Occupational exposure to asthmagens and adult onset wheeze and lung function in people who did not have childhood wheeze: a 50-year cohort study

Nara Tagiyeva[1], Edmund Teo[1], Shona Fielding[1], Graham Devereux[1], Sean Semple[1], Graham Douglas[2]

[1]Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

[2]Respiratory Unit, Aberdeen Royal Infirmary, Aberdeen, UK

Corresponding author: Nara Tagiyeva, Child Health, 3rd floor Royal Aberdeen Children's Hospital, University of Aberdeen, Westburn Road, AB25 2ZG, tagiyeva@hotmail.com, +44 1224 438453

Abstract

Background: There are few prospective studies that relate the development of adult respiratory disease with exposure to occupational asthmagens.

Objective: To evaluate the risk of adult onset wheeze (AOW) and obstructive lung function associated with occupational exposures over 50 years.

Methods: A population-based randomly selected cohort of children who had not had asthma or wheezing illness, recruited in 1964 at age 10-15 years, was followed-up in 1989, 1995, 2001 and 2014 by spirometry and respiratory questionnaire. Occupational histories were obtained in 2014 and occupational exposures determined with an asthma-specific job exposure matrix. The risk of AOW and lung function impairment was analysed in subjects without childhood wheeze using logistic regression and linear mixed effects models.

Results: All 237 subjects (mean age 61 years, 47% male, 52% ever smoked) who took part in the 2014 follow-up had completed spirometry. Among those who did not have childhood wheeze, spirometry was measured in 93 subjects in 1989, in 312 in 1995 and in 270 subjects in 2001 follow-up. For longitudinal analysis of changes in FEV_1 between 1989 and 2014 spirometry records were available on 191 subjects at three time points and on 45 subjects at two time points, with a total number of 663 records. AOW and FEV_1<LLN were associated with occupational exposure to food-related asthmagens (adjusted odds ratios (adjORs) 95%CI: 2.7 [1.4, 5.1] and 2.9 [1.1, 7.7]) and biocides/fungicides (adjOR 95%CI: 1.8 [1.1, 3.1] and 3.4 [1.1, 10.8]), with evident dose-response effect (p-trends<0.05). Exposure to food-related asthmagens was also associated with reduced FEV_1, FVC and $FEF_{25-75\%}$ (adjusted regression coefficients 95%CI:-7.2 [-12.0,-2.4], -6.2 [-10.9,-1.4], and -13.3 [-23.4,-3.3]). Exposure to wood dust was independently associated with AOW, obstructive lung function and reduced $FEF_{25-75\%}$. Excess FEV_1 decline of 6-8ml/year was observed with occupational exposure to any asthmagen, biocides/fungicides and food-related asthmagens (p<0.05).

Conclusions: This longitudinal study confirmed previous findings of increased risks of adult onset wheezing illness with occupational exposure to specific asthmagens. A novel finding was the identification of food-related asthmagens and biocides/fungicides as potential new occupational risk factors for lung function impairment in adults without childhood wheeze.

Key words: adult onset wheeze, ventilatory function, occupational exposure, asthmagens, cohort, job exposure matrix

1. INTRODUCTION

Current evidence suggests that 17% of adult–onset asthma (ERS 2013) and up to 20% (50% among never smokers) of chronic obstructive pulmonary disease (COPD) (Sigsgaard et al. 2010) can be attributed to work-related exposure. Although the prevalence of asthma in some westernised countries appears to be falling (Asher and Pearce 2014), the individual and societal burden of asthma remains high. Moreover the worldwide prevalence of asthma and COPD is rising (Anandan et al. 2010; GOLD 2014), and therefore the search for preventable environmental risk factors remains important.

Studies have shown certain occupational sensitisers to be associated with an increased risk of asthma, e.g. isocyanates, latex (Bakerly et al. 2008), the role of irritant exposures in asthma aetiology is less well established (Brooks and Bernstein, 2011). Most evidence for the association between occupational exposure and respiratory symptoms, ventilatory function impairment and decline comes either from studies that examine specific exposures within single industries or occupational settings (Shi et al. 2010) or from general population cross-sectional (Le Moual et al. 2004; Humerfelt et al. 1993) and case-control (Wang et al. 2010) studies. Such studies have inherent weaknesses, including healthy worker effect, self-selection in job choice, case/control selection bias and the issue of generalisability, which may also preclude causal inference. Another weakness of epidemiological studies is their inability to accurately ascribe exposure measures. A few studies have prospectively examined associations with exposure to specific occupational substances in population-based cohorts, but with relatively short follow-up periods (Lillienberg et al. 2013; Humerfelt et al. 1993; Mehta et al. 2012).

The Aberdeen population-based WHEASE (What Happens Eventually to Asthmatic children: Sociologically and Epidemiologically) cohort study of children recruited in 1964 (Dawson et al. 1969) at age 10-15 years and followed up until 2014 (age 58-64 years) (Tagiyeva et al. 2015) provides a rare opportunity to investigate the effects of lifetime occupational exposures on respiratory morbidity in later life.

The aim of the current study was to investigate, in a community-based setting, whether occupational exposures to known asthmagens, assessed by job exposure matrix (JEM), were related to the development of adult onset wheeze (AOW), spirometry-defined airflow obstruction, or impaired ventilatory function at age 58-64 years and to longitudinal changes in ventilatory function over 25-year follow up among those who did not have wheezing illness as children.

2. MATERIALS AND METHODS

2.1. Subjects

In 1964, the British Medical Research Council Medical Sociology Research Unit conducted a random community survey of all children attending primary school in the city of Aberdeen, Scotland in 1962 and still resident in Aberdeen at the time of selection. A 1-in-5 random sample was selected totalling 2,743 of whom 2,511 were interviewed at home with their parents. Amongst the 2,511 children aged 10-15 years interviewed, 288 were reported as having had wheeze and 2,223 as having no respiratory symptoms. In a further study in 1964, those children who had wheezed were examined by a paediatrician, and 121 were classified as having asthma and 167 as having wheeze in the presence of upper respiratory tract infection (then termed wheezy bronchitis) (Dawson et al. 1969). In 2014, a total of 583

individuals who took part in at least one previous follow up were traced and invited to take part. The current study reviews the outcome in 330 children who were traceable in 2014, of whom 239 did not have respiratory symptoms recorded in 1964. The analysis presented is for 237 participants due to the availability of occupational exposure.

