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CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease

M C Matheson, G Benke, J Raven, M R Sim, H Kromhout, R Vermeulen, D P Johns, E H Walters, M J Abramson

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Background: Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. Although the main risk factor is smoking, 15–19% of COPD even in smokers has been attributed to occupational exposures. The aim of this study was to investigate the association between occupational exposure and risk of COPD.
Methods: Participants were part of a cross sectional study of risk factors for COPD. A total of 1232 completed a detailed respiratory questionnaire, spirometric testsing and measurement of gas transfer. Job histories were coded according to the International Standard Classification of Occupations. These codes were then used to establish occupational exposures using the ALOHA job exposure matrix.
Results: The prevalence of emphysema was 2.4%, chronic obstructive bronchitis 1.8%, and COPD 3.4%. Subjects ever exposed to biological dusts had an increased risk of chronic obstructive bronchitis (OR 3.19; 95% CI 1.27 to 7.97), emphysema (OR 3.18; 95% CI 1.41 to 7.13), and COPD (OR 2.70, 95% CI 1.39 to 5.23). These risks were higher in women than in men. For biological dust, the risk of emphysema and COPD was also significantly increased in both the duration of exposure categories, again in women but not in men. No significant increased risks for COPD were found for mineral dust (OR 1.13; 95% CI 0.57 to 2.27) or gases/fumes (OR 1.63; 95% CI 0.83 to 3.22).
Conclusion: In this general population sample of adults, occupational exposures to biological dusts were associated with an increased risk of COPD which was higher in women. Preventive strategies should be aimed at reducing exposure to these agents in the workplace.

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in many countries, including Australia. Chronic irritation of the airways by inhaled substances such as cigarette smoke is the major known risk factor for COPD. However, it has recently been estimated that 15–19% of COPD in smokers and as much as 31% in never smokers may be attributed to occupational exposures.[1 2] Recently it was reported among persons with COPD that any past occupational exposure is associated with poorer health status and increased healthcare utilisation.[3] Studies in both the general community and workplace settings have found exposures to dusts, gases, and fumes to be associated with symptoms of COPD and reductions in lung function. Many of the past community based studies of occupational exposure and COPD have used self-reported exposures[4–8] which can be subject to recall bias. Job exposure matrices (JEMs) are less affected by this recall bias because they rely on job titles for estimating occupational exposures.[9]

The importance of dust exposure—specifically, mineral dust in underground miners—for the development of respiratory symptoms, airflow obstruction, and COPD has been well established.[10 11] Most community based studies have tended to group dust exposures together rather than distinguishing between mineral and biological dust exposure. Over recent decades it has increasingly been recognised that occupations with biological or organic dust exposure have an increased prevalence of respiratory symptoms and chronic bronchitis.[12–16] While it is clear that respiratory symptoms and chronic bronchitis are associated with biological dust exposure, the relationship with emphysema and COPD is less certain. A community based study assessing occupational exposures using an ad hoc JEM that separated biological and mineral dust exposures found high levels of biological dust exposure to be associated with cough and reduced lung function.[17] However, this study was in a population of younger adults and was unable to examine an association between biological dust exposure and risk of emphysema or COPD.

We investigated the association between occupational exposures and risk of developing COPD among a general population sample aged 45–70 years in Melbourne, Australia. Specifically, we wished to examine separately the effects of biological and mineral dust in a community based sample of older adults who were more likely to have developed COPD. We assessed lifetime occupational exposures to examine the effect of duration of exposure on risk of COPD.

