ORIGINAL ARTICLE

Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age

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ABSTRACT

Rationale Population-based studies have found evidence of a relationship between occupational exposures and Chronic Obstructive Pulmonary Disease (COPD), but these studies are limited by the use of prebronchodilator spirometry. Establishing this link using postbronchodilator is critical, because occupational exposures are a modifiable risk factor for COPD.

Objectives To investigate the associations between occupational exposures and fixed airflow obstruction using postbronchodilator spirometry.

Methods One thousand three hundred and thirty-five participants were included from 2002 to 2008 follow-up of the Tasmanian Longitudinal Health Study (TAHS). Spirometry was performed and lifetime work history calendars were used to collect occupational history. ALOHA plus Job Exposure Matrix was used to assign occupational exposure, and defined as ever exposed and cumulative exposure unit (EU)-years. Fixed airflow obstruction was defined by postbronchodilator FEV_1/FVC <0.7 and the lower limit of normal (LLN). Multinomial logistic regressions were used to investigate potential associations while controlling for possible confounders.

Results Ever exposure to biological dust (relative risk (RR)=1.58, 95% CI 1.01 to 2.48), pesticides (RR=1.74,95% CI 1.00 to 3.07) and herbicides (RR=2.09,95% CI 1.18 to 3.70) were associated with fixed airflow obstruction. Cumulative EU-years to all pesticides (RR=1.11,95% CI 1.00 to 1.25) and herbicides (RR=1.15,95% CI 1.00 to 1.32) were also associated with fixed airflow obstruction. In addition, all pesticides exposure was consistently associated with chronic bronchitis and symptoms that are consistent with airflow obstruction. Ever exposure to mineral dust, gases/fumes and vapours, gases, dust or fumes were only associated with fixed airflow obstruction in non-asthmatics only.

Conclusions Pesticides and herbicides exposures were associated with fixed airflow obstruction and chronic bronchitis. Biological dust exposure was also associated with fixed airflow obstruction in non-asthmatics. Minimising occupational exposure to these agents may help to reduce the burden of COPD.

Key messages

What is the key question?
► What are the associations between occupational exposure and fixed airflow obstruction?

What is the bottom line?
► This study has shown that pesticides and herbicides exposures were associated with fixed airflow obstruction, chronic bronchitis and respiratory symptoms.

Why read on?
► This study is the first to describe an association between all pesticides exposure and fixed airflow obstruction, and certain exposures were only associated with fixed airflow obstruction in non-asthmatics but not in asthmatics.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) characterised by postbronchodilator (BD) fixed airflow obstruction (AO) is a chronic debilitating respiratory condition and a growing cause of mortality and morbidity worldwide.[1] Tobacco smoking remains the predominant risk factor for COPD.[2] However, it is now well established that non-smokers also develop COPD and the interest in non-smoking-related risk factors for COPD have exponentially increased in the recent past.[3] Occupational exposures are an important potentially modifiable risk factor for COPD, and while the population-based studies conducted to date have provided valuable information about the importance of these exposures in COPD they have had some important limitations.

We recently performed a systematic review assessing the association between occupational exposure to dusts, gases and fumes, and COPD in population-based studies that used job exposure matrices.[4] Our review found an overall association between occupational exposures to mineral dust and gases/fumes and COPD. However, the results varied by definitions of COPD and only one study to date had used post-BD spirometry to define COPD.[5] This is an important limitation in the current literature as the post-BD measurement of AO is the gold standard to define fixed AO,[6] which is the hallmark feature of COPD.[1] The one study that did use post-BD to define AO did not find any

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association between dust, gases/fumes and fixed AO.[5] However, the age range of this cohort was very broad and more than a quarter of the cohort were younger than 45 years. This highlights a further limitation of the existing studies in this area; they are relatively young cohorts who are not likely to have developed significant fixed AO. Furthermore, only few population-based studies have investigated the effects of lifetime occupational exposures assessed over an individual's complete working life,[5 7 8] which allows for assessment of cumulative exposure.[9] Our systematic review concluded that the combination of young cohorts with pre-BD lung function and the lack of assessment of lifetime occupational exposures highlight the need for further studies in this area addressing these issues.

Another limitation of the existing literature around occupational exposures and COPD is the lack of studies examining pesticide exposures. There is increasing evidence that pesticide exposure is associated with respiratory symptoms and diseases, with the strongest evidence for asthma.[10 11] Recent studies from the Netherlands have found an association between pesticide and COPD,[12] and lung function decline.[13] However, these studies are again limited by the use of pre-BD spirometry, which does not allow for the identification of fixed AO.

