupational codes blind to COPD status, ruling out any differential misclassification. Further, the valid occupational exposure assessment, based on the application of the expert-based ALOHA+JEM, a general population-based JEM, designed to evaluate semi-quantitatively potential occupational hazards for COPD risk in community studies [11](#_ENREF_11). Finally, the collection of individual lifetime job-histories that allowed us to increase statistical power, to minimize the risk of a healthy worker survivor effect bias, and to explore exposure-response trends by using categories of cumulative exposure, so supporting the validity of our positive risk associations.

Nevertheless, we acknowledge some limitations. We submitted OSCAR to the UK Biobank participants with an available email address only and we did not have access to ‘non-responders’ data, so we could not compare them with our study participants in relation to potential confounders. Therefore, we cannot rule out a certain degree of selection bias also due to the nature of the entire Biobank cohort (i.e. more women, educated, non-smokers, and mostly ‘White’) that might have affected our ability to detect increased COPD risk for some of the few anticipated occupational hazards such as mineral dusts.

Spirometry tests were conducted without bronchodilator, but we controlled for potential COPD misclassification with asthma by restricting our analyses to those reporting never having had a diagnosis of, or treatment for, asthma. Of note, the COPD prevalence estimated in our sample was within the range of that expected in the UK based on our spirometry definition, and study population age range [6](#_ENREF_6).

Also, although we used a standard job coding classification and valid occupational assessment tools, we cannot rule out a certain degree of exposure misclassification. However, using a JEM (in which the same exposure is assigned to groups of subjects) may introduce a Berkson type error, which (differently from classical random error) may affect precision but usually causes little or no bias in risk estimates [33](#_ENREF_33)[34](#_ENREF_34).

Further, some of the agents that could have explained our previous findings are not included in the applied JEM, such as diesel motor exhaust, that we hypothesised for the association of “warehouse stock handler, stacker” job and COPD risk.

Finally, because of substantial overlap of exposure, we were not able to disentangle specific pesticide subtypes responsible for the observed increased COPD risk.

In conclusion, investigating the lifetime job-histories of about 100,000 individuals from a general population, we found that cumulative exposure to pesticides is associated with an increased COPD risk, with positive exposure-response trends. The unique large sample, and the confirmation of our results in sensitivity analyses, in particular in never-smokers, support the validity of these findings and that they deserve further investigation. Future studies focused on evaluating the effect of specific pesticide types on causing chronic airway obstruction are warranted in order to inform focussed workplace preventive strategies and avoid the associated COPD burden.

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**Contributors:** S. De Matteis conceived and performed the statistical analyses, interpreted the results, and wrote the article. P. Cullinan, L. Rushton and D. Jarvis, as PIs of the HSE-COPD project, coordinated and supervised the analyses, and contributed to the interpretation of the results. H. Kromhout and R. Vermeulen developed the ALOHA+ JEM. D. Consonni and S. Hutchings contributed to data management and statistical analyses. L. Darnton, S. Sadhra, D. Fishwick are participants of the HSE-COPD project. All authors contributed to the interpretation of the results, and reviewed the final manuscript.

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**Table 1** Selected characteristics of study participants with complete lifetime job-histories (n= 94,514), overall and by sex, in the UK Biobank study, 2006-2010, UK.