METHODS

Participants

A two stage cross sectional epidemiological study was conducted to investigate risk factors for COPD in middle aged and older adults. The subjects were 7005 adults aged between 45 and 70 years. The sample was randomly selected from the electoral rolls for three inner south eastern Melbourne electorates. The methods and results of the postal survey have been previously reported.[18] Screening questionnaires were completed by 4923 subjects, a 70% response rate. Of these, 2900 respondents were invited by letter at random to attend the lung function laboratory for further evaluation. Individuals who did not respond to the letter were then

Abbreviations: BHR, bronchial hyperreactivity; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; JEM, job exposure matrix; TLCO, lung carbon monoxide transfer

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contacted by telephone, with 1232 subjects attending (42% response rate). The study was approved by the ethics committee of the Alfred Hospital. All participants gave written informed consent.

Laboratory visit

Participants were invited to the lung function laboratory at the Alfred Hospital where they completed a detailed respiratory questionnaire. The interviewer administered questionnaire comprised validated items on bronchial symptoms from the IUATLD questionnaire,[19] British Medical Research Council items on cough, sputum and shortness of breath,[20] demographic data, past and family history, and environmental risk factors from the main ECRHS questionnaire (http://www.ecrhs.org/Quests/mainquest.pdf).

Lung function testing

Forced expiratory volume in 1 second (FEV_1) was measured with a rolling seal spirometer (Sensormedics, California, USA) and recorded as the best of five blows that met the American Thoracic Society (ATS) criteria. Carbon monoxide lung transfer factor (TLCO) was measured by the single breath carbon monoxide method using the MedGraphics Profiler system (St Paul, MN, USA) according to ATS guidelines.[21] Predicted values for FEV_1 and forced vital capacity (FVC) were calculated from age, height and sex using equations by Knudson *et al*,[22] and for TLCO using the equations by Quanjer *et al*.[23] Methacholine (USP Methapharm Inc, Brantford, Ontario, Canada) was delivered by a Mefar 3B dosimeter (Mefar, Bovezzi, Italy) until FEV_1 fell by 20% from the initial value or up to a cumulative dose of 2 mg. Spirometric tests, methacholine challenge, and TLCO measurements were satisfactorily completed by 1224, 1115, and 1221 subjects, respectively.

Definitions

- *Morning cough* was defined as a positive response to: ''Do you usually cough first thing in the morning in the winter?''
- *Chronic cough* was defined as a positive response to: ''Do you cough like this on most days for as much as 3 months each year?''
- *Morning phlegm* was defined as a positive response to: ''Do you usually bring up phlegm from your chest first thing in the morning in the winter?''
- *Chronic bronchitis* was defined as a positive response to: ''Have you brought up phlegm on most days for as much as 3 months of a year for at least 2 successive years?''
- *Dyspnoea* was defined as a positive response to: ''Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?''
- *Mild airflow obstruction* was defined as FEV_1/FVC ratio <70%.
- *Moderate airflow obstruction* was defined as FEV_1/FVC ratio <70% together with FEV_1 <80% predicted.[24]
- *Chronic obstructive bronchitis* was defined as mild airflow obstruction with chronic sputum production.
- *Asymptomatic emphysema* was defined as mild airflow obstruction and TLCO <80% predicted.
- *Symptomatic emphysema* also included dyspnoea.
- *COPD* was defined as either chronic obstructive bronchitis or symptomatic emphysema.

Occupational exposure

Occupational exposure was classified using lifetime work history calendars that were collected from participants during the laboratory visit. A total of 1213 subjects provided completed calendars. Participants were asked to list all the jobs they had held in their lifetimes in the work history calendars. The calendars collected information on job title, industry, company name, year started, and year ended. The reported jobs in the calendars were coded according to the International Standard Classification of Occupations (ISCO-88) code's four-digit classification.[25] This classification included 390 occupational titles. These codes were then used to establish occupational exposures to biological dusts, mineral dusts, gases, vapours and fumes using a modified version of the ad hoc JEM for COPD called the ALOHA JEM.[17] The ALOHA JEM classified subjects based on job code into high, low, or no exposure categories (2, 1 or 0) for biological dust, mineral dust, and gases/fumes. For this study the groups of low and high exposed individuals were combined because the small number of subjects in the highly exposed category limited the statistical analysis. The number of years worked with a given exposure and exposure intensity (that is, high biological dust exposure) was calculated for each job and then summed for each individual. This was termed cumulative exposure (years) and was calculated for each exposure type. To allow for the combination of high and low exposure groups, years of exposure were weighted by 4 for high exposure and by 1 for low exposure.[26] The median value of the weighted cumulative exposure years was used as a cut off point between the two exposure categories, excluding individuals without exposure.