Members of the cohort were reassessed in 1989 (aged 35-40, n=360), 1995 (aged 41-46, n=1542), 2001 (aged 47-52, n=381), and 2014 (aged 58-64, n=330) (Tagiyeva et al. 2015) (Table 1) to address differing topical clinical questions using subsets of the original sample. The 1989, 1995 and 2001 follow-up phases included 93, 312 and 270 subjects with measured ventilatory function respectively, who had never wheezed as children (Godden et al. 1994; Bodner et al. 1998; Edwards et al. 2003).

Table 1. The WHEASE cohort recruitment and follow up

Original cohort	
1964	The Medical Research Council random survey of Aberdeen schoolchildren Age 10-15 years 2743 invited, 2511 participated: response rate 92% 121 child asthma, 167 child wheezy bronchitis, 2223 child non-wheezers Spirometry measured in 288 child asthma & wheezy bronchitis
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What Happens Eventually to Asthmatic children: Sociologically and Epidemiologically (WHEASE) cohort	
1989	WHEASE 1 to follow all child asthma and wheeze cases and selected non-wheezers Age 35-40 years 455 traced and invited, 360 participated: response rate 79% Participants included: 97 child asthma, 132 child wheezy bronchitis, 131 child non-wheezers

	Spirometry measured in 272, including 93 child non-wheezers
1995	WHEASE 2 to follow all child non-wheezers Age 41-46 years 1758 traced and invited to postal survey, 1542 participated in postal survey: response rate 88% Participants in postal survey: 102 AOW, 1440 never-wheezers Clinical assessment (including spirometry) carried out in 312: 102 AOW and 217 randomly selected never-wheezers
2001	WHEASE 3 to follow all in WHEASE 1 and those with spirometry in WHEASE 2 Age 47-52 years 605 traced and invited, 381 participated: response rate 63% Participants included: 46 child asthma, 65 child wheezy bronchitis, 270 child non-wheezers Spirometry measured in 372, including 270 child non-wheezers
2014	WHEASE 4 to follow all WHEASE 1, 2 & 3 with previously measured spirometry Age 58-64 years 583 traced and invited, 330 participated: response rate 57% Participants included: 38 child asthma, 53 child wheezy bronchitis, 239 child non-wheezers Spirometry measured in 329, including 239 child non-wheezers Occupational histories collected from 328, including 237 child non-wheezers

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2.2.Assessments and outcomes

Each follow up was carried out in the Chest Clinic, Aberdeen Royal Infirmary, and included the updated version of the MRC respiratory questionnaire (Medical Research Council 1986) administered during in-person interview (Supplemental Material, MRC questionnaire), and spirometry performed according to internationally accepted guidelines. The 2014 spirometry followed ATS/ERS guidelines (Pellegrino et al. 2005) with pre- and post-administration of 400µg salbutamol using a Vitalograph Compact II spirometer (Vitalograph, Buckingham, UK). Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and forced expiratory flow over the middle half of FVC ($FEF_{25–75}$) were recorded. Socio-demographic characteristics and history of cigarette smoking were also ascertained at interview.

During the 2014 assessment a structured and detailed lifetime occupational history was recorded. This included descriptions of job title, main job services/tasks provided, industry, company, years job started and stopped, and type of employment (full- or part-time).

2.3.Occupational data management

Free-text descriptions of occupations and industries for all lifetime jobs were coded into four-digit Standard Occupational Classification (SOC2000) codes developed by the UK Office for National Statistics (Office for National Statistics 2008) using the Computer Assisted Structured Coding Tool (CASCOT) (Jones and Elias 2014). This generated certainty scores (1-100%) indicating the degree of certainty that the given code is correct. CASCOT derived occupational codes scores of >50% were accepted, and those scored ≤50% coded manually. This coding strategy has been shown to have 91% agreement with manually coded occupations (Tagiyeva et al. 2010).

In the current study, we used a JEM previously developed to evaluate exposure to 11 specific asthmagens (Tagiyeva et al, 2010), suitable for the UK workplace environment, based for 6 of them (latex, wood, animal, enzyme, flour, isocyanate) on an update of exposure assessment from the JEM developed by Kennedy et al 2000. The presence and intensity of occupational exposure to 11 major occupational asthmagen groups: biocides/fungicides, glues/resins, latex, dyes, solder/flux, food-related asthmagens, wood dust, animal dust, enzyme products, flour/grains dust, and isocyanates, was assessed by two UK-based occupational hygienists based on the usual workplace environment in the UK during the 1990s while accounting for hazard controls that were commonly in place. This allowed for semi-quantitative evaluation (high, medium, low, zero) of intensity of exposure. This procedure is detailed in Tagiyeva et al (2010). Exposure to recognised occupational asthmagens was estimated by assigning an asthma-specific JEM to each 353 four-digit SOC2000 code. As occupational exposure data approximate to log-normal distribution, use of lognormal models for analysing workplace pollutant data is well established (Krishnamoorthy et al 2006). In the current study for each subject, the cumulative index of lifetime exposure was estimated by multiplying a logarithmic scale of exposure intensity by the number of years of exposure. Logarithmic values of 1, 3 and 10 were used to represent the difference in assessed exposure categories of low, medium and high based on subjective assessment of the level of past exposure from airborne hazardous substances (Cherrie and Schneider 1999).

2.4.Statistical Analysis

The primary outcomes were: adult onset wheeze (AOW), defined as wheeze ever reported at any follow up between 16-64 years of age, ventilatory function and airflow obstruction at age 58-64 years and changes in ventilatory function during the 25-year follow-up period.

Spirometric indices were expressed as percent predicted as defined by the ERS Global Lung Initiative, 2012 (Quanjer et al. 2012). Reduced FEV_1 was defined as post-bronchodilator FEV_1<lower 95% confidence limit of the internationally agreed predictive equations for normality (LLN) (Pellegrino et al. 2005; Quanjer et al. 2012). Airflow obstruction was defined as post-bronchodilator FEV_1/FVC <0.7 (GOLD 2014).