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Women** | **Men** | **Total** |
|  | **n** | **%** | **n** | **%** | **n** | **%** |
| **Subjects** | 52,733 | 55.8 | 41,781 | 44.2 | 94,514 | 100 |
| **Age category (years)** |  |  |  |  |  |  |
| 40-44 | 5,378 | 10.2 | 3,887 | 9.3 | 9,265 | 9.8 |
| 45-49 | 7,741 | 14.7 | 4,951 | 11.9 | 12,692 | 13.4 |
| 50-54 | 9,780 | 18.5 | 6,370 | 15.2 | 16,150 | 17.1 |
| 55-59 | 11,567 | 21.9 | 8,639 | 20.7 | 20,206 | 21.4 |
| 60-64 | 12,091 | 22.9 | 11,072 | 26.5 | 23,163 | 24.5 |
| 65-69 | 6,063 | 11.5 | 6,714 | 16.1 | 12,777 | 13.5 |
| 70-74 | 113 | 0.2 |  148 | 0.4 |  261 |  0.3 |
| **Age (years)** |  |  |  |  |  |  |
| Mean (SD) | 55.4 | (7.5) | 56.6 | (7.7) | 55.9 | (7.6) |
| **Smoking status** |  |  |  |  |  |  |
| Never | 33,608 | 63.7 | 21,966 | 52.6 | 55,574 | 58.8 |
| Former (quit >6 months ago) | 16,576 | 31.4 | 17,066 | 40.8 | 33,642 | 35.6 |
| Current | 2,549 |  4.8 |  2,749 |  6.6 | 5,298 |  5.6 |
| **Smoking pack-years\*** |  |  |  |  |  |  |
| Median (IQR) | 14.0 | (7-24) | 17.5 | (9-30) | 15.7 | (8-27) |
| **Time since quitting smoking (years)†** |  |  |  |  |  |  |
| Median (IQR) | 20.0 | (9-29) | 22.0 | (10-30) | 21.0 | (10-29) |
| **Doctor’s diagnosis of asthma, n (%)** |  |  |  |  |  |  |
| Never | 46,554 | 88.3 | 37,449 | 89.6 | 84,003 | 88.9 |
| Ever | 6,179 | 11.7 | 4,332 | 10.4 | 10,511 | 11.1 |

\*Smoking pack-years = (n cigarettes/day ÷ 20 cigarettes/pack) × n years; amongst ever smokers. †Time since quitting smoking = years since last smoked cigarette to time of interview; amongst former smokers. Abbreviations: IQR= Inter Quartile Range; SD=Standard Deviation