Given the limitations in the studies conducted to date, we investigated the association between occupational exposure and COPD using post-BD spirometry in a general population. We explored both ever exposure and cumulative exposure unit (EU)-years of occupational exposure. Some of the results of this study have been previously published in the form of an abstract.[14]

METHODS

Study design and participants

We included participants from the 2002 to 2008 follow-up of the population-based Tasmanian Longitudinal Health Study (TAHS), details of which have been reported elsewhere,[15] and are summarised in figure 1. Briefly, TAHS started in 1968 when all children aged 7 years (n=8583) attending school in Tasmania were enrolled in a study of asthma. Their parents completed a respiratory health questionnaire, and the children underwent a clinical examination and lung function measurements. Follow-up surveys were conducted in 1974, 1979 and 1991 at the ages of 12, 18 and 30 years, respectively. The 2002–2008 follow-up started in 2002 when participants were in their fifth decade of life. We traced 7562 (88.1%) of the original 1968 cohort to a residential address and achieved a response of 5729 (78.4%) to a postal survey. A subgroup of these respondents, selected from their participation in previous follow-ups and enriched for participants with a history of asthma and bronchitis, were invited to participate in a more detailed laboratory study and information was collected using questionnaire, pre-BD and post-BD lung function test, skin prick testing, lung volumes and diffusing capacity. Of 2387 invited, 1397 (58.6%) took part in full laboratory testing, 354 (14.8%) completed a telephone questionnaire only and 636 (26.7%) withdrew from the study. The 2002 to 2008 follow-up was approved by the Human Research Ethics Committee of the University

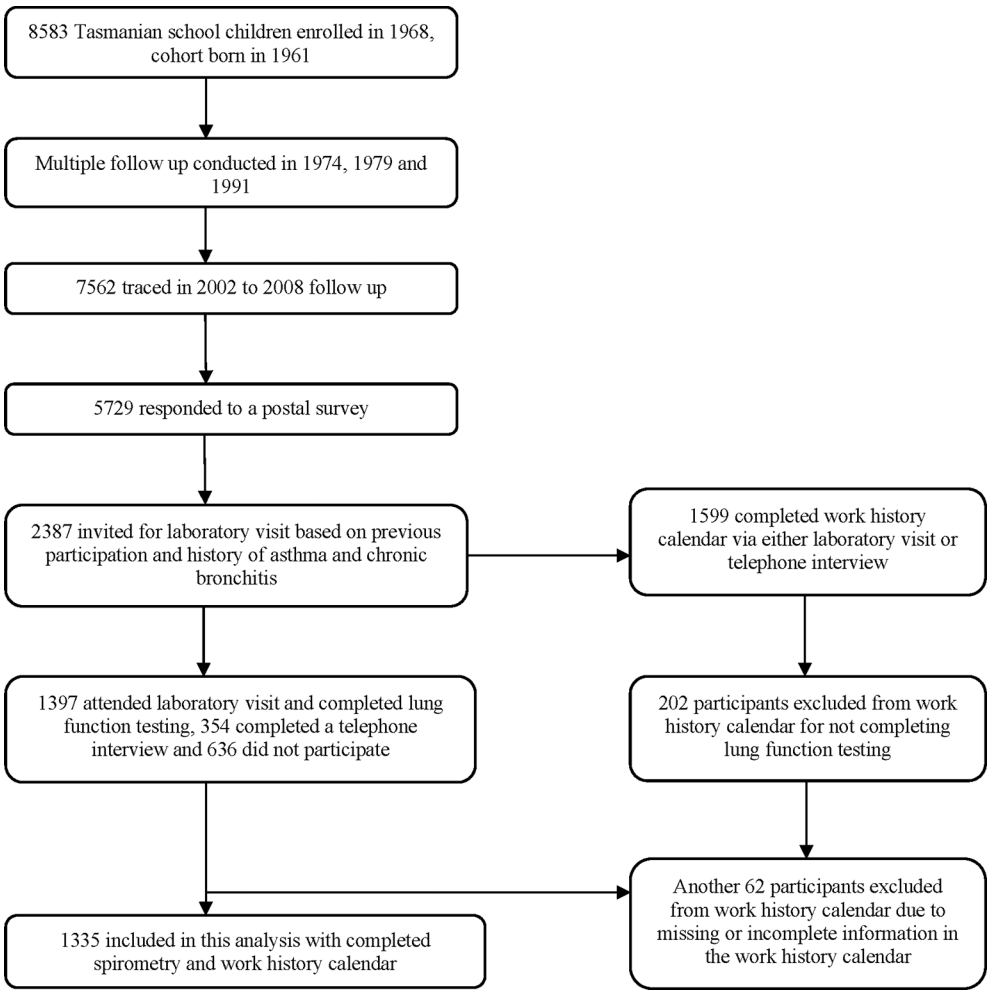

Figure 1 Tasmanian Longitudinal Health Study flow diagram.

of Melbourne (HREC no. 040375). All participants provided written informed consent.

