OPEN ACCESS

Original research

Asthma in pesticide users: an update from the Great Britain Prospective Investigation of Pesticide Applicators' Health (PIPAH) cohort study

David Fishwick [1], Anne-Helen Harding,[2] Y Chen [2], Neil Pearce [3], Gillian Frost [2]

[1]Centre for Workplace Health, Science Division, Health and Safety Executive, Buxton, UK
[2]Science Division, Health and Safety Executive, Buxton, UK
[3]Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK

Correspondence to
Professor David Fishwick, Centre for Workplace Health, Science Division, Health and Safety Executive, London, London, UK; d.fishwick@sheffield.ac.uk

Received 18 February 2021
Accepted 25 November 2021
Published Online First 4 February 2022

To cite: Fishwick D, Harding A-H, Chen Y, *et al*. *Occup Environ Med* 2022;**79**:380–387.

ABSTRACT

Objectives To define the prevalence and incidence of asthma in a large working population of pesticide workers and to assess which exposures are potentially of relevance to causing or aggravating this condition.

Methods A baseline cross-sectional study at recruitment (2013–2017, n=5817), with follow-up in 2018 (n=2578), was carried out in predominantly Great Britain based pesticide workers. At baseline, participants completed a health and work questionnaire which included questions on demographic, lifestyle, socioeconomic and work-related factors, pesticide use and doctor diagnosed health conditions. In January 2018, a follow-up questionnaire focused on respiratory ill health, with questions covering self-reported respiratory symptoms and doctor diagnosed respiratory conditions. The associations of various exposures with asthma were estimated using logistic regression adjusting for age as a continuous variable, and for sex where possible. An estimate of hours worked with pesticides in the previous year was calculated for each participant.

Results At baseline, 608 (10.4%) had doctor diagnosed asthma. In 2018 the figure was 297 (11.5% of the follow-up population); the incidence of new asthma cases between surveys was 1.7 cases per 1000 participants per year. At follow-up, 18.1% reported wheeze in the last 12 months, 73.2% of those with self-reported asthma noted it to be persistent and using a more specific definition of asthma (doctor diagnosed asthma with at least one asthma-related symptom in the last year); 6.8% (95% CI 5.9% to 7.9%) fulfilled this definition. At follow-up, 127 participants felt that their asthma was caused or made worse by their work, with 77 (63.6%) nominating organic dust, 13 (10.7%) unspecified dust, 12 (9.9%) chemicals, 9 (7.4%) mixed exposures, 7 (5.8%) physical agents and 3 (2.5%) fumes or other irritants. There was little or no association between high pesticide exposure and doctor diagnosed asthma or self-reported recent wheeze, although there was an elevated risk for work-related wheeze (OR for high exposure=2.67; 95% CI 1.16 to 6.18). High pesticide exposure (high vs low exposure category OR 2.68, 95% CI 1.28 to 5.60) was also associated with work-related chest tightness. Exposure to organic dusts was associated (significantly, p=0.026) with persistent asthma when adjusted for the effects of age and smoking.

Conclusions This large study of pesticide workers has identified expected levels of doctor diagnosed asthma, and high levels of self-reported respiratory symptoms. Pesticide exposure was associated with an increased risk of self-reported work-related wheeze, but not with asthma or wheeze in general. Further work is needed to identify more clearly which exposures within a complex mixed exposure profile are likely causative in order to best focus interventions to reduce work-related asthma and related conditions.

Key messages

What is already known about this subject?

⇒ Pesticide exposure is complex, and various exposures have been linked to non-malignant and malignant health outcomes. The levels of evidence underpinning these associations are variable. Real-world health data from pesticide exposed working populations are uncommon.

What are the new findings?

⇒ This study identifies a substantial prevalence and incidence of self-reported asthma, and high levels of respiratory complaints in pesticide users. Some of these appear to have a dose response relationship. Pesticide exposure was associated with an increased risk of self-reported work-related wheeze. However, workers more often report organic dust exposures as the perceived cause of their ill health, rather than pesticide or chemical exposures.

How might this impact on policy or clinical practice in the foreseeable future?

⇒ Pesticide exposures should remain an important focus for regulatory and health and safety authorities. Further work should be carried out to identify which particular types of exposure are important to respiratory health, and to inform evidence-based workplace interventions to reduce risks to health.

INTRODUCTION

Occupational exposures to pesticides have been linked to increased levels of reported respiratory symptoms,[1 2] changes in pulmonary function[3–6] and specific diagnoses including asthma. The effects may not be confined just to adults, as a recent systematic review of childhood data also suggests that

pesticide exposures may be linked to adverse health outcomes in children[7]; specifically, asthma, wheezing, cough, acute respiratory infection, allergic rhinitis and skin disorders.