Exposures of interest were categorised as ever exposed versus never exposed and further categorised high, medium, low and zero exposure, latter to ascertain if degree/intensity of exposure had a different association with outcome. High, medium and low categories were generated using tertiles of cumulative indices of lifetime exposure. Exposures of interest in the longest and current/last held jobs were examined in separate models.

Demographic characteristics were described using number and percentage if categorical variables or mean (standard deviation) if continuous (as normally distributed). Normality was assessed by skewness and kurtosis tests and histograms. Univariate comparisons of binary exposure (biocides/fungicides, glues/resins, latex, solder/flux, food-related asthmagens, wood dust, animal dust) with binary outcomes (AOW, FEV_1 < LLN, FEV_1/FVC < 0.7) were carried out using Chi-squared tests. For continuous outcomes (FEV_1, FVC, $FEF_{25\%-75\%}$) independent samples t-tests were used to assess differences in outcome between the exposure groups. Following this, logistic and linear regression analyses were implemented to adjust for

confounders (gender, smoking ever, highest education qualification). Different models were fitted: model A looked at the total count of exposures with outcome, model B a categorised count of exposures (0, 1-3, ≥4), model C the binary 'any asthmagen', and finally the D models looked at each exposure on its own with outcome. Any significant relationship in models D was further explored by categorising the exposure into none/low/med/high exposure.

Linear mixed effect models with unstructured covariance were used to analyse changes in FEV_1 between 1989 and 2014 in the exposed and non-exposed. Subjects with at least two spirometry test results were included in this analysis. Random effects were participant and participant*time with fixed effects of time and the confounding variables. Time was entered as a continuous variable into the model taking the values of 0, 6, 12, and 25 years to represent assessments made in 1989, 1995, 2001, and 2014. Inclusion of an interaction term for time and exposure to individual substances allowed the production of estimates of change in FEV_1 between exposed and non-exposed. Analyses were performed using SPSS v22.0 (Armonk, NY, USA) and SAS v9.3 (SAS Institute Inc., Cary, USA).

All analyses were adjusted for sex, history of having ever smoked more than 100 cigarettes, and the highest educational qualification obtained, used as an indicator of childhood and early adulthood socio-economic status. Linear mixed effect models were also adjusted for age (in 1989). Interactions between exposure and smoking were analysed using separate logistic regression models for each asthmagen. Pack year data for smoking were not available, neither were the data to assess the temporal relationship between exposure and the onset of AOW.

Participants with unknown occupational history were excluded from the analysis. Jobs with less than one year duration were excluded from the estimation of exposure.

3. RESULTS

Of the 239 WHEASE participants assessed in 2014 with no history of childhood wheezing illness, occupational history was available for 237; of these 15% reported a diagnosis of asthma and 6% a diagnosis of COPD. Approximately 8% of the cohort had FEV_1<LLN and 39% had $FEV_1/FVC<0.7$. Characteristics of subjects who reported AOW and those who had never reported wheeze are detailed in Table 2. Those who had developed wheeze as adults were more likely to be overweight, have a history of smoking, be diagnosed with asthma and COPD, and have reduced ventilatory function.

Table 2. Main demographic and health indicators of the study population in 2014

Socio-demographic characteristics	No childhood wheeze n 237	AOW[a] n 95	Never wheezed, n 142	p for difference AOW vs never wheezed[b]
Male sex, n (%)	111 (46.8)	46 (48.4)	65 (45.8)	0.689
Age, years, mean±SD	60.6±1.5	60.8±1.5	60.5±1.5	0.149
BMI, kg/m^2, mean±SD	28.4±5.5	29.6±6.0	27.7±5.0	0.008
Smoking ever, n (%)	124 (52.3)	61 (64.2)	63 (44.4)	0.003
Smoking currently, n (%)	41 (17.3)	21 (22.1)	20 (14.1)	0.110
Current exposure to ETS[c], n (%)	42 (17.7)	25 (26.3)	17 (12.0)	0.005
University degree and higher, n (%)	42 (17.7)	15 (15.8)	27 (19.0)	0.524
Current work status, n (%)				
Full-time	110 (46.4)	40 (42.1)	70 (49.3)	0.003
Part-time	57 (24.1)	18 (18.9)	39 (27.5)	
Unemployed	6 (2.5)	3 (3.2)	3 (2.1)	

Retired	44 (18.6)	18 (18.9)	26 (18.3)	
Not working due to ill health	20 (8.4)	16 (16.8)	4 (2.8)	
Clinical, questionnaire-based, n (%)				
Diagnosed asthma ever	34 (14.7)	33 (37.1)	1 (0.7)	<0.001
Diagnosed COPD ever	15 (6.3)	15 (15.8)	0 (0.0)	<0.001
Spirometry, postbronchodilator				
FEV_1 % predicted, mean±SD	97.2±16.3	92.2±18.3	100.6±13.9	<0.001
FVC % predicted, mean±SD	108.6±15.5	107.2±17.3	109.5±14.1	0.257
$FEF_{25-75\%}$ % predicted, mean±SD	77.8±33.6	68.0±33.0	84.4±32.5	<0.001
FEV_1<LLN, n (%)	20 (8.4)	15 (15.8)	5 (3.5)	0.001
FEV_1/FVC <0.7, n (%)	92 (38.8)	47 (49.5)	45 (31.7)	0.006
FEV_1 % predicted <80%, n (%)	30 (12.7)	21 (22.1)	9 (6.3)	<0.001

[a]Adult onset wheeze. [b]Chi-squared test for categorical and t-test for continuous data analysis. [c]Environmental tobacco smoke.

3.1.Exposure to occupational asthmagens

All study participants had between one and six different jobs in their lifetime (median 2, IQR 2-3). Most commonly reported occupations were storage and goods handling occupations, van drivers and maintenance managers among men and cleaning, general office workers, and sales assistants among women. Occupations in the WHEASE cohort categorised by exposure to at least one asthmagen and to 11 major occupational asthmagen groups by the intensity of exposure are presented in Table S1, Supplemental Material. While most occupations were not associated with any asthmagen exposures, others were characterised by multiple exposures patterns.