**Table 2** COPD prevalence ratios (PR) and 95% confidence intervals (CI) associated with exposure ALOHA+JEM agents in the 94,514 subjects with lifetime job-history in the UK Biobank study: all subjects, never asthmatics, and never smokers.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **COPD****Cases** |  | **Non-COPD subjects** |  | **All Subjects** |  |  |  | **Never Asthmatics** |  | **Never Smokers** |  |
| **Exposure** | **n** | **%** | **n** | **%** | **PR1** | **95% CI** | **PR2** | **95% CI** | **PR2** | **95% CI** | **PR2** | **95% CI** |
| **Total** | **7,603** | **100** | **86,911** | **100** |  |  |  |  |  |  |  |  |
| **Vapours, gases, dusts, fumes** |  |  |  |  |  |  |  |  |  |  |  |  |
|  Never | 3,986 | 52.4 | 46,166 | 53.1 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  Ever | 3,617 | 47.6 | 40,745 | 46.9 | 0.97 | 0.92-1.02 | 0.97 | 0.91-1.04 | 1.00 | 0.92-1.07 | 0.93 | 0.85-1.01 |
|  Only low | 2,821 | 37.1 | 32,287 | 37.2 | 0.97 | 0.93-1.02 | 0.97 | 0.91-1.03 | 1.00 | 0.92-1.08 | 0.93 | 0.85-1.01 |
|  Ever high |  796 | 10.5 | 8,458 | 9.7 | 0.95 | 0.87-1.03 | 0.98 | 0.87-1.11 | 0.98 | 0.84-1.13 | 0.91 | 0.76-1.10 |
|  |  |  |  |  | P=0.15 |  | P=0.39 |  | P=0.78 |  | P=0.09 |  |
| **Organic dusts** |  |  |  |  |  |  |  |  |  |  |  |  |
|  Never | 5,390 | 70.9 | 62,371 | 71.8 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  Ever | 2,213 | 29.1 | 24,540 | 28.2 | 1.00 | 0.95-1.05 | 1.01 | 0.94-1.09 | 1.01 | 0.92-1.10 | 0.94 | 0.85-1.05 |
|  Only low | 1,952 | 25.7 | 22,031 | 25.4 | 0.99 | 0.94-1.04 | 1.00 | 0.93-1.08 | 1.01 | 0.92-1.10 | 0.95 | 0.85-1.06 |
|  Ever high |  261 | 3.4 | 2,509 | 2.9 | 1.07 | 0.94-1.21 | 1.03 | 0.88-1.22 | 0.99 | 0.81-1.20 | 0.92 | 0.72-1.17 |
|  |  |  |  |  | P=0.80 |  | P=0.76 |  | P=0.71 |  | P=0.13 |  |
| **Mineral dusts** |  |  |  |  |  |  |  |  |  |  |  |  |
|  Never | 6,134 | 80.7 | 71,064 | 81.8 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  Ever | 1,469 | 19.3 | 15,847 | 18.2 | 0.94 | 0.88-1.00 | 0.92 | 0.84-1.01 | 0.94 | 0.84-1.05 | 0.95 | 083-1.09 |
|  Only low | 1,031 | 13.6 | 11,546 | 13.3 | 0.91 | 0.84-0.97 | 0.95 | 0.86-1.04 | 0.96 | 0.86-1.08 | 0.97 | 0.84-1.11 |
|  Ever high |  438 | 5.8 | 4,301 | 5.0 | 1.04 | 0.93-1.15 | 1.07 | 0.91-1.27 | 1.02 | 0.83-1.25 | 1.03 | 0.79-1.34 |
|  |  |  |  |  | P=0.36 |  | P=0.96 |  | P=0.88 |  | P=0.73 |  |
| **Gases and fumes** |  |  |  |  |  |  |  |  |  |  |  |  |
|  Never | 4,702 | 61.8 | 54,684 | 62.9 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  Ever | 2,901 | 38.2 | 32,227 | 37.1 | 0.97 | 0.92-1.02 | 1.00 | 0.93-1.07 | 1.02 | 0.94-1.11 | 0.95 | 0.87-1.05 |