In relation to reported symptoms, a comprehensive review[8] noted that there was strong evidence for an association between pesticide exposure at work and wheezing, and especially so in agricultural jobs. For example, one study of livestock farm workers in Iowa, reported an association between pesticide exposure and elevated levels of wheeze, following adjustment for age and smoking, although comment was made that the results may have been affected by exposures to other environmental agents such as animal allergens.[9]

In this review,[8] there was also a suggestion of a link between such exposures and chronic obstructive pulmonary disease (COPD) and chronic bronchitis. Evidence relating to 'occupational asthma' (as opposed to reported wheeze for example) was sourced from a variety of studies; including case studies (acute and chronic pesticide exposure), population-based studies and direct study of populations of pesticide workers. Notably, some studies have found non-significant associations[10] and 'inverse–effect' relationships[11] between pesticide exposure and the presence of asthma.

In terms of the effects on pulmonary function, de Jong *et al*[12] reported that exposure to pesticides, assessed by the ALOHA+job exposure matrix, was associated with excess longitudinal decline in FEV_1, particularly in those workers who had ever smoked. The effect was relatively modest, although significant, with an excess fall in FEV_1 of 6.9mls/year in the high exposure category.

Individual studies often use varying definitions of health endpoints, complex and often mixed inhaled exposure profiles at work, and while links between exposure and health consequences are often identified, causality is often difficult to ascertain. Real-life workplace data are also often difficult to source, and particularly so for studies focusing on pesticide and related exposures.

Our own interest in pesticides and ill health, as the UK regulator of workplace health and safety, was initially developed with the HSE sponsored Pesticides Users' Health Study in the late 1990s. A survey of pesticide use found that there was substantial heterogeneity in pesticide type used, with a very large number of active pesticide ingredients used.[13] Health outcome data collected in this survey were restricted to respondents being asked their self-reported view about being made ill by exposure to pesticides. Although the health of these study participants is followed up using cancer and death registration data and hospital episode statistics, information on chronic disease and on factors that may be associated with disease is limited.

Because of these initial findings from, and shortcomings of, the Pesticides Users Health Study (PUHS), the Prospective Investigation of Pesticide Applicators' Health (PIPAH) study was established in order to further quantify exposures and health endpoints in pesticide users.

The aim of the study was to determine the prevalence and incidence of asthma in a large population of pesticide workers, and to investigate which exposures potentially cause or aggravate this condition. We report here the findings from the baseline and first respiratory follow-up questionnaire.

METHODS

Study population

The PIPAH study was established with the aim of monitoring the long-term health of men and women who use pesticides as a part of their work. The details of the source population and study recruitment are published in detail elsewhere.[14] Briefly, the source population chosen for study was identified using a variety of professional registers, given that we wished to solely recruit individuals applying pesticides on a professional basis in Great Britain. In particular, City and Guilds (http://www.cityandguilds.com/), who manage the National Register of Sprayer Operators (NRoSO, https://www.nroso.org.uk/) and previously managed the National Amenity Sprayer Operators' Register (NAsOR), were engaged with to identify potential participants. Participants from the Health and Safety Executive's PUHS[15] were also invited to participate. Recruitment was carried out in two main stages and continues on an annual basis.

First, in 2013, the NRoSO and NAsOR members were recruited. Approximately 21 000 members of NRoSO and NAsOR were sent a survey pack inviting them to participate in the PIPAH study. The consent form and baseline questionnaire were included, and participants were enrolled on receipt of these by the study team. Second, in 2014, around 7500 participants from the Pesticide Users' Health Survey were approached for possible recruitment. Each consenting participant who completed the general questionnaire at study baseline was invited to complete the follow-up respiratory questionnaire sent to them in 2018.

Study questionnaires: The baseline questionnaire (time zero) contained questions relating to demography, smoking and other lifestyle information, diet, general occupational information, specific self-reported occupational exposures and a comprehensive set of questions relating to health end points including doctor diagnosed conditions. Questions relating to pesticide use focused on pesticide groups and crop types. The baseline survey was designed to be self-administered, and questions where possible were used that had previously been used, and ideally validated against health end points, in other studies. The questionnaire was tested face to face with a group of pesticide users prior to inclusion in the main study. A copy of the baseline questionnaire is available online.[16]

A follow-up respiratory questionnaire (time up to 5 years) enquired specifically about doctor diagnosed respiratory conditions and self-reported complaints. However, the participant was given additional opportunities to record the work-related nature of these reported problems, and any links to exposures at work. More specifically, section one dealt with the respiratory health of the participant, self-reported symptoms and their relationship to work, a freehand section for further comment about exposures at work and how they relate to respiratory complaints and a question to document doctor diagnosed conditions. Section two documented the nature and extent of work with pesticides, including questions about work context and main work areas. A copy of the respiratory questionnaire is available online.[16]

Assessment of diagnosed asthma: Participants were asked 'Has a doctor ever told you that you have asthma?' in the baseline and follow-up questionnaires. A participant was assumed to have asthma if they responded 'yes' to this question. In the follow-up questionnaire only, participants were also asked about respiratory symptoms, including wheezing or whistling in the chest. New cases of asthma at follow-up were those who reported a doctor diagnosis of asthma in the follow-up questionnaire only. Incident cases of asthma at follow-up were new cases who reported an age at diagnosis greater than baseline age minus 4 years. This range was used after investigating differences in the age of diagnosis stated by those who reported asthma at baseline and at follow-up; 68% of the differences fell within the range ±4 years of the mean difference (0.61).