Data collection

Pre-BD and post-BD lung function was measured with the Easyone Ultrasonic spirometer (ndd, Medizintechnik, AG, Switzerland). Participants were asked not to smoke for 4–6 hours before testing. FEV_1 and FVC were measured according to international guidelines and the highest value for FEV_1 and FVC obtained from three acceptable and repeatable tests was recorded.[16] Spirometry was repeated 10–15 min after short-acting bronchodilator (200 μg salbutamol) administration via a spacer.

Outcome definitions

Fixed AO was defined according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: ratio of post-BD FEV_1 and FVC (FEV_1/FVC) <0.70.[17] We also used the lower limit of normal (LLN) to define fixed AO, on the basis of Global Lung Function Initiative 2012 regression equations.[18]

- Chronic bronchitis was defined as a cough with phlegm on most days for at least 3 months of each year for 2 successive years.[17]
- Chronic cough was defined as usually cough without a cold on most days for at least 3 months for at least 2 years.
- Chronic phlegm was defined as usually phlegm without a cold on most days for at least 3 months for at least 2 years.
- Dyspnoea was defined as shortness of breath when hurrying on level ground or walking up a slight hill.

Occupational exposures

Occupational exposures were classified using the lifetime work history calendar that was collected from participants during the laboratory visit or telephone interview. A total of 1599 participants provided complete work histories, but this analysis was restricted to 1335 participants who completed both spirometry testing at the 2002 to 2008 follow-up and the work history calendar. Participants were asked to list all the jobs they had held in their lifetime including job title, industry name, employer name, year work started and ended. The job titles reported by the participants were coded according to the International Standard Classification of Occupations-88 four-digit classification.[19] These codes were then used to establish occupational exposures to biological dust, mineral dust, gases/fumes, vapours, gases, dust or fumes (VGDF), all pesticides, herbicides and insecticides using a modified version of the ALOHA Job Exposure Matrix called the ALOHA plus Job Exposure Matrix.[12] The ALOHA plus Job Exposure Matrix classified participants based on job codes into no, low, or high exposure categories. For this analysis, we combined low and high exposure categories because of a small number of participants in the low exposed group limited the statistical analysis. Ever exposure was calculated by summing exposures over all jobs for each participant. In case of participants having two different jobs at the same time, exposures from both jobs were averaged and rounded up to the nearest integer (0.5=1 and 1.5=2).[12]

The ALOHA plus Job Exposure Matrix was also used to calculate cumulative EU- years by multiplying the number of years worked multiplied by the exposure intensity (ie, low or high exposure) for each job and then summed for each participant over the entire job history. To allow for the combination of low and high exposure groups, years of exposure were weighted by four for high exposure and one for low exposure.[5 7] This cumulative EU-years was calculated for each of the exposure types and scaled continuous variable of cumulative exposure per 10 years. Participants missing any years in the lifetime work history calendar were excluded from the cumulative EU-years analysis and so 1255 participants were included in the unadjusted analysis.

Statistical analysis

All the statistical analyses were conducted using Stata V.13.1 (StataCorp, College Station, Texas, USA). The population prevalence of the outcomes were estimated as observed proportions with 95% CI based on the binomial distribution. The estimate prevalences was calculated using inverse-probability-of-inclusion weights to adjust for the enriched sample of the 2002 to 2008 follow-up. The associations between outcomes and occupational exposures were estimated using multinomial logistic regression models. We adjusted for sex, smoking, pack-years, asthma in childhood and adulthood, and socioeconomic status in childhood and adulthood. Due to the correlation between any VGDF exposure and all pesticides exposure (see online supplementary table 6) all models that examined biological dust, mineral dust, gases/fumes or VGDF exposures were additionally adjusted for ever exposure to all pesticides. Similarly, models examining all pesticides, herbicides or insecticides exposure were additionally adjusted for VGDF exposure.

Effect modification by sex, smoking and current asthma was assessed by including interaction terms (occupational exposure×sex, occupational exposure×smoking, occupational exposure×current asthma) in the models. We performed a multiple imputation analysis to impute the values of missing confounders and compared this analysis with the complete-case analysis. The results of the imputed analysis did not differ from the complete-case analysis and the results of the imputation analysis are presented in online supplementary tables 3, 4 and 5). A p value ≤0.05 was considered to be statistically significant.