The lifetime occupational exposure to each specific asthmagen is presented in Table 3 and Figure 1. Two thirds of the participants were exposed to at least one asthmagen over their working lifetime, and more than half of those were exposed to between one and five

238 occupational asthmagens. Biocides/fungicides were the most common asthmagens (49%
239 exposed), followed by glues/resins, latex and dyes. Using an index of cumulative exposure,
240 which accounted for both, exposure duration and estimated intensity, the highest exposures
241 were found for wood dust and latex (Table 3).
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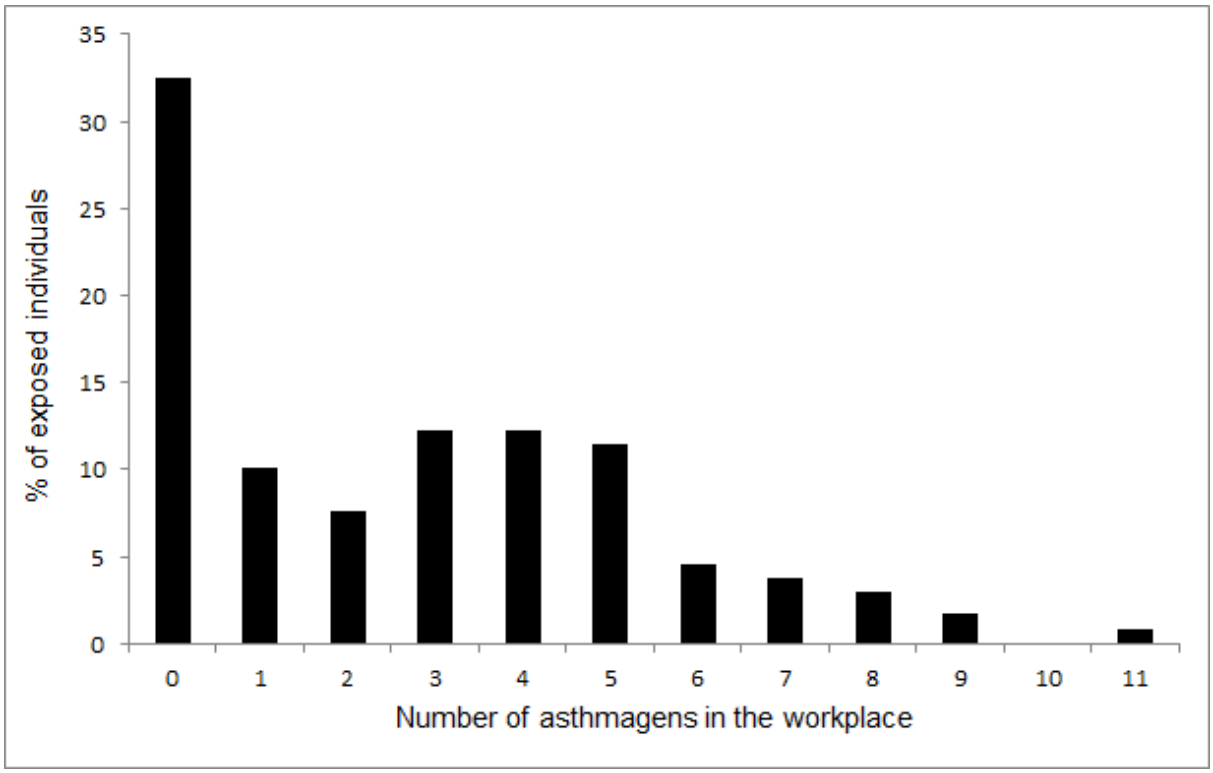

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244 Figure 1. Lifetime prevalence of exposure to the total number of occupational asthmagens in
245 the WHEASE cohort, n analysed=237

Table 3. Lifetime occupational exposures to asthmagens by duration of exposure and cumulative exposure index calculated within those exposed in the WHEASE cohort, n analysed = 237

Occupational exposures to	Exposed, n (%)	Duration of exposure, years, median (IQR)	Cumulative exposure index[a], median (IQR[b])
Any asthmagen	160 (67.5)	-	-
Biocides/fungicides	115 (48.5)	20.0 (8-36)	29.0 (11.0-45.0)
Glues/resins	92 (38.8)	20.5 (7-41)	29.5 (12.0-46.0)
Latex	83 (35.0)	19.0 (5-35)	36.0 (8.5-149.5)
Dyes	75 (31.6)	15.0 (6-33)	21.0 (9.0-42.0)
Solder/flux	56 (23.6)	20.0 (10-38)	33.0 (13.0-72.0)
Food-related asthmagens	53 (22.4)	10.0 (5-30)	30.0 (9.25-59.50)
Wood dust	48 (20.3)	17.0 (6-37)	44.0 (20.75-121.50)
Animal dust	43 (18.1)	12.0 (5-27)	21.5 (9.75-66.0)
Enzyme products	28 (11.8)	10.0 (4-22)	14.0 (4.5-26.5)
Flour/grains dust	26 (11.0)	6.0 (3-14)	17.0 (6.0-50.0)
Isocyanates	22 (9.3)	18.5 (6-41)	24.5 (11.25-42.0)

[a]Cumulative exposure measurement that combines logarithmic intensity of occupational exposure as estimated by JEM and duration of exposure. [b]Interquartile range

3.2.Outcomes in 2014 and occupational exposure to asthmagens

In univariate analyses, no difference in the prevalence of respiratory outcomes was found with exposure to any of dyes (n exposed=75), enzyme products (n=28), flour/grain dust (n=26), and isocyanates (n=22). With other asthmagens, the prevalence of all outcomes was higher in the exposed compared to non-exposed (Supplemental Material, Table S2).

Consistent upward trends in the prevalence of AOW, diagnosed COPD, FEV_1<LLN and $FEV_1/FVC<0.7$ were observed among those exposed to food-related asthmagens and to biocides/fungicides, and in the prevalence of AOW and $FEV_1/FVC<0.7$ among those exposed to wood dust.