Statistical analysis

All analyses were conducted using the Stata Version 6.0 statistical package (Stata Corporation, Texas, USA). Comparisons of exposures between sexes, age, and smoking categories were performed using χ^2 tests. The associations of respiratory symptoms, chronic bronchitis, and COPD with occupational exposures were expressed by odds ratios (OR) and 95% confidence intervals (95% CI) estimated by multiple logistic regression. Occupational exposure to each agent was considered individually, comparing those exposed to all others. All analyses were adjusted for age (as a continuous variable), sex, smoking status (never smoker, ex-smoker or current smoker) and pack-years. Pack-years were calculated as number of cigarettes smoked per day divided by 20 multiplied by the number of years of smoking.

Modification of the effect of occupational exposure by sex and smoking was assessed by including an interaction term (occupational exposure*sex, occupational exposure*smoking) in the models. A p value of <0.05 was considered statistically significant.

To assess whether asthma significantly affected the results, the analyses were repeated without asthma subjects (n = 139). Asthma was defined as the combination of wheezing in the last 12 months together with bronchial hyperreactivity (BHR).[27] BHR was defined as a provocative dose of methacholine causing a 20% fall in FEV_1 (PD_{20}) less than 2 mg. These analyses produced very similar results with only slight changes in point estimates, so only the results for the total dataset are presented.

RESULTS

Prevalence of exposure and characteristics of study population

The prevalences of the different workplace exposures as assessed by the ALOHA JEM are shown in table 1. More than 60% of the study group had some occupational exposure, either high or low exposure to dusts, gases or fumes. The most common exposure was to gases and fumes among 54.1% of subjects. Exposure to biological and mineral dusts was slightly less (39.2% and 32.1%, respectively).

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Table 1 Characteristics and occupational exposures of study population (n = 1213)

	N (%)	Biological dust n (%)	Mineral dust n (%)	Gases/fumes n (%)
No exposure		729 (60.1)	814 (67.1)	550 (45.3)
Low		367 (30.3)	228 (18.8)	488 (40.2)
High		117 (9.7)	171 (14.1)	175 (14.4)
Median (IQR) duration (years)		16 (6–30)	13 (6–38)	15 (5.5–33)
Sex				
Men	625 (51.5)	226 (36.2)†	284 (45.4)	374 (59.8)
Women	588 (48.5)	258 (43.9)	115 (19.6)†	289 (49.2)†
Age (years)				
<49	213 (17.6)	81 (38.0)	69 (32.4)	122 (57.3)
50–54	274 (22.6)	111 (40.5)	90 (32.9)	142 (51.8)
55–59	231 (19.0)	79 (34.2)	68 (29.4)	124 (53.7)
60–64	206 (17.1)	86 (41.8)	71 (34.5)	106 (51.5)
⩾65	289 (23.8)	127 (43.9)	101 (34.9)	169 (58.5)
Smoking status				
Never smoker	608 (50.1)	238 (39.1)	169 (27.8)	313 (51.5)
Ex-smoker	436 (35.9)	181 (41.5)	172 (39.5)†	258 (59.2)†
Current smoker	169 (13.9)	65 (38.5)	58 (34.3)	92 (54.4)

IQR, interquartile range.
†$p<0.05$.
Reference categories are female, age <49 years, and never smokers.

Women were more frequently exposed to biological dust than men, while men were significantly more exposed to mineral dust and gases/fumes than women. There was no trend in exposure by age categories. Ex-smokers were significantly more likely to be exposed to mineral dusts and to gases/fumes than never smokers.