|  Only low | 2,421 | 31.8 | 26,889 | 30.9 | 0.98 | 0.93-1.04 | 0.99 | 0.92-1.06 | 1.01 | 0.93-1.10 | 0.94 | 0.85-1.03 |
|  Ever high |  480 | 6.3 | 5,138 | 6.1 | 0.87 | 0.79-0.97 | 0.89 | 0.77-1.04 | 0.93 | 0.77-1.12 | 0.99 | 0.78-1.25 |
|  |  |  |  |  | P=0.03 |  | P=0.26 |  | P=0.80 |  | P=0.48 |  |
| **Pesticides** |  |  |  |  |  |  |  |  |  |  |  |  |
|  Never | 7,285 | 95.8 | 83,905 | 96.5 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  Ever |  318 | 4.2 | 3,600 | 3.5 | 1.11 | 0.99-1.25 | 1.13 | 1.01-1.28 | 1.17 | 1.02-1.34 | 1.29 | 1.09-1.54 |
|  Only low |  174 | 2.3 | 1,797 | 2.1 | 0.98 | 0.84-1.15 | 1.01 | 0.86-1.18 | 1.13 | 0.94-1.35 | 1.24 | 0.99-1.57 |
|  Ever high |  144 | 1.9 | 1,209 | 1.4 | 1.32 | 1.12-1.56 | 1.32 | 1.08-1.60 | 1.26 | 1.00-1.60 | 1.39 | 1.04-1.86 |
|  |  |  |  |  | P=0.008 |  | P=0.004 |  | P=0.01 |  | P=0.001 |  |
| **Aromatic/chlorinated solvents** |  |  |  |  |  |  |  |  |  |  |  |  |
|  Never | 6,401 | 84.2 | 73,476 | 84.5 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  Ever | 1,202 | 15.8 | 13,435 | 15.5 | 0.97 | 0.91-1.04 | 1.03 | 0.93-1.14 | 1.05 | 0.93-1.18 | 1.03 | 0.89-1.18 |
|  Only low |  954 | 12.6 | 10,303 | 11.9 | 1.02 | 0.95-1.10 | 1.05 | 0.94-1.16 | 1.07 | 0.94-1.21 | 1.06 | 0.91-1.22 |
|  Ever high |  248 | 3.3 | 3,132 | 3.6 | 0.80 | 0.69-0.91 | 0.94 | 0.73-1.21 | 1.04 | 0.77-1.42 | 0.62 | 0.42-0.92 |
|  |  |  |  |  | P=0.03 |  | P=0.89 |  | P=0.60 |  | P=0.64 |  |
| **Other solvents** |  |  |  |  |  |  |  |  |  |  |  |  |
|  Never | 5,537 | 72.8 | 62,928 | 72.4 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  Ever | 2,066 | 27.2 | 23,983 | 27.6 | 0.96 | 0.91-1.01 | 0.98 | 0.90-1.06 | 0.98 | 0.89-1.09 | 1.05 | 0.93-1.18 |
|  Only low | 1,979 | 26.0 | 23,076 | 26.6 | 0.96 | 0.91-1.02 | 0.99 | 0.91-1.08 | 0.99 | 0.89-1.09 | 1.04 | 0.93-1.18 |
|  Ever high |  87 | 1.1 | 907 | 1.0 | 0.95 | 0.76-1.18 | 1.03 | 0.79-1.32 | 1.00 | 0.74-1.35 | 1.18 | 0.79-1.74 |
|  |  |  |  |  | P=0.15 |  | P=0.69 |  | P=0.71 |  | P=0.22 |  |
| **Metals** |  |  |  |  |  |  |  |  |  |  |  |  |
|  Never | 6,744 | 88.7 | 76,834 | 88.4 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  Ever |  859 | 11.3 | 10,077 | 11.6 | 0.89 | 0.82-0.97 | 0.92 | 0.83-1.02 | 0.91 | 0.80-1.03 | 0.90 | 0.78-1.04 |
|  Only low |  637 | 8.4 | 7,218 | 8.3 | 0.94 | 0.86-1.03 | 0.94 | 0.84-1.05 | 0.94 | 0.82-1.07 | 0.93 | 0.79-1.08 |
|  Ever high |  222 | 2.9 | 2,859 | 3.3 | 0.78 | 0.67-0.90 | 0.88 | 0.67-1.16 | 0.83 | 0.60-1.16 | 1.18 | 0.77-1.79 |
|  |  |  |  |  | P<0.001 |  | P=0.038 |  | P=0.043 |  | P=0.23 |  |

