Original research

Lifetime occupational exposures and chronic obstructive pulmonary disease risk in the UK Biobank cohort

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2020-216523).

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Received 12 November 2020
Accepted 4 November 2021
Published Online First 26 January 2022

ABSTRACT

Background and aim Occupational exposures are important, preventable causes of COPD. We previously found an increased risk of COPD among six occupations by analysing lifetime job histories and lung function data in the population-based UK Biobank cohort. We aimed to build on these findings and elucidate the underlying potential causal agents to focus preventive strategies.
Methods We applied the ALOHA+job exposure matrix (JEM) based on the International Standard Classification of Occupations V.1988 codes, where exposure to 12 selected agents was rated as 0 (no exposure), 1 (low) or 2 (high). COPD was spirometrically defined as FEV_1/FVC less than the lower limit of normal. We calculated semiquantitative cumulative exposure estimates for each agent by multiplying the duration of exposure and squared intensity. Prevalence ratio (PR) and 95% CI for COPD were estimated using robust Poisson regression adjusted for centre, sex, age, smoking and coexposure 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 and smoking data and were included in the analysis. Pesticide exposure showed increased risk of COPD for ever exposure (PR=1.13, 95% CI 1.01 to 1.28) and high cumulative exposure (PR=1.32, 95% CI 1.12 to 1.56), with positive exposure–response trends (p trend=0.004), which 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 risk of COPD. Focused preventive strategies for workers exposed to pesticides can prevent the associated COPD burden.

Key messages

What is the key question?
- ⇒ What are the occupational exposures associated with risk of COPD in the general population?

What is the bottom line?
- ⇒ In a large population-based study, lifetime cumulative exposure to pesticides was 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 increased the risk of COPD.
- ⇒ Focused preventive strategies are warranted.

INTRODUCTION

Occupational exposures are important, preventable causes of COPD, and it has been recently estimated that about 14% of all cases are work-related.[1] Identification of specific occupations and the underlying exposures associated with increased risk of COPD is key to preventing the associated public health burden, both in terms 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; and the definition of COPD 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] a very large population-based study that allowed us to evaluate a broad range of occupations in relation to spirometrically defined risk of COPD also in analyses restricted to never-smokers. By analysing lifetime job histories and lung function data in this cohort, we previously found six occupations that increased the risk of COPD; in particular, agriculture-related jobs emerged to be at a higher risk.[3] To follow up and progress these findings, we applied a job exposure matrix (JEM) to selected agents, including pesticides, previously reported to be associated with risk of COPD in order to identify potential underlying causal agents and inform 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] Briefly, a random sample of adults aged 40–69 years were identified from the

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To cite: De Matteis S, Jarvis D, Darnton L, *et al*. *Thorax* 2022;**77**:997–1005.

list 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 of 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 (91%) underwent lung function testing at recruitment as detailed in the spirometry protocol.[2] All spirometry tests were performed according to the American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines[4]; however, only up to three attempts were required to provide two reproducible manoeuvres. Bronchial reversibility was not tested. In our work, we included acceptable spirometry data based on a quality appraisal of the flow curves as previously described.[3 5] We used the spirometry threshold FEV_1/FVC less than the lower limit of normal (ie, the 5% lower tail of the normal distribution of the average predicted FEV_1/FVC in a reference healthy never-smoking population) as a *proxy* for COPD based on the age range of our study population.[6] We used the Hankinson equation to calculate the individual predicted values for FEV_1/FVC.[6–8] 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 of all 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] Briefly, OSCAR is a categorical decision tree based on the hierarchical structure of the UK Standard Occupational Classification (SOC) V.2000.[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 four-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+JEM, an extension of the ALOHA-JEM that was developed using industrial hygienists' expert assessment to evaluate the occupational hazards for COPD in community-based studies.[11] This semiquantitative JEM assigns, for every job coded using the four-digit codes of the International Standard Classification of Occupations V.1988 (ISCO-88),[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://wwwonsgovuk/.

Statistical analysis

To evaluate the association between lifetime occupational exposures and risk of COPD, 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] to estimate the prevalence ratio (PR) and 95% CI for ever exposure; intensity of exposure (never, only low, ever high); duration of exposure (years), either continuous or categorised (never exposed, 0.5 to <10 years, 10+ years); and cumulative exposure, in exposure unit-years (EU-years), either continuous or categorised (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 the products of exposure duration and the squared intensity covering all lifetime job periods.[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 model, where the PR for each category of agents was adjusted by the covariates listed above; and PR2 model, additionally adjusted for coexposures 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 the 25th, 50th, 75th and 90th percentiles. The two covariates were entered in the models after natural log-transformation for the reason given above.

