

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

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12 **Abstract**

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

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

17 **Methods:** A population-based randomly selected cohort of children who had not had asthma
18 or wheezing illness, recruited in 1964 at age 10-15 years, was followed-up in 1989, 1995,
19 2001 and 2014 by spirometry and respiratory questionnaire. Occupational histories were
20 obtained in 2014 and occupational exposures determined with an asthma-specific job
21 exposure matrix. The risk of AOW and lung function impairment was analysed in subjects
22 without childhood wheeze using logistic regression and linear mixed effects models.

23 **Results:** All 237 subjects (mean age 61 years, 47% male, 52% ever smoked) who took part in
24 the 2014 follow-up had completed spirometry. Among those who did not have childhood
25 wheeze, spirometry was measured in 93 subjects in 1989, in 312 in 1995 and in 270 subjects
26 in 2001 follow-up. For longitudinal analysis of changes in FEV₁ between 1989 and 2014
27 spirometry records were available on 191 subjects at three time points and on 45 subjects at
28 two time points, with a total number of 663 records. AOW and FEV₁<LLN were associated
29 with occupational exposure to food-related asthmagens (adjusted odds ratios (adjORs)
30 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]
31 and 3.4 [1.1, 10.8]), with evident dose-response effect (p-trends<0.05). Exposure to food-
32 related asthmagens was also associated with reduced FEV₁, FVC and FEF_{25-75%} (adjusted
33 regression coefficients 95%CI:-7.2 [-12.0,-2.4], -6.2 [-10.9,-1.4], and -13.3 [-23.4,-3.3]).
34 Exposure to wood dust was independently associated with AOW, obstructive lung function
35 and reduced FEF_{25-75%}. Excess FEV₁ decline of 6-8ml/year was observed with occupational
36 exposure to any asthmagen, biocides/fungicides and food-related asthmagens (p<0.05).

37 **Conclusions:** This longitudinal study confirmed previous findings of increased risks of adult
38 onset wheezing illness with occupational exposure to specific asthmagens. A novel finding
39 was the identification of food-related asthmagens and biocides/fungicides as potential new
40 occupational risk factors for lung function impairment in adults without childhood wheeze.
41 **Key words:** adult onset wheeze, ventilatory function, occupational exposure, asthmagens,
42 cohort, job exposure matrix

43 **1. INTRODUCTION**

44 Current evidence suggests that 17% of adult-onset asthma (ERS 2013) and up to 20% (50%
45 among never smokers) of chronic obstructive pulmonary disease (COPD) (Sigsgaard et al.
46 2010) can be attributed to work-related exposure. Although the prevalence of asthma in some
47 westernised countries appears to be falling (Asher and Pearce 2014), the individual and
48 societal burden of asthma remains high. Moreover the worldwide prevalence of asthma and
49 COPD is rising (Anandan et al. 2010; GOLD 2014), and therefore the search for preventable
50 environmental risk factors remains important.

51

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

66

67 The Aberdeen population-based WHEASE (What Happens Eventually to Asthmatic children:
68 Sociologically and Epidemiologically) cohort study of children recruited in 1964 (Dawson et
69 al. 1969) at age 10-15 years and followed up until 2014 (age 58-64 years) (Tagiyeva et al.
70 2015) provides a rare opportunity to investigate the effects of lifetime occupational exposures
71 on respiratory morbidity in later life.

72
73 The aim of the current study was to investigate, in a community-based setting, whether
74 occupational exposures to known asthmagens, assessed by job exposure matrix (JEM), were
75 related to the development of adult onset wheeze (AOW), spirometry-defined airflow
76 obstruction, or impaired ventilatory function at age 58-64 years and to longitudinal changes in
77 ventilatory function over 25-year follow up among those who did not have wheezing illness
78 as children.

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80

81 **2. MATERIALS AND METHODS**

82 **2.1. Subjects**

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

92 individuals who took part in at least one previous follow up were traced and invited to take
 93 part. The current study reviews the outcome in 330 children who were traceable in 2014, of
 94 whom 239 did not have respiratory symptoms recorded in 1964. The analysis presented is for
 95 237 participants due to the availability of occupational exposure.