RESULTS

Characteristics of study population

A comparison of responders and non-responders to the laboratory study and postal survey for selected characteristics can be found in the online supplementary table 1. Briefly selected characteristics of the participants those who did and did not attend the laboratory study were similar. Table 1 shows the characteristics of included study participants. The mean age of the participants was 44.8 years (±0.8 SD), over half (51.6%) were men, 87.4% were currently employed and 25.1% were current smokers, with a median smoking history of 21 pack-years (Table 1). There was very little difference in the prevalence of fixed AO when using the GOLD (6%; 95% CI 4.8 to 7.6) or LLN (6%; 95% CI 4.8 to 7.5) criteria. The prevalence of chronic bronchitis was 8.6% (95% CI 7.6 to 9.9) and dyspnoea 12.1% (95% CI 10.4 to 14.1). Over 28% of all participants had ever reported asthma.

Ever exposure

Table 2 shows the association between ever exposure and fixed AO, chronic bronchitis and respiratory symptoms. Ever exposed to biological dust was associated with fixed AO (relative risk (RR)=1.58, 95% CI 1.01 to 2.48), while mineral dust was associated with symptoms. Ever exposed to gases/fumes was not associated with fixed AO or symptoms.

Ever exposure to all pesticides was associated with GOLD-defined fixed AO, chronic bronchitis and also with all respiratory symptoms (table 2). Ever exposed to herbicides was also associated with fixed AO, chronic bronchitis and chronic cough. Ever exposed to insecticides was associated with chronic bronchitis and

Table 1 Characteristic of the population

Study characteristics	n (%)*	95% CI
Age, years (mean, SD) (n=1334)	44.8 (0.8)	44.7 to 44.9
Sex, % (n=1335)		
Men	684 (51.6)	48.5 to 54.9
Women	651 (48.3)	45.0 to 51.5
Smoking history (n=1330)		
Never, n (%)	566 (45.3)	42.1 to 48.6
Past, n (%) Pack-years, median (IQR) (n=1292)	394 (29.6) 7.5 (2–17)	26.7 to 32.6
Current, n (%) Pack-years, median (IQR) (n=1292)	370 (25.1) 21 (10–30)	22.4 to 27.9
Currently employed, n (%) (n=1332)	1136 (87.4)	85.2 to 89.3
Fixed airflow obstruction (AO)		
Fixed AO-GOLD (n=1335)	113 (6.0)	4.8 to 7.6
Stage I: FEV_1/FVC <0.7 and FEV_1 ≥80%	62 (3.7)	2.7 to 5.1
Stage II: FEV_1/FVC <0.7 and FEV_1 <80%	51 (2.3)	1.7 to 3.2
Fixed AO-LLN (n=1335)	112 (6.0)	4.8 to 7.5
Chronic bronchitis (n=1322)	246 (8.7)	7.6 to 9.9
Respiratory symptoms		
Chronic cough (n=1316)	185 (8.8)	7.4 to 10.3
Chronic phlegm (n=1317)	171 (6.8)	5.8 to 8.1
Dyspnoea (n=1334)	227 (12.1)	10.4 to 14.1

*The estimated prevalences were calculated using inverse-probability-of-inclusion weights to adjust for the enriched sample of the fifth decade follow-up survey.
AO, airflow obstruction; GOLD, Global Obstructive Lung Disease; LLN, lower limit of normal.

chronic cough. Using LLN definition of fixed AO (table 2), we found a significant association between ever exposure to herbicides and fixed AO and a trend of association between all pesticides and insecticides and fixed AO. In general, using both definitions, we found both all pesticides and herbicides were associated with fixed AO.

Cumulative EU-years

For every 10-year increase in cumulative EU-years of exposure to biological dust, there was a 7% increase of chronic cough (RR=1.07, 95%CI 1.00 to 1.15). Cumulative EU-years of exposure to mineral dust and gases and fumes were associated with a 5% increase of dyspnoea (table 3). Cumulative EU-years of exposure to all pesticides was consistently associated with both definitions of fixed AO, chronic bronchitis, chronic cough and chronic phlegm. Cumulative EU-years of exposure to herbicides was associated with fixed AO and chronic bronchitis. Cumulative EU-years of exposure to insecticides was associated with 15% increase of chronic bronchitis (RR=1.15, 95%CI 1.02 to 1.29).