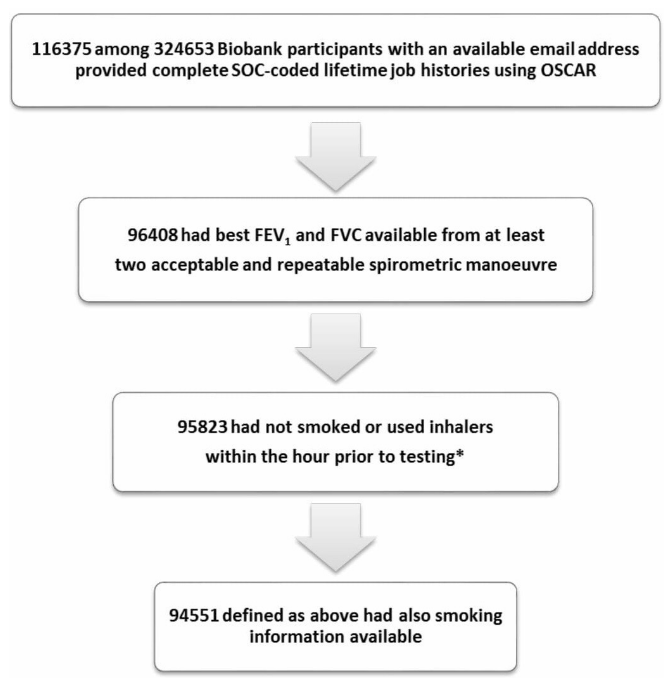

Figure 1 Flow chart showing the selection of subjects from the UK Biobank study, 2006–2010. *Absolute contraindications to spirometry included chest infection in the last month (ie, influenza, bronchitis, severe cold, pneumonia); history of detached retina; heart attack or surgery to the eyes, chest or abdomen in the last 3 months; history of a collapsed lung; pregnancy (first or third trimester); and currently on medication for TB. OSCAR, Occupations Self-Coding Automatic Recording; SOC, Standard Occupational Classification.

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 prebronchodilator 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 V.16.

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 and smoking data and were included in the analysis (figure 1).

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 and the average age was 56 years (SD: 7.6). Most were never-smokers (n=55 574, 58.8%) and only a minority were current smokers (n=5298, 5.6%). About 11% of the participants reported a diagnosis of asthma. The prevalence of spirometry-defined COPD was 8.0% (corresponding to 7603 cases). As expected, the frequency of COPD was higher among current smokers (16.8%) than among former smokers (8.6%) and never-smokers (6.9%).

The results were similar in women and men.

Based on the Spearman's correlation matrix, there was a significant overlap between exposures (see online supplemental table 1), particularly between subgroups of pesticides and solvents. Moreover, there were sparse data for the subgroups of pesticides, making it impossible to disentangle their specific effects. For these reasons, we combined in the analyses the subgroups of pesticides (ie, herbicides, insecticides, fungicides) and aromatic and chlorinated solvents.

The percentage of participants exposed varied considerably across the occupational agents (table 2): a relatively small percentage of cohort members were exposed to pesticides (4.2% among COPD cases and 3.5% among subjects without COPD), 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 the multivariable analyses adjusted for the core covariates, ever exposure to pesticides was associated with increased risk of COPD. This was also confirmed after adjustment for coexposure to other JEM agents and in the sensitivity analyses restricted to never-asthmatics and never-smokers. In addition, positive exposure–response trends in the level of intensity (ever high vs only low) were found.

When considering categories of lifetime cumulative exposures in EU-years (table 3), the positive association of pesticides with increased risk of COPD 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 PR of 1.08 (95% CI 1.03 to 1.14) and 1.09 (95% CI 1.03 to 1.15), respectively.