96
 97 Members of the cohort were reassessed in 1989 (aged 35-40, n=360), 1995 (aged 41-46,
 98 n=1542), 2001 (aged 47-52, n=381), and 2014 (aged 58-64, n=330) (Tagiyeva et al. 2015)
 99 (Table 1) to address differing topical clinical questions using subsets of the original sample.
 100 The 1989, 1995 and 2001 follow-up phases included 93, 312 and 270 subjects with measured
 101 ventilatory function respectively, who had never wheezed as children (Godden et al. 1994;
 102 Bodner et al. 1998; Edwards et al. 2003).

103
 104

105 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
	
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	<p>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%</p> <p>Participants in postal survey: 102 AOW, 1440 never-wheezers</p> <p>Clinical assessment (including spirometry) carried out in 312: 102 AOW and 217 randomly selected never-wheezers</p>
2001	<p>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%</p> <p>Participants included: 46 child asthma, 65 child wheezy bronchitis, 270 child non-wheezers</p> <p>Spirometry measured in 372, including 270 child non-wheezers</p>
2014	<p>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%</p> <p>Participants included: 38 child asthma, 53 child wheezy bronchitis, 239 child non-wheezers</p> <p>Spirometry measured in 329, including 239 child non-wheezers</p> <p>Occupational histories collected from 328, including 237 child non-wheezers</p>

107 **2.2. Assessments and outcomes**

108 Each follow up was carried out in the Chest Clinic, Aberdeen Royal Infirmary, and included
109 the updated version of the MRC respiratory questionnaire (Medical Research Council 1986)
110 administered during in-person interview (Supplemental Material, MRC questionnaire), and
111 spirometry performed according to internationally accepted guidelines. The 2014 spirometry
112 followed ATS/ERS guidelines (Pellegrino et al. 2005) with pre- and post-administration of
113 400µg salbutamol using a Vitalograph Compact II spirometer (Vitalograph, Buckingham,
114 UK). Forced expiratory volume in one second (FEV₁), forced vital capacity (FVC) and forced
115 expiratory flow over the middle half of FVC (FEF₂₅₋₇₅) were recorded. Socio-demographic
116 characteristics and history of cigarette smoking were also ascertained at interview.

117

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

121

122 **2.3. Occupational data management**

123 Free-text descriptions of occupations and industries for all lifetime jobs were coded into four-
124 digit Standard Occupational Classification (SOC2000) codes developed by the UK Office for
125 National Statistics (Office for National Statistics 2008) using the Computer Assisted
126 Structured Coding Tool (CASCOT) (Jones and Elias 2014). This generated certainty scores
127 (1-100%) indicating the degree of certainty that the given code is correct. CASCOT derived
128 occupational codes scores of >50% were accepted, and those scored ≤50% coded manually.
129 This coding strategy has been shown to have 91% agreement with manually coded
130 occupations (Tagiyeva et al. 2010).

131

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

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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 FEV₁ was defined as post-bronchodilator FEV₁ < 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 FEV₁/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, FEV₁ < LLN, FEV₁/FVC < 0.7) were carried out using Chi-squared tests. For continuous outcomes (FEV₁, 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

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

188

189 Linear mixed effect models with unstructured covariance were used to analyse changes in
190 FEV₁ between 1989 and 2014 in the exposed and non-exposed. Subjects with at least two
191 spirometry test results were included in this analysis. Random effects were participant and
192 participant*time with fixed effects of time and the confounding variables. Time was entered
193 as a continuous variable into the model taking the values of 0, 6, 12, and 25 years to represent
194 assessments made in 1989, 1995, 2001, and 2014. Inclusion of an interaction term for time
195 and exposure to individual substances allowed the production of estimates of change in FEV₁
196 between exposed and non-exposed. Analyses were performed using SPSS v22.0 (Armonk,
197 NY, USA) and SAS v9.3 (SAS Institute Inc., Cary, USA).