Compared to non-exposed those exposed to food-related asthmagens had reduced FEV_1, FVC and $FEF_{25-75\%}$ ($p<0.01$). A similar trend for FEV_1, and $FEF_{25-75\%}$ ($p<0.05$) was observed with exposure to biocides/fungicides (Supplemental Material, Table S3). AOW, COPD, and reduced FEV_1 were also more common with exposure to a greater number of asthmagens in the workplace (Supplemental Material, Table S4).

Table 4 presents the results of adjusted logistic and linear regression models of the relationship between the outcomes and the number of occupational pollutants and exposure ever to specific asthmagens. Exposure to a greater number of asthmagens was associated with a higher likelihood of having AOW, with occupational exposure to more than four asthmagens being associated with three times increased risk of AOW (Table 4). No association was found between total number of asthmagens and spirometric outcomes. Occupational exposure to glues, latex, solder was also associated with increased risk of AOW, but not spirometric indices. Occupational exposure to food-related asthmagens was associated with increased likelihood of AOW, FEV_1<LLN, and reduced FEV_1, FVC and $FEF_{25-75\%}$, whereas exposure to wood dust was associated with increased likelihood of AOW, $FEV_1/FVC<0.7$, and reduced $FEF_{25-75\%}$, and exposure to biocides/fungicides was associated with increased likelihood of AOW and FEV_1<LLN (Table 4). Inclusion of appropriate interaction terms demonstrated no significant interaction between cigarette smoking and the

associations with exposure to food-related asthmagens, wood dust or biocides/fungicides. Due to the small number of cases, COPD could not be analysed in such multi-variate models.

Separate models were run to examine exposures to specific asthmagens in the longest and current/last held jobs. While the prevalence of exposure was markedly lower in these models (Tables S5-S6, Supplemental Material), compared to the models examining lifetime exposure, the results in general were consistent. AOW, FEV_1<LLN, and reduction in $FEF_{25-75\%}$ were related to exposure to biocides/fungicides (n exposed=70, adjusted ORs 95%CI 2.56 [1.41, 4.64], 3.37 [1.25, 9.09], regression coefficient 95%CI -10.96 [-20.16, -1.76], respectively) and reduction in FVC to exposure to food asthmagens (n exposed=25, adjusted regression coefficient 95%CI -7.67 [-14.03, -1.31]) in the longest held job (Supplemental Material, Table S5). Analysis of exposures in the current/last held jobs produced similar but less marked results with or without additional adjustment for age at hire (Supplemental Material, Table S6a and S6b).

Table 4. Adjusted logistic and linear regression analyses of the associations between respiratory outcomes and occupational asthmagen exposure in the WHEASE cohort in 2014; n analysed=237

Asthmagen exposure	Adjusted[a] OR 95%CI			Adjusted[a] regression coefficient 95%CI		
	AOW	FEV_1<LLN	FEV_1/FVC<0.7	FEV_1 % predicted	FVC % predicted	$FEF_{25-75\%}$ % predicted
Model A Total number (0-11) [b]	1.24 (1.11, 1.39)	1.17 (0.97, 1.42)	1.04 (0.93, 1.16)	-0.36 (-1.16, 0.44)	-0.44 (-1.22, 0.35)	-0.98 (-2.64, 0.68)
Model B 0	-	-	-	-	-	-
1-3	0.63 (0.30, 1.35)	1.91 (0.35, 10.36)	1.28 (0.62, 2.64)	-0.96 (-6.09, 4.17)	-0.55 (-5.56, 4.45)	1.06 (-9.67, 11.79)
≥4	3.24 (1.62, 6.46)	4.22 (0.83, 21.50)	1.27 (0.63, 2.56)	-1.32 (-6.31, 3.67)	-1.44 (-6.31, 3.43)	-3.26 (-13.62, 7.11)
Model C Any asthmagen, n 160	1.59 (0.86, 2.92	2.91 (0.62, 13.70)	1.28 (0.68, 2.38)	-1.15 (-5.63, 3.33)	-1.02 (-5.39, 3.35)	-1.26 (-10.60, 8.09)
Models D						
Biocides/fungicides, n 115	1.79 (1.04, 3.11)	3.37 (1.06, 10.78)	1.47 (0.84, 2.58)	-3.18 (-7.28, 0.93)	-2.98 (-6.99, 1.03)	-6.43 (-14.97, 2.11)
Glues/resins, n 92	2.95 (1.62, 5.39)	1.31 (0.44, 3.89)	0.92 (0.50, 1.70)	2.56 (-1.88, 6.99)	1.94 (-2.39, 6.27)	0.45 (-8.79, 9.70)
Latex, n 83	2.93 (1.66, 5.17)	2.42 (0.92, 6.38)	1.31 (0.74, 2.31)	-2.06 (-6.28, 2.15)	-1.28 (-5.41, 2.84)	-5.19 (-13.94, 3.56)
Solder/flux, n 56	2.28 (1.17, 4.42)	1.06 (0.31, 3.62)	1.05 (0.53, 2.06)	3.87 (-1.14, 8.88)	3.08 (-1.82, 7.97)	6.21 (-4.21, 16.63)
Food-related, n 53	2.66 (1.39, 5.09)	2.87 (1.07, 7.66)	1.52 (0.79, 2.91)	-7.20 (-12.03, -2.36)	-6.19 (-10.93, -1.44)	-13.34 (-23.41, -3.27)
Wood dust, n 48	2.08 (1.03, 4.21)	2.66 (0.84, 8.41)	2.46 (1.19, 5.09)	-3.21 (-8.56, 2.14)	0.21 (-5.03, 5.44)	-13.76 (-24.75, -2.77)
Animal dust, n 43	2.02 (1.02, 4.01)	1.64 (0.52, 5.19)	1.29 (0.64, 2.61)	-3.21 (-8.44, 2.03)	-3.46 (-8.56, 1.65)	-8.45 (-19.29, 2.39)

Model A explores the total count of exposures with outcome, model B explores a categorised count of exposures (0, 1-3, ≥4), model C explores the binary 'any asthmagen' exposure, models D explore each exposure on its own with outcome.