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

The 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 the risk of COPD, with positive exposure–response

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

	Women		Men		Total	
Characteristics	n	%	n	%	n	%
Subjects	52 733	55.8	41 781	44.2	94 514	100
Age category (years)						
40–44	5378	10.2	3887	9.3	9265	9.8
45–49	7741	14.7	4951	11.9	12 692	13.4
50–54	9780	18.5	6370	15.2	16 150	17.1
55–59	11 567	21.9	8639	20.7	20 206	21.4
60–64	12 091	22.9	11 072	26.5	23 163	24.5
65–69	6063	11.5	6714	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	2549	4.8	2749	6.6	5298	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						
Never	46 554	88.3	37 449	89.6	84 003	88.9
Ever	6179	11.7	4332	10.4	10 511	11.1

*Smoking pack-years=(n cigarettes/day ÷ 20 cigarettes/pack) × n years, among ever-smokers.
†Time since quitting smoking=years since last smoked cigarette to time of interview, among former smokers.

Table 2 COPD PR and 95% CI associated with exposure to ALOHA+JEM agents in 94 514 subjects with lifetime job history in the UK Biobank study: all subjects, never-asthmatics and never-smokers

	COPD cases		Subjects without COPD		All subjects				Never-asthmatics		Never-smokers	
Exposure	n	%	n	%	PR1	95% CI	PR2	95% CI	PR2	95% CI	PR2	95% CI
Total	7603	100	86 911	100								
Vapours, gases, dusts, fumes												
Never	3986	52.4	46 166	53.1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Ever	3617	47.6	40 745	46.9	0.97	0.92 to 1.02	0.97	0.91 to 1.04	1.00	0.92 to 1.07	0.93	0.85 to 1.01
Only low	2821	37.1	32 287	37.2	0.97	0.93 to 1.02	0.97	0.91 to 1.03	1.00	0.92 to 1.08	0.93	0.85 to 1.01
Ever high	796	10.5	8458	9.7	0.95	0.87 to 1.03	0.98	0.87 to 1.11	0.98	0.84 to 1.13	0.91	0.76 to 1.10
					P=0.15		P=0.39		P=0.78		P=0.09	
Organic dusts												
Never	5390	70.9	62 371	71.8	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Ever	2213	29.1	24 540	28.2	1.00	0.95 to 1.05	1.01	0.94 to 1.09	1.01	0.92 to 1.10	0.94	0.85 to 1.05
Only low	1952	25.7	22 031	25.4	0.99	0.94 to 1.04	1.00	0.93 to 1.08	1.01	0.92 to 1.10	0.95	0.85 to 1.06
Ever high	261	3.4	2509	2.9	1.07	0.94 to 1.21	1.03	0.88 to 1.22	0.99	0.81 to 1.20	0.92	0.72 to 1.17
					P=0.80		P=0.76		P=0.71		P=0.13	
Mineral dusts												
Never	6134	80.7	71 064	81.8	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Ever	1469	19.3	15 847	18.2	0.94	0.88 to 1.00	0.92	0.84 to 1.01	0.94	0.84 to 1.05	0.95	083 to 1.09
Only low	1031	13.6	11 546	13.3	0.91	0.84 to 0.97	0.95	0.86 to 1.04	0.96	0.86 to 1.08	0.97	0.84 to 1.11
Ever high	438	5.8	4301	5.0	1.04	0.93 to 1.15	1.07	0.91 to 1.27	1.02	0.83 to 1.25	1.03	0.79 to 1.34
					P=0.36		P=0.96		P=0.88		P=0.73	
Gases and fumes												
Never	4702	61.8	54 684	62.9	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Ever	2901	38.2	32 227	37.1	0.97	0.92 to 1.02	1.00	0.93 to 1.07	1.02	0.94 to 1.11	0.95	0.87 to 1.05
Only low	2421	31.8	26 889	30.9	0.98	0.93 to 1.04	0.99	0.92 to 1.06	1.01	0.93 to 1.10	0.94	0.85 to 1.03
Ever high	480	6.3	5138	6.1	0.87	0.79 to 0.97	0.89	0.77 to 1.04	0.93	0.77 to 1.12	0.99	0.78 to 1.25
					P=0.03		P=0.26		P=0.80		P=0.48	
Pesticides												
Never	7285	95.8	83 905	96.5	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Ever	318	4.2	3600	3.5	1.11	0.99 to 1.25	1.13	1.01 to 1.28	1.17	1.02 to 1.34	1.29	1.09 to 1.54
Only low	174	2.3	1797	2.1	0.98	0.84 to 1.15	1.01	0.86 to 1.18	1.13	0.94 to 1.35	1.24	0.99 to 1.57
Ever high	144	1.9	1209	1.4	1.32	1.12 to 1.56	1.32	1.08 to 1.60	1.26	1.00 to 1.60	1.39	1.04 to 1.86
					P=0.008		P=0.004		P=0.01		P=0.001	
Aromatic/chlorinated solvents												