198

199 All analyses were adjusted for sex, history of having ever smoked more than 100 cigarettes,
200 and the highest educational qualification obtained, used as an indicator of childhood and early
201 adulthood socio-economic status. Linear mixed effect models were also adjusted for age (in
202 1989). Interactions between exposure and smoking were analysed using separate logistic
203 regression models for each asthmagen. Pack year data for smoking were not available, neither
204 were the data to assess the temporal relationship between exposure and the onset of AOW.

205

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

208

209

210 3. RESULTS

211 Of the 239 WHEASE participants assessed in 2014 with no history of childhood wheezing
 212 illness, occupational history was available for 237; of these 15% reported a diagnosis of
 213 asthma and 6% a diagnosis of COPD. Approximately 8% of the cohort had $FEV_1 < LLN$ and
 214 39% had $FEV_1/FVC < 0.7$. Characteristics of subjects who reported AOW and those who had
 215 never reported wheeze are detailed in Table 2. Those who had developed wheeze as adults
 216 were more likely to be overweight, have a history of smoking, be diagnosed with asthma and
 217 COPD, and have reduced ventilatory function.

218

219

220 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)	
<i>Clinical, questionnaire-based, n (%)</i>				
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
<i>Spirometry, postbronchodilator</i>				
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

221 ^aAdult onset wheeze. ^bChi-squared test for categorical and t-test for continuous data analysis.

222 ^cEnvironmental tobacco smoke.

223

224

225 **3.1.Exposure to occupational asthmagens**

226 All study participants had between one and six different jobs in their lifetime (median 2, IQR
227 2-3). Most commonly reported occupations were storage and goods handling occupations,
228 van drivers and maintenance managers among men and cleaning, general office workers, and
229 sales assistants among women. Occupations in the WHEASE cohort categorised by exposure
230 to at least one asthmagen and to 11 major occupational asthmagen groups by the intensity of
231 exposure are presented in Table S1, Supplemental Material. While most occupations were not
232 associated with any asthmagen exposures, others were characterised by multiple exposures
233 patterns.

234

235 The lifetime occupational exposure to each specific asthmagen is presented in Table 3 and
236 Figure 1. Two thirds of the participants were exposed to at least one asthmagen over their
237 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).
242



243
244 Figure 1. Lifetime prevalence of exposure to the total number of occupational asthmagens in
245 the WHEASE cohort, n analysed=237

246 Table 3. Lifetime occupational exposures to asthmagens by duration of exposure and
 247 cumulative exposure index calculated within those exposed in the WHEASE cohort, n
 248 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)

249 ^aCumulative exposure measurement that combines logarithmic intensity of occupational
 250 exposure as estimated by JEM and duration of exposure. ^bInterquartile range

251

252 3.2.Outcomes in 2014 and occupational exposure to asthmagens

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

257 Consistent upward trends in the prevalence of AOW, diagnosed COPD, $FEV_1 < LLN$ and
258 $FEV_1/FVC < 0.7$ were observed among those exposed to food-related asthmagens and to
259 biocides/fungicides, and in the prevalence of AOW and $FEV_1/FVC < 0.7$ among those exposed
260 to wood dust.

261
262 Compared to non-exposed those exposed to food-related asthmagens had reduced FEV_1 , FVC
263 and $FEF_{25-75\%}$ ($p < 0.01$). A similar trend for FEV_1 , and $FEF_{25-75\%}$ ($p < 0.05$) was observed with
264 exposure to biocides/fungicides (Supplemental Material, Table S3). AOW, COPD, and
265 reduced FEV_1 were also more common with exposure to a greater number of asthmagens in
266 the workplace (Supplemental Material, Table S4).