299 [a]Adjusted for: sex, smoking ever and highest educational qualification obtained.

300 [b]Continuous data analysis. Presented ORs/regression coefficients and 95%CIs are per each additional asthmagen

Similar associations were demonstrated in adjusted logistic and linear regression models that used cumulative exposure categories instead of exposure ever (Table 5). A significant trend across a range of exposures was seen between exposure to biocides/fungicides and development of AOW, FEV_1<LLN and reduced $FEF_{25-75\%}$, and between food-related asthmagens and AOW, FEV_1<LLN, reduced FEV_1, FVC, and $FEF_{25-75\%}$.

306 Table 5. Adjusted logistic and linear regression analyses of the associations between respiratory outcomes and cumulative exposure to selected
307 asthmagens in WHEASE cohort in 2014; n analysed=237

Exposure to	Categories	N	Adjusted[a] OR 95%CI						Adjusted[a] regression coefficient 95%CI					
			AOW		FEV_1<LLN		FEV_1/FVC<0.7		FEV_1 % predicted		FVC % predicted		$FEF_{25-75\%}$ % predicted	
Biocides/ fungicides	None	122	-		-		-		-		-		-	
	Low	35	1.11 (0.49, 2.50)	p trend 0.006	2.46 (0.56, 10.84)	p trend 0.024	0.98 (0.43, 2.24)	p trend 0.076	-0.003 (-5.87, 5.86)	*p trend 0.054*	-2.92 (-8.67, 2.84)	p trend 0.192	4.17 (-7.98, 16.32)	p trend 0.044
	Med	40	1.68 (0.79, 3.57)		3.33 (0.84, 13.22)		1.70 (0.79, 3.65)		-7.54 (-13.09, -2.00)		-5.74 (-11.18, -0.29)		-12.77 (-24.27, -1.27)	
	High	40	2.82 (1.33, 5.99)		4.51 (1.14, 17.87)		1.80 (0.84, 3.86)		-1.6 (-7.10, 3.88)		-0.40 (-5.79, 4.99)		-9.07 (-20.46, 2.32)	
Food-related asthmagens	None	184	-		-		-		-		-		-	
	Low	17	1.99 (0.70, 5.68)	p trend 0.002	0.66 (0.08, 5.76)	p trend 0.012	1.60 (0.56, 4.56)	p trend 0.365	-0.14 (-7.86, 7.57)	p trend 0.003	-1.63 (-9.24, 5.98)	p trend 0.026	-0.35 (-16.44, 15.73)	p trend 0.010
	Med	21	2.09 (0.82, 5.32)		5.34 (1.53, 18.72)		1.93 (0.74, 5.02)		-10.09 (-16.96, -3.22)		-7.07 (-13.84, -0.30)		-21.39 (-35.72, -7.07)	
	High	15	5.49 (1.61, 18.68)		3.36 (0.74, 15.20)		1.01 (0.32, 3.17)		-10.74 (-18.83, -2.66)		-9.88 (-17.84, -1.91)		-16.04 (-32.89, 0.82)	
Wood dust	None	189	-		-		-		-		-		-	
	Low	17	2.00 (0.70, 5.66)	p trend 0.068	1.05 (0.11, 9.63)	p trend 0.068	2.86 (0.97, 8.44)	p trend 0.050	-4.15 (-11.97, 3.66)	p trend 0.304	0.87 (-6.80, 8.54)	p trend 0.823	-19.28 (-35.33, -3.22)	p trend 0.044
	Med	16	2.21 (0.75, 6.54)		4.61 (0.93, 22.81)		2.46 (0.81, 7.50)		-6.43 (-14.50, 1.64)		-2.55 (-10.47, 5.37)		-15.86 (-32.44, 0.72)	
	High	15	2.04 (0.66, 6.32)		2.88 (0.61, 13.69)		2.05 (0.64, 6.55)		1.63 (-6.86, 10.12)		2.53 (-5.80, 10.87)		-4.60 (-22.04, 12.84)	

308 [a]Adjusted for: sex, smoking ever and highest educational qualification obtained.

3.3.Ventilatory function between 1989-2014 and occupational asthmagen exposure

Among WHEASE 2014 participants, spirometry was performed on 191 subjects at three time points and on 45 subjects at two time points between 1989 and 2014, with a total number of 663 spirometry records available for longitudinal analysis. The results of linear mixed effects modelling to assess changes in FEV_1 between 1989 and 2014 in relation to exposure to selected asthmagens are presented in Table 6. When compared to those not exposed, participants exposed to any asthmagen, biocides/fungicides or food-related asthmagens lost an additional 6-8ml per year in FEV_1.

Table 6. Changes in FEV_1 in WHEASE cohort between 1989 and 2014 in relation to exposure ever to selected asthmagens, linear mixed effects modelling adjusted for sex, age, smoking, educational qualifications, n cases 236*, n records analysed 663

Asthmagen, n exposed	Difference in decline in exposed vs non-exposed, FEV_1 ml/year	
	Estimate (95% CI of difference)	*p*-value
Any asthmagen, n 160	-5.70 (-11.30, -0.10)	0.046
Biocides/fungicides, n 115	-6.32 (-11.60, -1.03)	0.019
Food-related asthmagens, n 53	-8.00 (-14.45, -1.55)	0.015
Wood dust, n 48	-5.66 (-12.32, 0.99)	0.095

*One subject with single spirometry record was excluded

4. DISCUSSION

This study showed that lifetime occupational exposure to food-related asthmagens, biocides/fungicides and wood dust was independently associated with AOW and reduced lung function. A dose-response relationship was found for food-related asthmagens and

biocides/fungicides exposure. Accelerated rate of FEV_1 decline was also seen with exposure to any asthmagen, biocides/fungicides or food-related asthmagens.