Levels of self-reported asthma are displayed in two formats. First, the total number self-reporting a doctor diagnosis of

Table 1 Personal characteristics at baseline by doctor diagnosed asthma status (N=5817)

Characteristic	No asthma diagnosis N=5209	Asthma* N=608	Asthma plus† N=50	Asthma only‡ N=558
Age				
Mean (SD)	54.3 (12.3)	52.3 (13.2)	60.1 (11.4)	51.7 (13.1)
Missing=58				
Gender				
Male (n, %)	5043, 98%	586, 97%	48, 98%	538, 97%
Missing=59				
Smoking status (n, %)				
Current	442, 9%	38, 7%	9, 19%	29, 6%
Ex-smoker	1285, 27%	171, 31%	19, 40.5%	152, 30%
Never-smoker	3017, 64%	349, 62%	19, 40.5%	330, 64%
Missing=515				
Pack years§				
Mean (SD)	16.2 (18.2)	14.9 (19.1)	27.6 (32.6)	13.0 (15.3)
Median (IQR)	10 (3.5–22.5)	10 (3–20)	18.8 (5–37.5)	10 (3–18)
Missing=563				
Family history of asthma (n, %)				
Yes	681, 13%	233, 38%	19, 38%	214, 38%
No	4528, 87%	375, 62%	31, 62%	344, 62%
Missing=0				

*All individuals with doctor diagnosed asthma
†Individuals with doctor diagnosed asthma plus at least one other self-reported respiratory diagnosis within the group of COPD, chronic bronchitis and hypersensitivity pneumonitis (HP)
‡Only the stipulated diagnosis of asthma, excluding all other self-reported respiratory diagnoses within the group of COPD, chronic bronchitis and HP
§Pack-years = (number of cigarettes smoked a day/20) multiplied by the number of years smoked; for those who smoke(d)
COPD, chronic obstructive pulmonary disease; N or n, count.

asthma are reported. Second, the number of participants with self-reported doctor diagnosed asthma who reported also wheeze or whistling in their chest in the last 12 months. This second category was included in order to make comparisons with the European Community Respiratory Health Survey prevalence data (ECRHS) data more sensible. The ECRHS defined doctor diagnosed asthma as ever having had asthma where the diagnosis had been confirmed by a doctor; and having at least one asthma-related symptom in the last 12 months.[17] Work-related asthma was defined as those reporting that their asthma was 'better on days off'.

Assessment of pesticide/occupational exposure: In the baseline questionnaire, participants were asked when they first used different types of pesticides, including herbicides, fungicides and insecticides. Duration of exposure was estimated from these responses by generating a variable indicating the number of years the participants had spent working with pesticides. When used in the follow-up analysis, the additional years that a participant had used pesticides between baseline and follow-up were added to the baseline value of this variable.

In the follow-up questionnaire, participants were asked if they had used pesticides in the past year, and if they had, whether they had worked in a range of areas of pesticide use, for example field crops, horticulture or forestry. They were also asked to report how many days, and typically how many hours per day, they had worked in each area in the past year. An estimate of hours worked with pesticides in the previous year was calculated for each participant by factoring the typical number of hours worked with pesticides per day by the number of days' work with pesticides in the last year. This continuous variable was then stratified into three groups; zero exposure, low and high. The latter two groups were split by the 50th centile of the continuous variable. Fifty percent of the 'zero' exposure group were retired while others had not sprayed pesticides for reasons such as changing jobs.

In order to categorise recorded free-text comments relating to agents that participants felt were aggravating their breathing at work, all freehand comments were reviewed and entered into one of six groups: these were (1) chemical, (2) organic dust, (3) unspecified dusts, (4) mixed exposures, (5) physical or (6) fumes or other irritants.

Data analysis

Data from both the baseline and the respiratory questionnaires were used in this analysis, carried out using Stata V.16 (StataCorp. 2019. Stata Statistical Software: Release 16, StataCorp). Following data cleaning and development of the derived variables, descriptive analyses were generated for the main demographic and measured variables for the different health outcomes. Categorical data were summarised by frequencies and percentages, and continuous variables by means and SD or if not normally distributed, by the median and IQR. Summary statistics were compared using statistical methods that do not depend on the underlying probability distribution of the data. Fishers' exact χ^2 test was used to compare categorical variables and continuous variables were compared using a bootstrapped unpaired t-test. Asthma incidence was estimated in Stata using the number of incident cases of asthma reported in the follow-up questionnaires and the total follow-up time between baseline and follow-up questionnaires. The effect estimates were estimated as prevalence ORs. Stata was used to estimate ORs and 95% CIs using logistic regression. The association between the number of years spent working with pesticides and asthma at baseline was investigated. The main focus of the logistic regression analyses were the follow-up health outcomes. All follow-up analyses were

Table 2 Farming exposure characteristics at baseline by doctor diagnosed asthma status (N=5817)