267
268 Table 4 presents the results of adjusted logistic and linear regression models of the
269 relationship between the outcomes and the number of occupational pollutants and exposure
270 ever to specific asthmagens. Exposure to a greater number of asthmagens was associated with
271 a higher likelihood of having AOW, with occupational exposure to more than four
272 asthmagens being associated with three times increased risk of AOW (Table 4). No
273 association was found between total number of asthmagens and spirometric outcomes.
274 Occupational exposure to glues, latex, solder was also associated with increased risk of
275 AOW, but not spirometric indices. Occupational exposure to food-related asthmagens was
276 associated with increased likelihood of AOW, $FEV_1 < LLN$, and reduced FEV_1 , FVC and
277 $FEF_{25-75\%}$, whereas exposure to wood dust was associated with increased likelihood of AOW,
278 $FEV_1/FVC < 0.7$, and reduced $FEF_{25-75\%}$, and exposure to biocides/fungicides was associated
279 with increased likelihood of AOW and $FEV_1 < LLN$ (Table 4). Inclusion of appropriate
280 interaction terms demonstrated no significant interaction between cigarette smoking and the

281 associations with exposure to food-related asthmagens, wood dust or biocides/fungicides.
282 Due to the small number of cases, COPD could not be analysed in such multi-variate models.
283
284 Separate models were run to examine exposures to specific asthmagens in the longest and
285 current/last held jobs. While the prevalence of exposure was markedly lower in these models
286 (Tables S5-S6, Supplemental Material), compared to the models examining lifetime
287 exposure, the results in general were consistent. AOW, FEV₁<LLN, and reduction in FEF_{25-75%}
288 were related to exposure to biocides/fungicides (n exposed=70, adjusted ORs 95%CI 2.56
289 [1.41, 4.64], 3.37 [1.25, 9.09], regression coefficient 95%CI -10.96 [-20.16, -1.76],
290 respectively) and reduction in FVC to exposure to food asthmagens (n exposed=25, adjusted
291 regression coefficient 95%CI -7.67 [-14.03, -1.31]) in the longest held job (Supplemental
292 Material, Table S5). Analysis of exposures in the current/last held jobs produced similar but
293 less marked results with or without additional adjustment for age at hire (Supplemental
294 Material, Table S6a and S6b).

295 Table 4. Adjusted logistic and linear regression analyses of the associations between respiratory outcomes and occupational asthmagen exposure
 296 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
<i>Model A</i> 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)
<i>Model B</i> 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)
<i>Model C</i> 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)
<i>Models D</i>						
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)

297 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
 298 the binary ‘any asthmagen’ exposure, models D explore each exposure on its own with outcome.

299 ^aAdjusted for: sex, smoking ever and highest educational qualification obtained.

300 ^bContinuous data analysis. Presented ORs/regression coefficients and 95% CIs are per each additional asthmagen

301 Similar associations were demonstrated in adjusted logistic and linear regression models that
302 used cumulative exposure categories instead of exposure ever (Table 5). A significant trend
303 across a range of exposures was seen between exposure to biocides/fungicides and
304 development of AOW, FEV₁<LLN and reduced FEF_{25-75%}, and between food-related
305 asthmagens and AOW, FEV₁<LLN, reduced FEV₁, 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)	
None	184	-	-		-		-		-		-		-	
Food- related asthmagens	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)	
	None	189	-		-		-		-		-		-	
Wood dust	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)	
	None	189	-		-		-		-		-		-	

308 ^aAdjusted 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 FEV₁ between 1989 and 2014 in relation to exposure to selected astmagens are presented in Table 6. When compared to those not exposed, participants exposed to any asthmagen, biocides/fungicides or food-related astmagens lost an additional 6-8ml per year in FEV₁.

Table 6. Changes in FEV₁ in WHEASE cohort between 1989 and 2014 in relation to exposure ever to selected astmagens, 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)	<i>p</i> -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 astmagens, 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 astmagens, biocides/fungicides and wood dust was independently associated with AOW and reduced lung function. A dose-response relationship was found for food-related astmagens and

327 biocides/fungicides exposure. Accelerated rate of FEV₁ decline was also seen with exposure
328 to any asthmagen, biocides/fungicides or food-related astmagens.