Evidence from previous population-based studies suggests that adult-onset asthma/wheezing is associated with certain occupations, broadly defined occupational exposures, and specific asthmagens (Le Moual et al. 2004; Ghosh et al. 2013; Lillienberg et al. 2013; Arif et al. 2003). It is important to note, however, that in contrast to the current study, which used participant-reported adult-onset wheeze (AOW), most published literature reports adult-onset asthma as an outcome. Occupational exposure to cleaning agents, containing biocides/fungicides (Scientific Committee on Emerging and Newly Identified Health Risks 2009) in particular, has been linked to an increased risk of adult asthma (Siracusa et al. 2013; Wang et al. 2010; Ghosh et al. 2013; Lillienberg et al. 2013). The current results are similar to previous studies linking occupational exposure to food and seafood, during harvesting and processing activities, to the development and exacerbation of asthma (Jeebhay and Cartier 2010). Evidence on exposure to wood dust has been, however, inconsistent. While the current results are in agreement with a recent meta-analysis of wood dust exposure and risk of adult-onset asthma (Perez-Rios et al. 2010), they are in contrast to large population-based studies that failed to find a link between adult-onset asthma and wood dust exposure in the workplace (Wang et al. 2010; Ghosh et al. 2013; Lillienberg et al. 2013).

Rapid decline in lung function with ongoing exposure to causative agents has been reported in diagnosed occupational asthma (Anees et al. 2006) and COPD (Harber et al. 2007) and also in studies of working population (Shi et al. 2010), while deceleration in FEV_1 reduction has been observed with removal of exposure in workers with occupational asthma (de Groene et al. 2011; Jeebhay and Cartier 2010). In the general population, however, an adverse effect

on lung function from occupational exposures has been reported less consistently and mostly in relation to major groups of airborne pollutants, e.g. dusts, gases, vapours, fumes (Humerfelt et al. 1993; de Jong et al. 2014), or total asthmagens (Wang et al. 2010). The current study demonstrates for the first time the decline in lung function resulting from occupational exposure to asthmagens in those with no childhood respiratory symptoms. The effect of asthmagen exposure on FEV_1 decline was comparable to that of cigarette smoking with excess FEV_1 decline of 5.2-16.1 ml/year (Xu et al. 1994). The effects were particularly evident and consistent for food-related asthmagens and were replicated in the cumulative exposure model demonstrating clear dose-response patterns. For both the longest and current/last held jobs associations were demonstrated between AOW, FEV_1<LLN, reduced FEV_1 and $FEF_{25-75\%}$ and exposure to biocides/fungicides, while exposure to food associated asthmagens was related to reduced FVC only. The results, however, are likely to be affected by a small sample size.

Whilst FEV_1 was associated with lifetime occupational exposure to food-related asthmagens, the ratio FEV_1/FVC was not significantly associated. This could potentially reflect the fact that the majority of the WHEASE population with airflow obstruction had mild COPD as defined by GOLD (GOLD 2014), of note other groups have reported associations between occupational exposures and severe, but not mild, COPD (Mehta et al. 2012). The analysis of severe COPD was not possible in the current study due to a small number of subjects. An alternative explanation for the disparity between the associations with FEV_1 and FEV_1/FVC is that exposure to food-related asthmagens is that such exposures may induce conditions with a restrictive component, this would be consistent with our finding of an association between exposure to food-related asthmagens and FVC. The only population-based study to our knowledge that also examined occupational exposure to wood dust in relation to lung

function failed to find the association with spirometric airflow obstruction (Bakke et al. 1991) found in the current study.

No association was found between AOW or lung function and enzyme products, flour/grain dusts or isocyanates, recognised causes of occupational asthma (Ghosh et al. 2013; Lillienberg et al. 2013). This is probably due to the small numbers exposed to these asthmagens in the WHEASE cohort (the lowest prevalence, <12%). A much larger study with 13284 participants (Lillienberg et al. 2013) also suffered from insufficient statistical power and had to merge subjects with similar exposures to find association with "plant antigens", including flour. Similar to others, the current study found no interaction of occupational exposure with smoking (de Jong et al. 2014).

The current study found no association between exposure to any occupational asthmagen and AOW or impaired lung function, although the trend was positive. This may reflect the fact that the study was underpowered to detect small differences. On the other hand others have also shown a higher magnitude and strength of the association with occupational exposure to specific rather than any asthmagen (Le Moual et al. 2004).

In the current study AOW and reduced FEV_1 were associated with exposure to a greater number of asthmagens individuals had worked with over their lifetime. A significant dose-effect relationship between the number of occupational agents (dusts, gases, vapours and fumes) to which subjects were exposed and decline in FEV_1 has been reported by others (Humerfelt et al. 1993). On the other hand, a higher number of workplace asthmagens, may be an indicator of higher concentrations of exposure, as workplaces using more chemicals may have poorer control measures and workers who moved jobs more frequently may have

had poorer training/knowledge of workplace risks and thus suffered higher exposures. It is, therefore, possibly the effect of exposure to higher concentrations, which may explain the increased risk of AOW and reduced lung function from having worked with a greater number of asthmagens. A synergistic effect of multiple exposures to different asthmagens in given jobs in the WHEASE cohort, however, cannot be disregarded.

Without specific allergy and inhalation tests, we can only speculate about potential pathogenic mechanisms for the current associations. Most disinfectants have an irritating effect on airways, although some may induce IgE and non-IgE immunological reactions (Siracusa et al. 2013). Food-related asthmagens exposure implies inhalation of high molecular weight (HMW) compounds which may act as complete antigens through an IgE-mediated mechanism (Maestrelli et al. 2009). Not all HMW proteins in food, however, are known allergens and reactions induced by them suggest both immune- and non-immune mechanisms (Jeebhay and Cartier 2010). In contrast, wood dusts are generally classified as low molecular weight group (LMW) compounds, which are incomplete antigens with unclear pathophysiological mechanisms, although the presence of specific IgE antibodies has been reported with exposure to some wood species (Maestrelli et al. 2009).

Significant associations were found between certain specific asthmagens, and reported AOW but not with reduced lung function. To minimise the possibility of false conclusions about causal associations with multiple testing carried out in the current study, only consistent associations were considered.