Characteristic	No asthma diagnosis N=5209	Asthma* N=608	Asthma plus† N=50	Asthma only‡ N=558
Years worked or lived on a farm				
Mean (SD)	37.0 (21.9)	33.6 (22.1)	30.9 (26.2)	33.8 (21.7)
Missing=183				
Have you ever lived on a farm?				
Yes (n, %)	4009, 78%	446, 74%	31, 63%	415, 75%
Missing=63				
How old were you when you first lived on a farm?§				
Mean (SD)	4.7 (9.0)	5.4 (9.6)	6.5 (10.9)	5.3 (9.5)
Median (IQR)	1 (0–3)	1 (0–6)	1 (0–11)	1 (0–5)
Missing=107				
Are you still living on a farm?§				
Yes (n, %)	3115, 78%	338, 76%	19, 61%	319, 77%
Missing=32				
Years spent working with pesticides				
Mean (SD)	23.9 (11.9)	22.5 (12.0)	27.9 (10.7)	22.0 (12.0)
Missing=78				
Ever worked with: (Yes (n, %))				
Pesticides (any type)	5157, 99%	603, 99%	49, 98%	554, 99%
Fungicides	4653, 91%	529, 89%	40, 80%	489, 90%
Insecticides	4656, 91%	535, 89%	42, 84%	493, 90%
Animal insecticides	1500, 30%	189, 32%	15, 31%	174, 32%
Plant growth regulators	4126, 81%	471, 78%	34, 68%	437, 80%
Herbicides	4923, 98%	570, 97%	44, 92%	526, 97%
Fumigants	1681, 33%	218, 37%	24, 50%	194, 36%
Wood preservers	2777, 55%	299, 51%	17, 35%	282, 52%
Treated seed	4185, 82%	486, 81%	33, 69%	453, 82%

*All individuals with doctor diagnosed asthma
†Individuals with doctor diagnosed asthma plus at least one other self-reported respiratory diagnosis within the group of COPD, chronic bronchitis and hypersensitivity pneumonitis (HP)
‡Only the stipulated diagnosis of asthma, excluding all other self-reported respiratory diagnoses within the group of COPD, chronic bronchitis and HP
§Of those who ever lived on a farm
COPD, chronic obstructive pulmonary disease; N or n, count.

adjusted for age in January 2018 as a continuous variable. Sex was included in the logistic regression models except where it was omitted because of collinearity. The validity of the assumptions in the regression models was tested using the Hosmer and Lemeshow's goodness-of-fit test and a link test to detect any specification error. Statistical significance was taken at the 5% level unless otherwise stated.

RESULTS

Recruitment to the baseline study has been described in detail elsewhere. In brief, altogether 5622 individuals responded for the baseline survey, giving a response rate of 20% for the two main recruitment waves in 2013 and 2014. By 2018, a further 178 individuals had joined the study through the on-going recruitment programme giving a total of 5817 participants at baseline. Of these, 574 only consented to the analysis of the baseline questionnaire and by 2018 there were 408 deaths or withdrawals from the study.

The 4818 participants, of the original 5817, remaining in 2018 were invited to complete the respiratory questionnaire in 2018. Of these 4818, 2578 (54%) responded.

Baseline population

The characteristics of the baseline population are shown in table 1, broken down by doctor diagnosed asthma categories. The mean age of the participants was 54.1 years and the vast majority (98%) were male. The majority were ex-smokers (28%) or never smokers (63%). A family history of asthma was only reported by 16%. As might be expected, those 558 participants (9.5%) with asthma only (asthma without other respiratory diagnoses) were younger (mean age 51.7 years) than the 50 participants with asthma plus at least one other respiratory diagnosis (mean age 60.1 years). The 'asthma plus' group had a higher percentage of current (19%) and former (41%) smokers and a higher mean number of pack-years (28 years) than the 'asthma only' group.

Table 2 shows the characteristics of the baseline population, again stratified by main self-reported doctor diagnosed condition. It is evident overall that participants had spent a long time living or working on a farm (a mean of 36.7 years) and started living on a farm at a very early age (median of 1 year of age, IQR 0–4). The latter age appeared similar across all diagnostic groups. Overall, the majority had ever lived on a farm (77%) and of these, in 2018 78% still lived on a farm. The exception to this was the 'asthma plus' group; a smaller percentage had ever lived on a farm (63%) and of these only 61% were still living on a farm. In terms of self-reported exposures to the different types of pesticides, the three most common categories were pesticides, fungicides and insecticides.

Respiratory Follow-up Population

The respiratory questionnaire follow-up population of 2578 participants were similar to the baseline population. They had a mean age of 60.0 years (SD 11.1) and 807 (34%) had ever smoked. The majority (2493, 97.4%) were male. 457 (18.1%) participants reported wheeze in their chest in the last 12 months and 297 (11.5%) had a doctor diagnosis of asthma. Of the 297 with asthma, the majority reported this to be a current problem (216, 73.2%).

Of the 265 participants that reported a doctor diagnosis of asthma at baseline and completed the follow-up questionnaire, 237 of these subsequently reported the same diagnosis at follow-up. There were 60 new cases of asthma reported at follow-up, representing 2.6% of the study group. However, 42 of these new cases reported an age of diagnosis less than their age at baseline minus 4 years and were probably prevalent cases at baseline. Consequently, it was assumed that there were 18 incident cases, representing an average of 3.6 cases per year over the 5-year period during which 10 513 person-years of follow-up accrued, or 1.7 (95% CI 1.0 to 2.7) cases per 1000 participants per year.