Continued

Table 2 Continued

Exposure	COPD cases n	%	Subjects without COPD n	%	All subjects PR1	95% CI	PR2	95% CI	Never-asthmatics PR2	95% CI	Never-smokers PR2	95% CI
Never	6401	84.2	73 476	84.5	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Ever	1202	15.8	13 435	15.5	0.97	0.91 to 1.04	1.03	0.93 to 1.14	1.05	0.93 to 1.18	1.03	0.89 to 1.18
Only low	954	12.6	10 303	11.9	1.02	0.95 to 1.10	1.05	0.94 to 1.16	1.07	0.94 to 1.21	1.06	0.91 to 1.22
Ever high	248	3.3	3132	3.6	0.80	0.69 to 0.91	0.94	0.73 to 1.21	1.04	0.77 to 1.42	0.62	0.42 to 0.92
					P=0.03		P=0.89		P=0.60		P=0.64	
Other solvents												
Never	5537	72.8	62 928	72.4	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Ever	2066	27.2	23 983	27.6	0.96	0.91 to 1.01	0.98	0.90 to 1.06	0.98	0.89 to 1.09	1.05	0.93 to 1.18
Only low	1979	26.0	23 076	26.6	0.96	0.91 to 1.02	0.99	0.91 to 1.08	0.99	0.89 to 1.09	1.04	0.93 to 1.18
Ever high	87	1.1	907	1.0	0.95	0.76 to 1.18	1.03	0.79 to 1.32	1.00	0.74 to 1.35	1.18	0.79 to 1.74
					P=0.15		P=0.69		P=0.71		P=0.22	
Metals												
Never	6744	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 to 0.97	0.92	0.83 to 1.02	0.91	0.80 to 1.03	0.90	0.78 to 1.04
Only low	637	8.4	7218	8.3	0.94	0.86 to 1.03	0.94	0.84 to 1.05	0.94	0.82 to 1.07	0.93	0.79 to 1.08
Ever high	222	2.9	2859	3.3	0.78	0.67 to 0.90	0.88	0.67 to 1.16	0.83	0.60 to 1.16	1.18	0.77 to 1.79
					P<0.001		P=0.038		P=0.043		P=0.23	

COPD defined as FEV_1/FVC less than the lower limit of normal.
PR and CI calculated with a Poisson model with robust variance adjusted for sex, study centre (22 categories), age (5-year categories) and lifetime smoking exposure (ever, pack-years and years since quitting). PR1: PR estimated from the basic model; PR2: PR estimated from a model also adjusted for coexposure to the other JEM agents.
P value from test for trend (categories: never, only low and ever high).
JEM, job exposure matrix; PR, prevalence ratio.