Interactions with sex, smoking and current asthma

We explored the potential interactions between occupational exposures and sex, smoking and current asthma. We did not find any interactions with sex or smoking (data not shown). However, we found significant interactions between ever exposure and current asthma. We found a significant interaction between current asthma and biological dust (interaction p=0.003), mineral dust (interaction p=0.03), gases/fumes (interaction p=0.005) and VGDF (interaction p=0.01) for GOLD-defined fixed AO (table 4). For all of these occupational exposures, there was association with fixed AO in the non-asthmatic group but not in the asthmatic group.

DISCUSSION

This is the first study to examine fixed AO using the gold standard measurement of post-BD spirometry and two measures of occupational exposure, ever exposure and lifetime cumulative EU-years. Using these robust measures, we have demonstrated significant and consistent associations between all pesticides exposure, fixed AO, chronic bronchitis and chronic cough. We are the first to show that ever exposure to pesticides is associated with fixed AO and increasing cumulative EU-years to pesticides are associated with fixed AO.

A number of previous workplace-based studies have reported increased prevalence of respiratory symptoms and reduced lung function among farmers or agriculture workers exposed to pesticides.[20–23] However, there has only been one population-based study published in relation to pesticides exposure and AO. This study examined two Dutch cohorts and found an association between pre-BD AO in people exposed to pesticides in one cohort, and a trend towards an association in the other for moderate/severe AO (defined as pre-BD FEV_1/FVC <70% and FEV_1 <80%).[12] Both cohorts in this study used pre-BD spirometry to define AO, which may have overestimated the prevalence of AO. They also used current or last held job and the results may have been confounded by past exposure. We have demonstrated, in a similarly aged population, an association between ever exposure and cumulative EU-years to all pesticides and fixed AO confirming that minimising exposure to all pesticides may help to reduce the burden of COPD.

We also observed significant association between chronic bronchitis, chronic cough and chronic phlegm with both ever exposure and cumulative EU-years to pesticides. We are first to show cumulative EU-years to pesticides is associated with chronic respiratory symptoms in a population-based study. Recent systematic reviews found chronic bronchitis was associated with pesticides exposure[10 24] and a study of the US farmers found association between exposure to pesticides and chronic bronchitis.[20] Similar to our findings, a study from Latin America also found an association between pesticides exposure and respiratory symptoms.[21] However, all these studies were conducted in specific occupational groups making the results not applicable to the broader general population, unlike the results from our study.

Pesticides can be classified according to their targets into three main areas: insecticides, herbicides and fungicides. Insecticides include organochlorines, organophosphates and carbamates. Herbicides include phenoxy herbicides and fungicides include dithiocarbamates, and all have been used extensively in agriculture to control pests and weeds.[10] Pesticides can enter the body through inhalation into the respiratory tract and absorption through the skin during use for fumigation, preparation and spraying or during manufacture, storage or transport.[10 24] Long-term exposure to organophosphate and carbamate pesticides has been shown to lead to inhibition of acetylcholinesterase synthesis from M2 muscarinic receptors that results in mucus hypersecretion and airway smooth muscle contraction causing breathlessness, cough and wheeze.[10 24] The inactive acetylcholinesterase is also responsible for thickening of alveolar-capillary membrane leading to reduced level of lung function.[25]

The ALOHA plus Job Exposure Matrix assigned exposure to pesticides as ever exposure to all pesticides and then also had subcategories of specific herbicides and insecticides exposures.

Table 2 Association between ever exposure and fixed airflow obstruction, chronic bronchitis and respiratory symptoms