Of the 297 with asthma, more than half (176, 59%) had current symptoms of wheeze and 9.0% reported these to be work-related (wheeze that was better on days off work).

At follow-up, 127 participants (43% of those with doctor diagnosed asthma) felt that their asthma was 'caused or made worse by their work'. They were asked to specify exposures they believed were responsible; and categorised as above. In decreasing proportion, the 121 responses received from these participants were 77 (63.3%) for organic dust, 13 (10.7%) for unspecified dust, 12 (9.9%) for chemicals, 9 (7.4%) for mixed

Table 3 Baseline characteristics of respondents and non-respondents to the 2018 follow-up questionnaire (N=5817)

Characteristic	Responders*		Non-responders†	
	No asthma diagnosis N=2313	Asthma N=265	No asthma diagnosis N=2896	Asthma N=343
Age				
Mean (SD)	55.6 (11.2)	54.2 (12.0)	53.2 (13.0)	50.9 (13.9)
Unpaired t-test (p value)‡	0.058		0.006	
Missing=58				
Gender				
Male (n, %)	2238 (97.4%)	255 (97.3%)	2805 (98.2%)	331 (96.8%)
χ^2 test (p value)§	0.840		0.091	
Missing=59				
Smoking status (n, %)				
Current	151 (7.1%)	13 (5.3%)	291 (11.1%)	25 (8.0%)
Ex-smoker	555 (26.0%)	83 (33.6%)	730 (27.9%)	88 (28.3%)
Never-smoker	1425 (66.9%)	151 (61.1%)	1592 (60.9%)	198 (63.7%)
χ^2 test (p value)§	0.036		0.242	
Missing=515				
Pack-years¶				
Mean (SD)	16.1 (17.9)	15.8 (22.4)	16.2 (18.4)	14.2 (15.8)
Unpaired t-test (p value)‡	0.909		0.325	
Median (IQR)	10.3 (3.5–22)	8.3 (3–20)	10 (3.5–22.5)	10.3 (3.6–20)
Missing=563				
Family history of asthma (n, %)				
Yes	287 (12.4%)	101 (38.1%)	394 (13.6%)	132 (38.5%)
No	2026 (87.6%)	164 (61.9%)	2502 (86.4%)	211 (61.5%)
χ^2 test (p value)§	<0.001		<0.001	
Missing=0				
Years worked or lived on a farm				
Mean (SD)	36.5 (22.5)	31.7 (22.8)	37.5 (21.5)	35.0 (21.5)
Unpaired t-test (p value)‡	0.002		0.052	
Median (IQR)	40 (18–55.0)	38.5 (7.5–51.3)	40 (22–54.4)	38.1 (20.5–52.2)
Missing=183				
Years spent working with pesticides				
Mean (SD)	25.0 (11.5)	24.2 (11.3)	23.0 (12.2)	21.1 (12.3)
Unpaired t-test (p value)‡	0.255		0.011	
Missing=78				

*Number of individuals who responded to the baseline and the follow-up questionnaire, and their doctor diagnosed asthma status at baseline
†Number of individuals who did not respond to the follow-up questionnaire, and their doctor diagnosed asthma status at baseline
‡P value for a bootstrapped unpaired t-test comparing those with and those without an asthma diagnosis
§P value for Fisher's exact χ^2 test comparing those with and those without an asthma diagnosis
¶Pack-years = (number of cigarettes smoked a day/20) multiplied by the number of years smoked; for those who smoke(d)
N or n, count.

exposures, 7 (5.8%) for physical agents and 3 (2.5%) for fumes or other irritants.

Using the more restricted (more specific) definition of asthma, with a combination of self-reported doctor diagnosed asthma and wheeze or whistling in their chest in the last 12 months, 6.8% (95% CI 5.9% to 7.9%) fulfilled this definition.

Table 3 compares the baseline characteristics by asthma diagnosis status of those who responded and those who did not respond to the follow-up questionnaire. For most characteristics, differences between responders and non-responders were small. Overall, there were more never smokers among the responders, and responders had on average worked with pesticides for 2 years longer than non-responders.

Table 4 shows the logistic regression results for three analyses using follow-up health outcomes: (1) the (binary presence or absence) of doctor diagnosed asthma, separately a model for (2) wheeze in the last 12 months and separately again a model for (3) work-related wheeze. OR estimates are adjusted for all other variables in the model. Analyses were not additionally adjusted for other variables; gender was included where possible but was dropped where collinearity arose.