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

Cumulative exposure categories	COPD cases		Subjects without COPD		All subjects				Never-asthmatics		Never-smokers	
(EU-years)	n	%	n	%	PR1	95% CI	PR2	95% CI	PR2	95% CI	PR2	95% CI
Total	7603	100	86 911	100								
Vapours, gases, dusts, fumes												
0	3986	52.4	46 166	53.1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
0.5–9	1266	16.7	13 885	16.0	1.01	0.95 to 1.08	0.99	0.91 to 1.06	1.00	0.91 to 1.09	0.96	0.86 to 1.06
≥10	2351	30.9	26 860	30.9	0.95	0.90 to 1.00	0.96	0.89 to 1.03	0.99	0.91 to 1.09	0.90	0.80 to 1.01
					P=0.055		P=0.30		P=0.95		P=0.06	
Organic dusts												
0	5390	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 to 1.09	1.02	0.93 to 1.11	0.99	0.89 to 1.11	0.97	0.86 to 1.11
≥10	1248	16.4	14 445	16.6	0.99	0.93 to 1.05	1.01	0.92 to 1.11	1.02	0.91 to 1.14	0.91	0.80 to 1.04
					P=0.75		P=0.81		P=0.82		P=0.17	
Mineral dusts												
0	6134	80.7	71 064	81.8	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
0.5–9	621	8.2	6620	7.6	0.99	0.91 to 1.08	0.97	0.87 to 1.08	0.97	0.85 to 1.10	1.03	0.88 to 1.20
≥10	848	11.2	9227	10.6	0.90	0.83 to 0.98	0.89	0.79 to 1.00	0.91	0.79 to 1.04	0.87	0.73 to 1.04
					P=0.018		P=0.051		P=0.19		P=0.24	
Gases and fumes												
0	4702	61.8	54 684	62.9	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
0.5–9	1244	16.4	13 690	15.8	1.01	0.95 to 1.08	0.99	0.91 to 1.07	1.00	0.91 to 1.10	0.92	0.82 to 1.03
≥10	1657	21.8	18 537	21.3	0.93	0.87 to 0.99	0.99	0.91 to 1.08	1.04	0.93 to 1.15	0.97	0.86 to 1.10
					P=0.040		P=0.99		P=0.44		P=0.59	
Pesticides												
0	7285	95.8	83 905	96.5	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
0.5–9	174	2.3	1784	2.0	0.99	0.84 to 1.16	1.00	0.85 to 1.17	1.03	0.85 to 1.24	1.21	0.96 to 1.52
≥10	144	1.9	1282	1.5	1.29	1.10 to 1.52	1.32	1.12 to 1.56	1.34	1.10 to 1.64	1.41	1.11 to 1.80
					P=0.010		P=0.004		P=0.005		P=0.001	
Aromatic/chlorinated solvents												
0	6401	84.2	73 476	84.5	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
0.5–9	540	7.1	5500	6.3	1.09	1.00 to 1.19	1.09	0.96 to 1.23	1.14	0.98 to 1.32	1.11	0.93 to 1.33
≥10	662	8.7	7935	9.1	0.88	0.81 to 0.96	1.00	0.86 to 1.11	0.96	0.82 to 1.12	0.94	0.78 to 1.13
					P=0.039		P=0.95		P=0.99		P=0.83	

Continued

Table 3 Continued

Cumulative exposure categories (EU-years)	COPD cases n	COPD cases %	Subjects without COPD n	Subjects without COPD %	All subjects PR1	All subjects 95% CI	All subjects PR2	All subjects 95% CI	Never-asthmatics PR2	Never-asthmatics 95% CI	Never-smokers PR2	Never-smokers 95% CI
Other solvents												
0	5537	72.8	62 928	72.4	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
0.5–9	815	10.7	8707	10.0	1.04	0.96 to 1.12	1.02	0.91 to 1.14	1.00	0.88 to 1.15	1.06	0.90 to 1.24
≥10	1251	16.5	15 276	17.6	0.92	0.86 to 0.98	0.95	0.86 to 1.06	0.96	0.85 to 1.09	1.07	0.92 to 1.24
					P=0.025		P=0.47		P=0.65		P=0.36	
Metals												
0	6744	88.7	76 834	88.4	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
0.5–9	316	4.2	3359	3.9	0.99	0.88 to 1.12	0.98	0.85 to 1.12	0.97	0.83 to 1.14	0.98	0.80 to 1.19
≥10	543	7.1	6718	7.7	0.84	0.76 to 0.92	0.93	0.82 to 1.05	0.91	0.78 to 1.07	0.89	0.75 to 1.06
					P<0.001		P=0.17		P=0.15		P=0.16	

COPD defined as FEV_1/FVC less than the lower limit of normal.
PR and CI calculated with a Poisson model with robust variance adjusted for sex, study centre (22 categories), age (5-year categories) and lifetime smoking exposure (ever, pack-years and years since quitting). PR1: PR estimated from the basic model; PR2: PR estimated from a model adjusted also for coexposure to the other JEM agents.
P value from test for trend (categories: cumulative EU-years).
EU-years, exposure unit-years; JEM, job exposure matrix; PR, prevalence ratio.

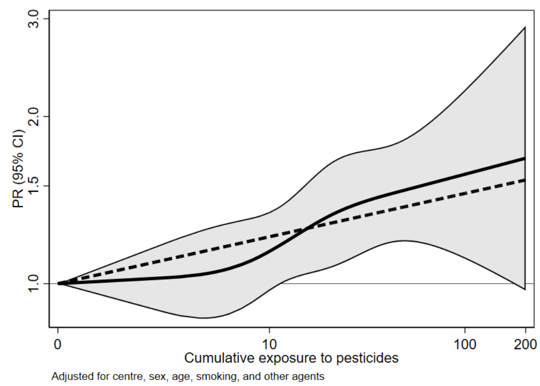

Figure 2 Association between fully adjusted PR of COPD and cumulative exposure to pesticides (EU-years, ln-transformed) using restricted cubic splines (knots at the 25th, 50th, 75th and 90th percentiles of the cumulative exposure among the exposed, ln-transformed) in the UK Biobank study, 2006–2010.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

trends. This result was also confirmed among never-smokers and never-asthmatics.