329

330 Evidence from previous population-based studies suggests that adult-onset asthma/wheezing
331 is associated with certain occupations, broadly defined occupational exposures, and specific
332 astmagens (Le Moual et al. 2004; Ghosh et al. 2013; Lillienberg et al. 2013; Arif et al.
333 2003). It is important to note, however, that in contrast to the current study, which used
334 participant-reported adult-onset wheeze (AOW), most published literature reports adult-onset
335 asthma as an outcome. Occupational exposure to cleaning agents, containing
336 biocides/fungicides (Scientific Committee on Emerging and Newly Identified Health Risks
337 2009) in particular, has been linked to an increased risk of adult asthma (Siracusa et al. 2013;
338 Wang et al. 2010; Ghosh et al. 2013; Lillienberg et al. 2013). The current results are similar
339 to previous studies linking occupational exposure to food and seafood, during harvesting and
340 processing activities, to the development and exacerbation of asthma (Jeebhay and Cartier
341 2010). Evidence on exposure to wood dust has been, however, inconsistent. While the current
342 results are in agreement with a recent meta-analysis of wood dust exposure and risk of adult-
343 onset asthma (Perez-Rios et al. 2010), they are in contrast to large population-based studies
344 that failed to find a link between adult-onset asthma and wood dust exposure in the workplace
345 (Wang et al. 2010; Ghosh et al. 2013; Lillienberg et al. 2013).

346

347 Rapid decline in lung function with ongoing exposure to causative agents has been reported
348 in diagnosed occupational asthma (Anees et al. 2006) and COPD (Harber et al. 2007) and
349 also in studies of working population (Shi et al. 2010), while deceleration in FEV₁ reduction
350 has been observed with removal of exposure in workers with occupational asthma (de Groene
351 et al. 2011; Jeebhay and Cartier 2010). In the general population, however, an adverse effect

352 on lung function from occupational exposures has been reported less consistently and mostly
353 in relation to major groups of airborne pollutants, e.g. dusts, gases, vapours, fumes
354 (Humerfelt et al. 1993; de Jong et al. 2014), or total asthmagens (Wang et al. 2010). The
355 current study demonstrates for the first time the decline in lung function resulting from
356 occupational exposure to asthmagens in those with no childhood respiratory symptoms. The
357 effect of asthmagen exposure on FEV₁ decline was comparable to that of cigarette smoking
358 with excess FEV₁ decline of 5.2-16.1 ml/year (Xu et al. 1994). The effects were particularly
359 evident and consistent for food-related asthmagens and were replicated in the cumulative
360 exposure model demonstrating clear dose-response patterns. For both the longest and
361 current/last held jobs associations were demonstrated between AOW, FEV₁<LLN, reduced
362 FEV₁ and FEF_{25-75%} and exposure to biocides/fungicides, while exposure to food associated
363 asthmagens was related to reduced FVC only. The results, however, are likely to be affected
364 by a small sample size.

365

366 Whilst FEV₁ was associated with lifetime occupational exposure to food-related asthmagens,
367 the ratio FEV₁/FVC was not significantly associated. This could potentially reflect the fact
368 that the majority of the WHEASE population with airflow obstruction had mild COPD as
369 defined by GOLD (GOLD 2014), of note other groups have reported associations between
370 occupational exposures and severe, but not mild, COPD (Mehta et al. 2012). The analysis of
371 severe COPD was not possible in the current study due to a small number of subjects. An
372 alternative explanation for the disparity between the associations with FEV₁ and FEV₁/FVC is
373 that exposure to food-related asthmagens is that such exposures may induce conditions with a
374 restrictive component, this would be consistent with our finding of an association between
375 exposure to food-related asthmagens and FVC. The only population-based study to our
376 knowledge that also examined occupational exposure to wood dust in relation to lung

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

379

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

388

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

394

395 In the current study AOW and reduced FEV₁ were associated with exposure to a greater
396 number of asthmagens individuals had worked with over their lifetime. A significant dose-
397 effect relationship between the number of occupational agents (dusts, gases, vapours and
398 fumes) to which subjects were exposed and decline in FEV₁ has been reported by others
399 (Humerfelt et al. 1993). On the other hand, a higher number of workplace asthmagens, may
400 be an indicator of higher concentrations of exposure, as workplaces using more chemicals
401 may have poorer control measures and workers who moved jobs more frequently may have

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

407

408

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

420

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

425

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

433

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

440

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

447

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

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

476

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

489

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

496

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

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

504

505

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

517

518 **5. CONCLUSIONS**

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

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

530

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537

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