COPD defined as FEV1/FVC<LLN. PRs and CIs calculated with a Poisson model with robust variance adjusted for sex, study centre (22 categories), age (5-years categories), and lifetime smoking exposure (ever, pack-years, and years since quitting). PR1: PRs estimated from the basic model PR2: PRs estimated from a model adjusted also for co-exposure to the other JEM agents. P: P value from test for trend (categories: never, only low, and ever high).

**Table 3** COPD prevalence ratios (PR) and 95% confidence intervals (CI) associated with categories of cumulative exposure to ALOHA+JEM agents in the 94,514 subjects with lifetime job-history in the UK Biobank study: all subjects, never asthmatics, and never smokers.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cumulative exposure categories (EU-years)** | **COPD****Cases** |  | **Non-COPD****subjects** |  | **All subjects** |  |  |  | **Never Asthmatics** |  | **Never Smokers** |  |
|  | **n** | **%** | **n** | **%** | **PR1** | **95%CI** | **PR2** | **95%CI** | **PR2** | **95%CI** | **PR2** | **95%CI** |
| **Total** | **7,603** | **100** | **86,911** | **100** |  |  |  |  |  |  |  |  |
| **Vapours, gases, dusts, fumes** |  |  |  |  |  |  |  |  |  |  |  |  |
|  0 | 3,986 | 52.4 | 46,166 | 53.1 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  0.5-9  | 1,266 | 16.7 | 13,885 | 16.0 | 1.01 | 0.95-1.08 | 0.99 | 0.91-1.06 | 1.00 | 0.91-1.09 | 0.96 | 0.86-1.06 |
|  ≥10 | 2,351 | 30.9 | 26,860 | 30.9 | 0.95 | 0.90-1.00 | 0.96 | 0.89-1.03 | 0.99 | 0.91-1.09 | 0.90 | 0.80-1.01 |
|  |  |  |  |  | P=0.055 |  | P=0.30 |  | P=0.95 |  | P=0.06 |  |
| **Organic dusts** |  |  |  |  |  |  |  |  |  |  |  |  |
|  0 | 5,390 | 70.9 | 62,371 | 71.8 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  0.5-9  |  965 | 12.7 | 10,095 | 11.6 | 1.01 | 0.94-1.09 | 1.02 | 0.93-1.11 | 0.99 | 0.89-1.11 | 0.97 | 0.86-1.11 |
|  ≥10  | 1,248 | 16.4 | 14,445 | 16.6 | 0.99 | 0.93-1.05 | 1.01 | 0.92-1.11 | 1.02 | 0.91-1.14 | 0.91 | 0.80-1.04 |
|  |  |  |  |  | P=0.75 |  | P=0.81 |  | P=0.82 |  | P=0.17 |  |
| **Mineral dusts** |  |  |  |  |  |  |  |  |  |  |  |  |
|  0 | 6,134 | 80.7 | 71,064 | 81.8 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  0.5-9  |  621 | 8.2 | 6,620 | 7.6 | 0.99 | 0.91-1.08 | 0.97 | 0.87-1.08 | 0.97 | 0.85-1.10 | 1.03 | 0.88-1.20 |
|  ≥10  |  848 | 11.2 | 9,227 | 10.6 | 0.90 | 0.83-0.98 | 0.89 | 0.79-1.00 | 0.91 | 0.79-1.04 | 0.87 | 0.73-1.04 |
|  |  |  |  |  | P=0.018 |  | P=0.051 |  | P=0.19 |  | P=0.24 |  |
| **Gases and fumes** |  |  |  |  |  |  |  |  |  |  |  |  |
|  0 | 4,702 | 61.8 | 54,684 | 62.9 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  0.5-9  | 1,244 | 16.4 | 13,690 | 15.8 | 1.01 | 0.95-1.08 | 0.99 | 0.91-1.07 | 1.00 | 0.91-1.10 | 0.92 | 0.82-1.03 |
|  ≥10  | 1,657 | 21.8 | 18,537 | 21.3 | 0.93 | 0.87-0.99 | 0.99 | 0.91-1.08 | 1.04 | 0.93-1.15 | 0.97 | 0.86-1.10 |
|  |  |  |  |  | P=0.040 |  | P=0.99 |  | P=0.44 |  | P=0.59 |  |
| **Pesticides** |  |  |  |  |  |  |  |  |  |  |  |  |
|  0 | 7,285 | 95.8 | 83,905 | 96.5 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  0.5-9  |  174 | 2.3 | 1,784 | 2.0 | 0.99 | 0.84-1.16 | 1.00 | 0.85-1.17 | 1.03 | 0.85-1.24 | 1.21 | 0.96-1.52 |
|  ≥10  |  144 | 1.9 | 1,282 | 1.5 | 1.29 | 1.10-1.52 | 1.32 | 1.12-1.56 | 1.34 | 1.10-1.64 | 1.41 | 1.11-1.80 |
|  |  |  |  |  | P=0.010 |  | P=0.004 |  | P=0.005 |  | P=0.001 |  |
| **Aromatic/chlorinated solvents** |  |  |  |  |  |  |  |  |  |  |  |  |
|  0 | 6,401 | 84.2 | 73,476 | 84.5 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  0.5-9  |  540 | 7.1 | 5,500 | 6.3 | 1.09 | 1.00-1.19 | 1.09 | 0.96-1.23 | 1.14 | 0.98-1.32 | 1.11 | 0.93-1.33 |
|  ≥10  |  662 | 8.7 | 7,935 | 9.1 | 0.88 | 0.81-0.96 | 1.00 | 0.86-1.11 | 0.96 | 0.82-1.12 | 0.94 | 0.78-1.13 |
|  |  |  |  |  | P=0.039 |  | P=0.95 |  | P=0.99 |  | P=0.83 |  |
| **Other solvents** |  |  |  |  |  |  |  |  |  |  |  |  |
|  0 | 5,537 | 72.8 | 62,928 | 72.4 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  0.5-9  |  815 | 10.7 | 8,707 | 10.0 | 1.04 | 0.96-1.12 | 1.02 | 0.91-1.14 | 1.00 | 0.88-1.15 | 1.06 | 0.90-1.24 |
|  ≥10  | 1,251 | 16.5 | 15,276 | 17.6 | 0.92 | 0.86-0.98 | 0.95 | 0.86-1.06 | 0.96 | 0.85-1.09 | 1.07 | 0.92-1.24 |
|  |  |  |  |  | P=0.025 |  | P=0.47 |  | P=0.65 |  | P=0.36 |  |
| **Metals** |  |  |  |  |  |  |  |  |  |  |  |  |
|  0 | 6,744 | 88.7 | 76,834 | 88.4 | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference | 1.00 | Reference |
|  0.5-9  |  316 | 4.2 | 3,359 | 3.9 | 0.99 | 0.88-1.12 | 0.98 | 0.85-1.12 | 0.97 | 0.83-1.14 | 0.98 | 0.80-1.19 |
|  ≥10  |  543 | 7.1 | 6,718 | 7.7 | 0.84 | 0.76-0.92 | 0.93 | 0.82-1.05 | 0.91 | 0.78-1.07 | 0.89 | 0.75-1.06 |
|  |  |  |  |  | P<0.001 |  | P=0.17 |  | P=0.15 |  | P=0.16 |  |