	Fixed AO-GOLD			Fixed AO-LLN			Chronic bronchitis			Chronic cough			Chronic phlegm			Dyspnoea		
Exposures	No 1222	Yes 113	RR (95% CI) *	No 1223	Yes 112	RR (95% CI)	No 1075	Yes 246	RR (95% CI)	No 1131	Yes 185	RR (95% CI)	No 1146	Yes 171	RR (95% CI)	No 1107	Yes 226	RR (95% CI)
Biological dust																		
Not exposed	541	37	Ref.	541	37	Ref.	483	87	Ref.	511	59	Ref.	508	61	Ref.	504	74	Ref.
Exposed	681	76	**1.58 (1.01 to 2.48)**	681	75	**1.56 (1.00 to 2.45)**	592	159	0.99 (0.67 to 1.48)	620	126	1.24 (0.83 to 1.84)	639	109	0.98 (0.66 to 1.46)	603	152	1.32 (0.95 to 1.85)
Mineral dust																		
Not exposed	585	42	Ref.	586	42	Ref.	522	98	Ref.	555	64	Ref.	563	57	Ref.	544	84	Ref.
Exposed	636	71	1.29 (0.81 to 2.04)	637	70	1.29 (0.81 to 2.04)	554	148	1.10 (0.72 to 1.67)	576	121	**1.62 (1.06 to 2.48)**	583	114	**1.51 (1.00 to 2.30)**	563	143	**1.57 (1.10 to 2.23)**
Gases/fumes																		
Not exposed	352	22	Ref.	353	22	Ref.	314	57	Ref.	335	33	Ref.	336	33	Ref.	327	48	Ref.
Exposed	869	91	1.50 (0.88 to 2.54)	870	90	1.47 (0.87 to 2.51)	762	189	0.91 (0.58 to 1.45)	796	152	1.25 (0.80 to 1.98)	810	138	1.20 (0.76 to 1.90)	780	179	1.31 (0.89 to 1.91)
VGDF																		
Not exposed	300	21	Ref.	301	21	Ref.	273	45	Ref.	293	23	Ref.	290	26	Ref.	281	41	Ref.
Exposed	921	92	1.29 (0.73 to 2.17)	922	91	1.25 (0.72 to 2.15)	803	201	0.95 (0.58 to 1.55)	838	162	**1.69 (1.01 to 2.84)**	856	145	1.31 (0.80 to 2.17)	826	186	1.29 (0.86 to 1.93)
All pesticides																		
Not exposed	1024	85	Ref.	1024	85	Ref.	916	183	Ref.	961	134	Ref.	971	124	Ref.	940	169	Ref.
Exposed	198	28	**1.74 (1.00 to 3.07)**	199	27	1.63 (0.91 to 3.07)	160	63	**1.81 (1.12 to 2.93)**	170	51	**1.77 (1.04 to 3.01)**	175	47	**2.06 (1.23 to 3.47)**	167	58	**1.95 (1.23 to 3.09)**
Herbicides																		
Not exposed	1061	87	Ref.	1061	87	Ref.	947	191	Ref.	993	141	Ref.	1002	132	Ref.	966	182	Ref.
Exposed	161	26	**2.09 (1.18 to 3.70)**	162	25	**1.95 (1.08 to 3.49)**	129	55	**1.81 (1.08 to 3.02)**	138	44	**1.79 (1.04 to 3.09)**	144	39	1.62 (0.93 to 2.83)	141	45	1.44 (0.89 to 2.34)
Insecticides																		
Not exposed	1060	91	Ref.	1060	91	Ref.	947	194	Ref.	996	141	Ref.	1002	135	Ref.	970	181	Ref.
Exposed	162	22	1.70 (0.93 to 3.10)	163	21	1.56 (0.84 to 2.90)	129	52	**1.64 (1.00 to 2.72)**	135	44	**1.74 (1.00 to 3.05)**	144	36	1.62 (0.93 to 2.84)	137	46	1.58 (0.97 to 2.57)

The bolded text identifies results reaching statistical significance ($p \leq 0.05$).
*Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma. The analyses with biological dust, mineral dust, gases/fumes and VGDF were additionally adjusted for all pesticides, whereas the analyses with all pesticides, herbicides and insecticides were additionally adjusted for VGDF exposure.
AO, airflow obstruction;GOLD, Global Obstructive Lung Disease; LLN, lower limit of normal; RR, relative risk; VGDF, vapour, gases, dust and fumes.

Table 3 Association between cumulative EU-years and fixed airflow obstruction, chronic bronchitis and respiratory symptoms (n=1255)

Cumulative exposures	Fixed AO-GOLD		Fixed AO-LLN		Chronic bronchitis		Chronic cough		Chronic phlegm		Dyspnoea	
	RR (95% CI)*	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value
Biological dust	1.05 (0.97 to 1.13)	0.22	1.03 (0.96 to 1.12)	0.35	1.06 (0.99 to 1.13)	0.07	**1.07 (1.00 to 1.15)**	**0.05**	1.01 (0.94 to 1.09)	0.68	0.99 (0.92 to 1.06)	0.82
Mineral dust	1.03 (0.97 to 1.10)	0.31	1.03 (0.97 to 1.11)	0.28	1.04 (0.98 to 1.11)	0.12	1.00 (0.93 to 1.07)	0.97	1.03 (0.96 to 1.10)	0.36	**1.05 (1.00 to 1.11)**	**0.05**
Gases/fumes	1.02 (0.96 to 1.09)	0.44	1.02 (0.96 to 1.09)	0.51	1.03 (0.97 to 1.09)	0.36	0.97 (0.91 to 1.04)	0.54	1.03 (0.98 to 1.10)	0.23	**1.05 (1.00 to 1.10)**	**0.05**
VGDF	1.02 (0.97 to 1.08)	0.32	1.03 (0.97 to 1.09)	0.33	**1.05 (1.00 to 1.10)**	**0.05**	1.03 (0.97 to 1.08)	0.24	1.03 (0.98 to 1.08)	0.25	1.02 (0.98 to 1.07)	0.25
All pesticides	**1.12 (1.00 to 1.25)**	**0.05**	**1.13 (1.00 to 1.29)**	**0.05**	**1.16 (1.10 to 1.30)**	**0.01**	**1.12 (1.00 to 1.28)**	**0.05**	**1.13 (1.00 to 1.30)**	**0.05**	0.94 (0.82 to 1.08)	0.40
Herbicides	**1.16 (1.00 to 1.32)**	**0.04**	**1.15 (1.00 to 1.36)**	**0.05**	**1.22 (1.05 to 1.41)**	**0.01**	1.12 (0.97 to 1.30)	0.12	1.10 (0.93 to 1.31)	0.23	0.91 (0.77 to 1.09)	0.33
Insecticides	1.10 (0.98 to 1.24)	0.10	1.10 (0.96 to 1.26)	0.19	**1.15 (1.02 to 1.29)**	**0.02**	1.06 (0.92 to 1.22)	0.38	1.13 (0.99 to 1.30)	0.08	0.94 (0.83 to 1.09)	0.51