In these models, the continuous variable 'years spent working with pesticides' and the categorical variable 'hours spent working with pesticides in the previous year' were not associated with the presence of doctor diagnosed asthma or self-reported recent wheeze. A logistic regression analysis of doctor diagnosed asthma at baseline found no evidence of an association with the number of years spent working with pesticide (p=0.513) in a model adjusted for age, gender and smoking status. The consistency between the baseline and follow-up findings suggest that any differences between responders and non-responders in the number of years spent working with pesticides did not bias the association between an asthma diagnosis and the years spent working with pesticides. The categorical hours variable

Table 4 Separate logistic regressions models for doctor diagnosed asthma and self-reported wheeze (any in the last 12 months)

Model—Asthma* N=2354	OR	95% CI	P value
Age (years)	0.98	0.96 to 0.99	0.004
Gender			
Male (reference)	1.00		
Female	0.98	0.45 to 2.14	0.962
Smoking status			
Never smoked (reference)	1.00		
Ever smoked	1.44	1.11 to 1.87	0.006
Years spent working with pesticides	1.01	0.99 to 1.02	0.461
Total hours' work with pesticides			0.017†
Low (reference)	1.00		–
Zero	1.26	0.92 to 1.73	0.150
High	0.76	0.55 to 1.04	0.081
Model—any wheeze in last 12 months* N=2316			
Age (years)	0.98	0.97 to 0.99	0.001
Gender			
Male (reference)	1.00		
Female	0.87	0.43 to 1.78	0.704
Never smoked (reference)	1.00		
Ever smoked	1.52	1.22 to 1.89	<0.001
Years spent working with pesticides	1.01	1.00 to 1.02	0.162
Total hours' work with pesticides			0.142†
Low (reference)	1.00		
Zero	1.31	0.99 to 1.73	0.056
High	1.04	0.81 to 1.35	0.745
Model—work-related wheeze* N=2172			
Age (years)	1.00	0.96 to 1.03	0.890
Never smoked (reference)	1.00		
Ever smoked	1.23	0.61 to 2.47	0.567
Years spent working with pesticides	1.01	0.98 to 1.05	0.451
Total hours' work with pesticides			0.031†
Low (reference)	1.00	–	–
Zero	1.04	0.37 to 2.98	0.936
High	2.67	1.16 to 6.18	0.021

The data from the 2018 respiratory questionnaire were used in this analysis. Total hours' work with pesticides are the number of hours spent working with pesticides in the previous year. Each variable was adjusted for the others in the model. Gender was omitted from the work-related wheeze because of collinearity. Age and years spent working with pesticides are continuous variables in these models; to assist interpretation an OR of 0.98 suggests that a 1-year increase in age lowers the odds of having the diagnosis or symptom by 2%.
*Reference category is all other participants without this diagnosis or symptom
†Overall test of significance for the 'Total hours work with pesticides' variable

was associated with work-related wheeze (suggestive of at least work-related asthma, and possibly occupational asthma) (high vs low exposure OR 2.67, 95% CI 1.16 to 6.18, p=0.021). Similarly, high hours' pesticide exposure (high vs low exposure category OR 2.68, 95% CI 1.28 to 5.60, p=0.009) was also a predictor for work-related chest tightness in an identically adjusted analysis.

Finally, table 5 shows factors that were associated with persistent asthma in those who reported a previous doctor diagnosed asthma. It shows in this rather restricted group analysis that exposure to organic dusts (significantly, p=0.026) predicted persistence of asthma, adjusted for the effects of age and smoking status.

Table 5 Logistic regression model for persistent asthma (2018, N=249)

Model—do you still have asthma (yes/no)	OR	95% CI	P value
Age	1.01	0.99 to 1.04	0.312
Never smoked (reference)	1.00		
Ever Smoked	0.92	0.51 to 1.64	0.775
Work-related cause*			0.027†
Chemical (any mention of)	5.88	0.74 to 46.7	0.094
Dust, organic	2.13	1.09 to 4.16	0.026

Participants who reported doctor diagnosed asthma at baseline and also reported doctor diagnosed asthma in the 2018 respiratory questionnaire were included in this model. Each variable was adjusted for the others in the model. Gender was omitted from the model because of collinearity. Age is a continuous variable in this model; to assist interpretation an OR of 0.98 suggests that a 1-year increase in age lowers the odds of having asthma by 2%.
*Reference category is 'no work-related cause of asthma'. 'Dust, unspecified' and 'other' were omitted because of collinearity.
†Overall test of significance for the 'work-related cause' variable

DISCUSSION

There have been few studies that report findings from workers applying pesticides and related chemicals in a variety of real-world scenarios, with additional data on changes in reported health conditions over time. This large study of pesticide workers identified a prevalence of asthma at baseline of 10.4%, and of 11.5% up to 5 years later in a smaller follow-up population. Both figures are consistent with the range of findings of other studies.[18] Using a more restricted definition of asthma that included both a self-reported diagnosis, but in addition the presence of a wheeze or whistling in their chest in the last 12 months, the prevalence fell as expected to 6.8%. This value is similar to the median value of 5.3% identified by a pan (predominantly) European study assessing asthma prevalence in populations, based on similar questions.[19] In other words, this study did not appear to identify an unusually high prevalence of asthma in relation to other pesticide using and general populations. Again, incidence of new cases between the two study time points was not identified to be excessive.