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

Agriculture has been consistently reported as a sector at high risk of COPD, and several occupational hazards, including organic and inorganic dusts, pesticides and diesel exhaust fumes, have been proposed as potential causal factors.[15–20] Of note, 'gardeners/groundsmen' for the first time appeared to be at

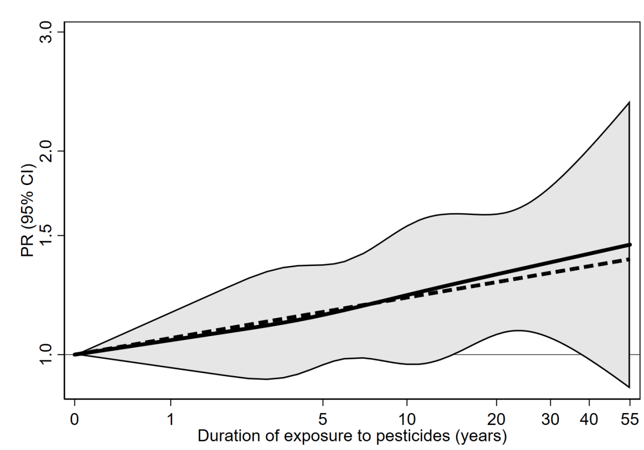

Figure 3 Association between fully adjusted PR of COPD and duration of exposure to pesticides (EU-years, ln-transformed) using restricted cubic splines (knots at the 25th, 50th, 75th and 90th percentiles of the cumulative exposure among the exposed, ln-transformed) in the UK Biobank study, 2006–2010.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

increased risk of COPD in our previous study,[3] and we hypothesised that pesticide exposure could be one of the potential causal factors. Moreover, we found elevated COPD prevalence in 'agriculture, and fishing occupations not elsewhere classified', and we hypothesised that pesticide exposure could also 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 the risk of COPD. We tried to disentangle the possible independent effects of pesticide exposure and those two occupations, but the high overlap between them (JEM assigns 'high pesticide exposure' to both jobs) prevented us from discriminating their relative role.

An association between pesticide exposure and COPD risk has been previously reported by two similar studies using the same ALOHA+JEM[18 21]; however, both had less power than ours and so were unable to adjust for coexposure to all other JEM agents. In addition, these studies did not evaluate the association among never-smokers and never-asthmatics to rule out any potential residual confounding effect of tobacco smoking and disease misclassification with asthma, respectively. A recent meta-analysis evaluating pesticide exposure and lung function metrics found tentative evidence that exposure to cholinesterase (ChE)-inhibiting pesticides is associated with a decreased FEV_1/FVC.[22] In relation to biological plausibility, ChE-inhibiting pesticides such as organophosphate have cholinergic effects resulting in increased bronchial secretion and bronchoconstriction.[23] Also, neutrophilic and oxidative stress-mediated inflammation has been hypothesised to contribute to pesticide-related chronic respiratory diseases pathogenesis,[24 25] and a recent mechanistic study found that stimulation of the alveolar macrophages and increase of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activation, resulting in tumour necrosis factor alpha (TNF-α) protein release, could be an additional underlying biological mechanism.[26]

We did not find a positive association with traditional 'dusty' exposures, in particular 'VGDF', and 'mineral dusts', previously reported to be associated with risk of COPD, even if mostly based on self-reported exposures.[1] We note that neither of the two previous studies that used ALOHA+JEM in relation to spirometrically defined risk of COPD found an association with dusty exposures.[21] A potential explanation is that, in our study sample, even if all 353 SOC-coded jobs were covered, some a priori jobs at high risk of COPD were under-represented (eg, coal miners), as reported in our previous job title analysis.[3] Consequently, the related underlying exposures (eg, 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 to be at increased risk of COPD, 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 from a 'developed' country where manual and non-skilled workers exposed to specific hazardous agents are under-represented,[27] and even more in a voluntary cohort that is internally valid, but may not be representative of the entire UK population, limiting the generalisability of the findings of the Biobank study.[28]