The bolded text identifies results reaching statistical significance (p≤0.05).
*Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma. The analyses with biological dust, mineral dust, gases/fumes and VGDF were additionally adjusted for all pesticides, whereas the analyses with all pesticides, herbicides and insecticides were additionally adjusted for VGDF exposure.
AO, airflow obstruction; EU, exposure unit; GOLD, Global Obstructive Lung Disease; LLN, lower limit of normal; RR, relative risk; VGDF, vapour, gases, dust and fumes.

The associations observed in this study were largely consistent across all three categories, with some not quite reaching statistical significance for some symptoms. The possible explanation for this slight variation across the subcategories of all pesticides exposure is differences in exposures between different occupational groups with some groups, for example, cattle farmers not being exposed to herbicides but to insecticides. Another example of this is forestry workers who formed a large proportion of our exposed workers (23.8%), but who had 'all pesticides exposure' and 'herbicides exposure' but not 'insecticides exposure'. Another explanation is the presence of very strong correlation between these exposures (see online supplementary table 6). In our study, participants with high all pesticides exposures included people who described themselves as farm hands/labourers, forestry workers, gardeners, horticultural/nursery workers, and crop/vegetable growers.

For the other common exposures to biological dust, mineral dust and gases/fumes, we only observed association with fixed AO for those ever exposed to biological dust. This finding is consistent with previous studies that have also found association between biological dust and COPD.[7 19] The finding with biological dust in the present study is also consistent with the meta-analysis conducted by our group, although the effect estimates did not reach statistical significance in our meta-analysis.[4] The reason for this slight variation in the effect estimate may be due to the inclusion of pre-BD in most of the included studies in our meta-analysis. We did not observe any association between mineral dust and gases/fumes exposure and fixed AO, but we did observe associations with respiratory symptoms. Several previous studies also found an association between dust exposure in general and respiratory symptoms.[26 27]

Our study observed a significant interaction between current asthma and four of the occupational exposures for fixed AO. In the non-asthmatics, there was an association between ever exposure to biological dust, mineral dust and gases/fumes and fixed AO, even with a low crude prevalence of 7.12% in non-asthmatics, compared with asthmatics (16.98%). We did not observe the same interaction for cumulative EU-years to these agents. This finding is suggestive of a healthy worker effect, that is, asthmatics who remain in the study are relatively unaffected by these occupational exposures. It also may suggest that asthma alone is a significant risk factor for fixed AO in middle-age and additional occupational exposure does not substantially increase the risk observed at this age. We did explore childhood asthma status, recorded prospectively in this cohort, but we did not find any interaction with occupational exposures and fixed AO. We also did not observe any interaction between current asthma and all pesticides for fixed AO suggesting the ever exposure and cumulative EU-years of all pesticides significantly associated with fixed AO independent of asthma.

Previous studies of occupational exposure and COPD using the ALOHA Job Exposure Matrix have taken asthma into account in their analysis by different methods. They have either excluded asthmatics completely[8 19 28] or performed sensitivity analysis to see if excluding participants with asthma influenced the results.[5 7] Including participants with asthma would inflate the prevalence of fixed AO, especially if pre-BD was used in a relatively young cohort, as was the case for several of these studies,[12 28] leading to spurious results. We included both childhood and adult asthma as a confounder in the statistical analyses and investigated the possible interaction with current asthma. Our study has demonstrated for the first time in a general population that asthma significantly modifies the effect of biological dust, mineral dust and gases, and fumes on fixed AO in middle-age.