The presence of self-reported doctor diagnosed asthma was associated with symptoms in most, and a high level of perception that workplace exposures may be responsible. Of interest was the nature of these potentially causative exposures; organic dust exposures themselves, rather than chemical exposures predominated. Self-reported organic dust exposure was significantly associated with persistent asthma symptoms when adjusted for smoking and age although the same relationship was not significant for pesticide exposures. The design of the study did not permit further comment on the relative contributions of organic versus chemical exposures, given that only the latter were documented in more detail.

It is noteworthy that adjusted regression analyses generally did not identify an association between asthma, or (all) wheeze and pesticide exposure estimated by the years spent working with pesticides and by hours worked with pesticides in the previous year. Indeed, the opposite relationship was suggested for asthma, with those in a low or zero pesticide exposure category having more asthma than those highly exposed. Work-related wheeze and chest tightness were, however, associated with pesticide exposure. This raises the possibility that work-related symptoms might occur in response to exposures but when they are diagnosed as asthma there is a tendency for workers to move into lesser exposed work tasks. The fact that the 'zero' pesticide exposure category represents individuals who had retired or moved

to other jobs may provide some support for this possibility. This suggests that a healthy worker selection may be occurring in the higher exposed group.

There are several limitations of this study which should be considered when interpreting the findings. Participants were recruited from various professional bodies and from an existing cohort study of pesticide users. At baseline, the age and sex distributions of the participants were similar to those in the source population: the male/female ratio was the same in the study cohort and the source population,[20] and the participants (mean age 54.1) were on average older than the members of the source population (mean age 48.8). Wider comparisons indicate that there were differences between the participants and the general population. The average age of study participants was nearly 15 years older than the general working population in England and Wales,[21] and the percentage of females (2.2%) in the PIPAH study was lower than was observed in the Labour Force Survey 2012 agricultural and related trades occupations.[22] Thirty-six per cent of study participants had 'other' (most likely vocational based) qualifications and 52% were self-employed, both percentages higher than in the general population.[23] Smoking prevalence in the PIPAH study was lower (9%) and the percentage reporting being current alcohol drinkers higher (94%) than in the general population.[24 25] It is not possible to comment on whether the differences observed between the study participants and the general population also exist in the wider population of pesticide users, or on whether the PIPAH study participants are representative of the pesticide user population overall. There may well have been significant selection (response) bias issues, although the fact that asthma prevalence and incidence were similar to those reported in other populations suggests this is not a significant problem. Similarly, self-reported health endpoints were not triangulated with health records, although both self-reported doctor-diagnosed conditions and the levels of self-reported symptoms were collected; the latter a marker, and indicator of severity of, such respiratory diagnoses. There were small differences between responders to the follow-up questionnaire and non-responders with respect to smoking status, age and the years spent working with pesticides. However, the proportion of asthma cases and individuals with a family history of asthma were very similar in the two groups. There may have been some bias in the response at follow-up, but it is not likely to have had a significant impact on any findings.

Self-reported health outcomes are vulnerable to under-reporting and over-reporting, or simply errors in completing the questionnaire. In this study, there were individuals who reported doctor diagnosed asthma at baseline but not at follow-up, and there were individuals who reported doctor diagnosed asthma only at follow-up but gave an age at diagnoses that was considerably younger than their age at baseline. The former may have under-reported at follow-up, and the latter appear to have under-reported at baseline.

Pesticide exposure attribution was also based on the self-reported nature and extent of pesticide and related exposures only. While no exposure measures were taken, the high level of detail recorded about work tasks, however, should allow subsequent application of other exposure quantification techniques including the use of a pesticide specific job exposure matrix. Non-pesticide exposures were only minimally recorded and thus it is difficult to comment on the differential contribution to asthma between chemical and organic dust exposures from these data. The latter shortfall is compounded by the essentially cross-sectional nature of the study design, limiting inference about asthma

In summary, this study did not appear to identify an unusually high prevalence of asthma in a large group of pesticide workers. There were associations between the presence of reported symptoms and pesticide exposure, but also importantly an association between both self-reported asthma and persistent asthma symptoms to self-reported exposures to other agents; in particular, the role of exposure to organic dusts was potentially implicated. Further work could usefully better define the relative importance of individual chemicals and organic dusts as potential causative factors for symptoms of asthma and self-reported asthma. A better understanding of likely causative agents will assist the prompt development of appropriate and evidence-based workplace interventions to reduce the risks of developing work-related respiratory conditions.

Contributors All authors contributed to the study design, data collection, analysis interpretation and preparation of this manuscript. DF is the lead contributor and guarantor.

Funding This work was supported by the Health and Safety Executive of Great Britain. The contents of this publication reflect the views of the authors and not necessarily those of HSE policy or policymakers.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study was approved by National Research Ethics Service Committee of Greater Manchester North-West (reference 12/NW/0654).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The authors would be happy to discuss options for access to data, but the data are the property of the UK Crown.