COPD defined as FEV1/FVC<LLN. PRs and CIs calculated with a Poisson model with robust variance adjusted for sex, study centre (22 categories), age (5-years categories), and lifetime smoking exposure (ever, pack-years, and years since quitting). PR1: PRs estimated from the basic model PR2: PRs estimated from a model adjusted also for co-exposure to the other JEM agents. P: P value from test for trend (categories: cumulative EU: exposure-units years).

[Figure legends]

**Figure 1.** Flowchart showing subjects selection in the UK Biobank study, 2006-2010, UK.

\*Absolute contraindications to spirometry included chest infection in the last month (i.e., influenza, bronchitis, severe cold, pneumonia); history of detached retina; heart attack or surgery to eyes, chest or abdomen in last 3 months; history of a collapsed lung; pregnancy (1st or 3rd trimester); and currently on medication for tuberculosis

**Figure 2.** Association between fully adjusted prevalence ratios (PR) of chronic obstructive pulmonary disease (COPD) and cumulative exposure to pesticides (EU-years, ln-transformed) using restricted cubic splines (knots at 25th, 50th, 75th and 90th percentiles of cumulative exposure among exposed, ln-transformed), in the UK Biobank study, 2006-2010, UK. The continuous curves are PR and 95% confidence bands; the dashed line shows the log-linear relationship PR=1.08 per ln(EU-years).

ln=natural logarithm

**Figure 3.** Association between fully adjusted prevalence ratios (PR) of chronic obstructive pulmonary disease (COPD) and duration of exposure to pesticides (EU-years, ln-transformed) using restricted cubic splines (knots at 25th, 50th, 75th and 90th percentiles of cumulative exposure among exposed, ln-transformed), in the UK Biobank study, 2006-2010, UK. The continuous curves are PR and 95% confidence bands; the dashed line shows the log-linear relationship PR=1.09 per ln(years).

ln=natural logarithm