We also did not find a positive association with metal exposure; this result confirms and supports our previous job title analysis.[3] This could be due to the low prevalence of metal-related occupations in our study setting, or to the limits of the applied JEM in detecting the risk specifically for this agent. In fact, other studies using the same JEM found similar results,[29 30] with just one reporting a positive association.[31] 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 is 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] Third is the valid job coding, which was based on a validated automatic online tool, OSCAR,[9] which coded each lifetime job collected using standard occupational codes blind to COPD status, ruling out any differential misclassification. A further strength is the valid occupational exposure assessment, which was based on the application of the expert-based ALOHA+JEM, a general population-based JEM designed to semiquantitatively evaluate potential occupational hazards for COPD risk in community studies.[11] Finally, the collection of individual lifetime job histories allowed us to increase the study's statistical power, to minimise the risk of a healthy worker survivor effect bias and to explore exposure–response trends using categories of cumulative exposure, 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 data of 'non-responders', 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 (ie, more women, educated, non-smokers and mostly 'white'), which might have affected our ability to detect the increased risk of COPD for some of the few anticipated occupational hazards such as mineral dusts.

Spirometry tests were conducted without a bronchodilator; however, 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]

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 the JEM (in which the same exposure is assigned to groups of subjects) may introduce a Berkson-type error, which (different from the classic random error) may affect precision, but usually causes little or no bias in risk estimates.[32 33]

Further, some of the agents that could have explained our previous findings using a job title approach[3] 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, due to the substantial overlap of exposure, we were not able to disentangle specific pesticide subtypes responsible for the observed increased risk of COPD.

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 risk of COPD, 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 deserve further investigation.

Future studies focused on evaluating the effect of specific types of pesticides on chronic airway obstruction are warranted in order to inform focused workplace preventive strategies and avoid the associated COPD burden.

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Acknowledgements We would like to thank Naomi Allen, Heather Young and Alan Young (Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK) for their important contribution to implementing the OSCAR tool in the UK Biobank web platform.

Contributors SDM conceived and performed the statistical analyses, interpreted the results and wrote the article. PC, LR and DJ, as PIs of the HSE-COPD project, coordinated and supervised the analyses and contributed to the interpretation of the results. PC is the guarantor. HK and RV developed the ALOHA+JEM. DC and SH contributed to data management and statistical analyses. LD, SSS and DF are participants of the HSE-COPD project. All authors contributed to the interpretation of the results and reviewed the final manuscript.

Funding This work was supported by contract OH1511 from the Health and Safety Executive (HSE). This research has been conducted using the UK Biobank resource under application number 178.

Disclaimer This publication and the work it describes, including any opinions and/or conclusions expressed, are those of the authors and do not necessarily reflect HSE policy.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval UK Biobank has received ethics approval from the National Health Service National Research Ethics Service (ref 11/NW/0382). All subjects signed written informed consent and all methods were carried out in accordance with relevant guidelines and regulations for human subjects.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. We used UK Biobank data to analyse and report the findings. Data access policy can be obtained from https://www.ukbiobank.ac.uk/.

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

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Online Data Supplement

Table S1. Spearman's correlation matrix between the 12 agents included in the ALOHA+ JEM.

	Vgdf	Organic dusts	Mineral dusts	Gases and fumes	All pesticides	Herbicides	Insecticides	Fungicides	Aromatic solvents	Chlorinated solvents	Other solvents	Metals
Vgdf	**1.00**											
Organic dusts	0.67	**1.00**										
Mineral dusts	0.51	0.37	**1.00**									
Gases and fumes	0.82	0.38	0.61	**1.00**								
Pesticides	0.20	0.30	0.35	0.24	**1.00**							
Herbicides	0.13	0.20	0.26	0.16	0.64	**1.00**						
Insecticides	0.19	0.29	0.34	0.23	**0.95**	0.65	**1.00**					
Fungicides	0.19	0.27	0.37	0.23	**0.92**	0.68	**0.92**	**1.00**				
Aromatic solvents	0.44	0.15	0.43	0.54	0.16	0.18	0.16	0.17	**1.00**			
Chlorinated solvents	0.41	0.10	0.39	0.49	0.05	0.02	0.04	0.05	**0.85**	**1.00**		
Other solvents	0.65	0.50	0.25	0.49	0.06	0.01	0.06	0.03	0.60	0.59	**1.00**	
Metals	0.33	0.03	0.47	0.41	0.08	0.02	0.06	0.09	0.55	0.51	0.42	**1.00**

Correlation coefficients >0.85 are in bold. Vgdf= Vapours, gases, dusts, fumes