ORCID iDs
David Fishwick http://orcid.org/0000-0001-5941-090X
Y Chen http://orcid.org/0000-0003-4218-084X
Neil Pearce http://orcid.org/0000-0002-9938-7852
Gillian Frost http://orcid.org/0000-0003-3339-8898

REFERENCES

1 Chakraborty S, Mukherjee S, Roychoudhury S, *et al*. Chronic exposures to cholinesterase-inhibiting pesticides adversely affect respiratory health of agricultural workers in India. *J Occup Health* 2009;51:488–97.
2 Fareed M, Pathak MK, Bihari V, *et al*. Adverse respiratory health and hematological alterations among agricultural workers occupationally exposed to organophosphate pesticides: a cross-sectional study in North India. *PLoS One* 2013;8:e69755.
3 Buralli RJ, Ribeiro H, Mauad T, *et al*. Respiratory condition of family farmers exposed to pesticides in the state of Rio de Janeiro, Brazil. *Int J Environ Res Public Health* 2018;15. doi:10.3390/ijerph15061203. [Epub ahead of print: 08 06 2018].
4 de Jong K, Boezen HM, Kromhout H, *et al*. Association of occupational pesticide exposure with accelerated longitudinal decline in lung function. *Am J Epidemiol* 2014;179:1323–30.
5 Sham'a FA, Skogstad M, Nijem K, *et al*. Cross-shift changes in lung function among Palestinian farmers during high- and low-exposure periods to pesticides: a longitudinal study. *Arch Environ Occup Health* 2015;70:218–24.
6 Ratanachina J, De Matteis S, Cullinan P, *et al*. Pesticide exposure and lung function: a systematic review and meta-analysis. *Occup Med* 2020;70:14–23.
7 Buralli RJ, Dultra AF, Ribeiro H. Respiratory and allergic effects in children exposed to pesticides-A systematic review. *Int J Environ Res Public Health* 2020;17:pii: E2740.
8 Ye M, Beach J, Martin JW, *et al*. Occupational pesticide exposures and respiratory health. *Int J Environ Res Public Health* 2013;10:6442–71.
9 Sprince NL, Lewis MQ, Whitten PS, *et al*. Respiratory symptoms: associations with pesticides, silos, and animal confinement in the Iowa farm family health and hazard surveillance project. *Am J Ind Med* 2000;38:455–62.
10 A review of the relationship between Pyrethrins, pyrethroid exposure and asthma and allergies. Available: http://nepis.epa.gov/EPA/html/DLwait.htm?url=/Adobe/PDF/P1006R0U.PDF [Accessed 01 May 2020].
11 Fieten KB, Kromhout H, Heederik D, *et al*. Pesticide exposure and respiratory health of indigenous women in Costa Rica. *Am J Epidemiol* 2009;169:1500–6.

12 de Jong K, Boezen HM, Kromhout H, *et al*. Association of occupational pesticide exposure with accelerated longitudinal decline in lung function. *Am J Epidemiol* 2014;179:1323–30.
13 Holmes E. *The Pesticide Users' Health Study: Survey of pesticide usage*. Health and Safety Executive Research Report RR957, 2013.
14 Harding A-H, Fox D, Chen Y, *et al*. Prospective Investigation of Pesticide Applicators' Health (PIPAH) study: a cohort study of professional pesticide users in Great Britain. *BMJ Open* 2017;7:e018212.
15 PUHS. Hse pesticide users' health study. Available: https://www.hsl.gov.uk/resources/major-projects/puhs [Accessed 28 Apr 2020].
16 PIPAH study questionnaires. The PIPAH study respiratory health and working with pesticides questionnaire. Available: https://www.hsl.gov.uk/media/19565/PIPAH%20Short%20Survey%202017.pdf [Accessed 04 May 2020].
17 Janson C, Chinn S, Jarvis D, *et al*. Physician-diagnosed asthma and drug utilization in the European community respiratory health survey. *Eur Respir J* 1997;10:1795–802.
18 Saglan Y, Bilge U, Oztas D, *et al*. The prevalence of asthma and asthma-like symptoms among seasonal agricultural workers. *Biomed Res Int* 2020;2020:5
19 Bukalasa JS, Brunekreef B, Brouwer M, *et al*. Associations of residential exposure to agricultural pesticides with asthma prevalence in adolescence: the PIAMA birth cohort. *Environ Int* 2018;121:435–42.
20 Fox D, Harding AH, Frost G. *The prospective investigation of pesticide applicators' health (PIPAH) study: baseline volunteer cohort*. Health and Safety Executive Research Report RR1119, 2017.
21 Office for National Statistics. Nomis: official labour market statistics. Available: https://www.nomisweb.co.uk/census/2011/data_finder?keyword=Age [Accessed 19 Jan 2021].
22 Labour force survey employment status by occupation. Available: https://webarchive.nationalarchives.gov.uk/20131117210344/http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-326437 [Accessed 19 Jan 2021].
23 Office for National Statistics. Census: key statistics for England and Wales, 2011. Available: http://www.ons.gov.uk/ons/dcp171778_290685.pdf [Accessed 21 Jan 2021].
24 NHS Digital. General lifestyle survey 2011. Available: http://www.hscic.gov.uk/catalogue/PUB11454 [Accessed 19 Jan 2021].
25 Office for National Statistics. General lifestyle survey 2010. Available: http://www.ons.gov.uk/ons/rel/ghs/general-lifestyle-survey/2010/drinking.xls, table 2.5b [Accessed 19 Jan 2021].