Approximately 8% of the cohort had FEV_1<LLN and 39% had $FEV_1/FVC<0.7$. This may reflect a bias towards people with airflow obstruction or at risk of airflow obstruction e.g. smokers participating in the study. The fixed 0.7 criterion has, however, the potential to misdiagnose cases of airway obstruction because FEV_1/FVC can vary with age, height and gender. FEV_1<LLN, although less widely used, has been shown to be more specific and it is now recommended that COPD should be defined by both FEV_1/FVC and FEV_1 being below the LLN using appropriate reference equations (Swanney et al. 2016).

Strengths of the current study include the prospective design, length of the follow-up (50-years) and objective pulmonary function testing on several occasions, used in addition to self–reported AOW. A further strength was the ability to study the impact of occupational exposure on adult airway disease in subjects without childhood wheezing illness. However, it is possible that some parents might not have recalled or forgotten to report relatively mild/transient wheeze in their children.

In contrast to others (Ghosh et al. 2013) we found no difference in the prevalence of exposure to asthmagens in the workplace between those who had and had not had wheezed as children, suggesting that there was no 'hire effect' or initial avoidance (Dumas et al. 2013) of certain occupations/exposures that could influence the results. The finding, consistent with other studies (Ghosh et al. 2013), that those with AOW had a higher unemployment rate compared to never-wheezers, could reflect continuing selection recruitment bias.

Examining the relation between exposures and outcomes in a population-based study reduced bias associated with the healthy worker effect seen in studies of working populations (Dumas et al. 2013). On the other hand, characterisation of occupational exposure in any population-

based study is imprecise. In the current study it was enhanced by the assessment of occupational exposure based on detailed lifetime occupational history and the asthma-specific JEM, limiting recall bias (de Vocht et al. 2005). Using JEM to the main classes of known occupational asthmagens was based on previous experience in population-based occupational/health studies (Tagiyeva et al. 2010). Validity of JEM is, however, a matter of debate (Le Moual et al. 2000). As an inherent limitation, the use of the JEM could lead to exposure misclassification, because JEMs do not reflect heterogeneity in the exposure within and between jobs/occupations (Peters et al. 2011). In contrast to expert assessment based on self-reported occupational exposures, it is likely to be non-differential misclassification that attenuates any association towards the null (Peters et al. 2011). Linkage of self-reported job titles to a JEM may also lead to potential misclassification, which cannot be disregarded even though extra information such as job tasks and industry, was also collected and used in assigning occupational exposures. Using asthma-specific JEM to known occupational asthmagens may miss some unknown asthmagen groups. Also, while the outcomes were analysed in relation to exposure to specific asthmagens, not occupations, exposure to other pollutants present in the workplace, such as additives in the food industry, may not have been accounted for. We also could not take into account the timing of exposure and the onset of AOW, we cannot therefore exclude the possibility of workers from a local industry associated with occupational asthma systematically moving to a large local employer with no occupational asthma risk. A further limitation is that the JEM utilised will not account for changes in the workplace environment/exposures since 1964. Although responder bias was reduced by using occupational history and not self-reported exposure to specific agents it might have been difficult for some to recall short-time jobs up to 50 years earlier. Multiple exposures to different asthmagens in the WHEASE cohort presented another limitation to the evaluation of the association between outcomes and a specific asthmagen.

The main limitation of this study was the small sample size and limited number of subjects exposed to specific asthmagens. This led to wide confidence intervals that may have precluded the detection of significant associations between certain exposures and outcomes. Also, due to a small number of subjects, sensitivity or stratified analyses could not been carried out to examine the effect by sex or smoking status. A further limitation was that the cohort was not designed to prospectively investigate the association between occupational exposures and respiratory health, in addition the various phases of follow up of the cohort have focussed on research issues topical at the time with the consequence that the follow up was not systematic, which affected the representativeness of the sample. Another important limitation was that the adjustment for smoking was carried out without quantification in terms of the number of cigarettes and years smoked, which could lead to residual confounding and potentially introduce a bias in the observed effects of occupational exposures.

There are a number of factors and exposures with a well-recognised adverse effect on asthma and ventilatory function impairment, such as air pollution (Forbes et al. 2009), maternal smoking (Prabhu et al. 2010) and diet in pregnancy (Allan et al 2015), birthweight (Turner et al. 2010) and other early life factors (Sly and Bush 2016), which could not been accounted for in the current study, however it seems unlikely that such factors would result in a systematic exposure to a particular occupational asthmagen.

Ventilatory function was measured according to the standards existing at each follow up and the same spirometer was used in 2001 and 2014 studies. Nevertheless, different equipment was used in earlier studies and different technicians/researchers carried out the measurements at each follow-up, which all could introduce biases when assessing longitudinal lung function

changes. Notably however the biases associated with less than optimal spirometry favour underestimation of airflow obstruction. These biases were minimised by using the same procedures and calibrations (3 litre syringe every 4 hours) in each of the WHEASE studies.

Aberdeen has been traditionally reliant on employment by fishing and agricultural industries, reflected by the fact that a 33% of those exposed to food-related asthmagens in this study were at some point employed in the fishing industry as fish packers, filleters, fishermen or fish and chip shop workers while 25% were employed in the meat processing industry as butchers or meat factory workers. In other UK (Ghosh et al. 2013) and international studies (Wang et al. 2010) low numbers of those exposed to fish/shellfish precluded analysis of the association. In contrast, in the West Midlands isocyanates were the main cause responsible for 21% of occupational asthma (Bakerly et al. 2008), but the least common exposure in this study (11.6% exposed among AOW). Therefore the findings of this study in relation to occupational exposures may not be widely generalisable but will be representative of occupants of similar areas in terms of the job market profile.

5. CONCLUSIONS

In conclusion, our study lends support to the association between occupational exposures to known asthmagens and adult-onset wheeze. In addition we identified exposure to food-related asthmagens, biocides/fungicides and wood dust, as risk factors for impaired lung function and accelerated lung function decline in those without preceding childhood wheezing illness. The demonstration of amenable to intervention, occupational risk factors for lung function impairment and accelerated decline pose the important implications for occupational interventions and policies. Due to low number of subjects in some exposure and

outcome categories results, however, should be interpreted with caution and need to be replicated in a larger prospective study of a general population. Future studies should also focus on identifying and characterising specific food allergens which are responsible for the associations found in the current study.

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