Table 4 Association between ever exposure to biological dust, mineral dust, gases/fumes and VGDF stratified by current asthma

	Current asthmatics			Non-asthmatics			
	Fixed AO-GOLD			Fixed AO-GOLD			
Exposures	No % (n/N)	Yes % (n/N)	RR (95% CI)	No % (n/N)	Yes % (n/N)	RR (95% CI)	Interaction p Value*
Biological dust	63% (167/265)	55.6% (25/45)	0.68 (0.35 to 1.34)	53.6% (512/955)	75% (51/68)	**2.80 (1.48 to 5.27)**	**0.003**
Mineral dust	56.% (149/266)	53.3% (24/45)	0.70 (0.35 to 1.38)	50.9% (486/955)	69.1% (47/68)	1.80 (0.98 to 3.32)	**0.03**
Gases/fumes	76.3% (203/266)	71.1% (32/45)	0.61 (0.29 to 1.29)	69.6% (665/955)	86.8% (59/68)	**2.92 (1.27 to 6.67)**	**0.005**
VGDF	79.7% (212/266)	73.3% (33/45)	0.57 (0.26 to 1.22)	74.1% (708/955)	86.8% (59/68)	**2.33 (1.01 to 5.34)**	**0.01**

The bolded text identifies results reaching statistical significance (p≤0.05).
*p≤0.05 for the interaction between exposure and current asthma.
†Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and all pesticides as coexposure.
No interaction was observed with exposure to all pesticides, herbicides and insecticides (results not shown).
AO, airflow obstruction; GOLD, Global Obstructive Lung Disease; RR, relative risk; VGDF, vapour, gases, dust and fumes.

Both GOLD and LLN definitions of fixed AO in our study produced similar effect estimates with most of the exposures except all pesticides exposure, where we found a significant association using GOLD definition, but when we used the LLN definition the association with all pesticides did not quite reach statistical significance. The previous study on occupational exposure and COPD in Switzerland also found similar to our results, although they used pre-BD to define COPD.[19] Post-BD is essential to define fixed AO, but there is still debate over the best cut-off values to define fixed AO.[29] The GOLD definition of fixed ratio (FEV_1/FVC <0.7) has been widely used for clinical application as well as large-scale population-based studies.[30 31] More recently, statistical reference equation-based LLN definition also provide an opportunity to overcome age-related overestimation of the total effect by GOLD.[31] We observed very little variation between the two definitions of fixed AO, with only one person being classified as having fixed AO by the GOLD and not the LLN definition. This person was on the borderline of being categorised as having fixed AO by the LLN definition. Other data from this individual (ie, heavy personal smoking history and occupational history with high likelihood of occupational exposure to herbicides and all pesticides) and the relatively small change in the estimates between the two definitions we would not regard this person as an extreme outlier or having undue influence and so he has not been removed from the analysis.

The availability of post-BD data was a major strength of our study. The availability of work history calendars for the participants' entire working life was also a major strength and enabled the calculation of ever exposure and cumulative EU-years. We have attempted to minimise any bias related to recalling of work exposures by using standardised lifetime work history calendars and then assigning exposure via the use of a Job Exposure Matrix to estimate cumulative EU-years across all jobs. Job Exposure Matrices are affected by non-differential misclassification of exposure, which occurs when there is heterogeneity of exposure in a given job or occupation. However, this generally results in misclassification towards the null, leading to an underestimation of the effect of the exposure on risk of the disease. Multiple comparisons were performed but the associations, particularly with all pesticides and herbicides exposure, were consistent across several outcomes, suggesting genuine associations rather than chance findings. However, our laboratory attendees, enriched for asthma and chronic bronchitis and had similar clinical profiles despite the lung function testing.

In conclusion, our study has shown that both ever and cumulative EU-years to pesticides are associated with fixed AO and respiratory symptoms. We have also shown this effect of pesticides is independent of asthma. For other occupational exposures to VDGF, we found an association with fixed AO only in those without current asthma. However, we did not find any significant association between fixed AO, and chronic bronchitis with exposure to mineral dust, gases/fumes and VGDF. Future population-based studies need to use post-BD to define fixed AO, which allows asthma to be adequately taken into account. Our study has shown even in a middle-aged group of people, a significant proportion of fixed AO is associated with occupational exposures. Our findings highlight the need to reduce workplace exposure to pesticides by improving adherence to use of recommended protective equipment, and workplace monitoring of exposure levels could be implemented. By enhanced monitoring and use of protective equipment, the burden of COPD caused by occupational exposures has the potential to be substantially reduced.

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