Prevalence of respiratory symptoms and conditions

Shortness of breath was the most prevalent symptom reported by subjects, with morning or chronic cough being the next most commonly reported symptoms (table 2). Morning phlegm and chronic bronchitis were the least commonly reported. Abnormalities in ventilatory function were at least as commonly found as the most common symptoms, while the prevalences of chronic obstructive bronchitis, emphysema, and COPD were relatively low. Most of the COPD was due to emphysema, not chronic obstructive bronchitis.

Prevalence of respiratory symptoms, airflow obstruction, and COPD by occupational exposure

In this population, the population attributable risk (PAR) for biological dust was 36.8% (95% CI 7.59 to 56.7) for COPD. The PAR for mineral dust was 7.9% (95% CI 0 to 27.1) and for gases/fumes was 26.6% (95% CI 0.0 to 51.9) for COPD. Chronic obstructive bronchitis, emphysema, and COPD were 2–3 times more prevalent in those with exposure to biological dust (table 3). Respiratory symptoms such as morning cough and dyspnoea were of borderline significance in those individuals with exposure to biological dust. For mineral dust there were no associations found with any symptom, airflow obstruction or case definition, while for fumes/gases there were only two significant associations (morning phlegm and chronic obstructive bronchitis).

Effect of sex

Table 4 shows the associations between occupational exposure and risk of chronic obstructive bronchitis, emphysema and COPD stratified by sex. We found significant associations between exposure to biological dust and chronic obstructive bronchitis, emphysema, and COPD in women but not in men. For COPD, this interaction between biological dust exposure and sex was statistically significant ($p = 0.04$). We also found chronic obstructive bronchitis to be associated with exposure to mineral dust and gases and fumes in women but not in men. This interaction between exposure and sex was statistically significant ($p = 0.04$) for mineral dust exposure but not for gases and fumes ($p = 0.30$).

Effect of smoking

We found similar associations in ever smokers and in never smokers for all conditions and exposures (data not shown). For biological dust we did find a significantly increased risk in ever smokers for emphysema and COPD. However, the difference in ORs between the ever smokers and never smokers was not statistically significant.

Table 2 Prevalence of respiratory symptoms, lung function, and conditions for the study group

Characteristic	N	n (%)	95% CI
Morning cough	1213	195 (16.1)	14.1 to 18.3
Chronic cough	1213	120 (9.9)	8.3 to 11.7
Morning phlegm	1213	90 (7.4)	6.0 to 9.0
Chronic bronchitis	1213	49 (4.0)	3.0 to 5.3
Dyspnoea	1213	277 (22.8)	20.5 to 25.3
Mild airflow obstruction	1213	226 (18.6)	16.5 to 21.0
Moderate airflow obstruction	1213	83 (6.8)	5.5 to 8.4
TLCO <80% predicted	1211	153 (12.6)	10.8 to 14.6
Chronic obstructive bronchitis	1213	22 (1.8)	1.1 to 2.7
Emphysema (symptomatic)	1211	29 (2.4)	1.6 to 3.4
Emphysema (asymptomatic)	1211	56 (4.6)	3.5 to 5.9
COPD	1211	42 (3.4)	2.5 to 4.7

TLCO, carbon monoxide lung transfer factor.

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Table 3 Relationship of respiratory symptoms, lung function, and conditions to occupational exposures

	N‡	Exposed§	Not exposed§	Odds ratio (95% CI)†
Biological dust		n = 484	n = 729	
Morning cough	195	91 (18.9)	104 (14.3)	1.41 (1.03 to 1.93)*
Chronic cough	120	57 (11.3)	63 (8.96)	1.40 (0.96 to 2.06)
Morning phlegm	90	40 (8.2)	50 (6.9)	1.25 (0.80 to 1.94)
Chronic bronchitis	49	26 (5.5)	23 (3.1)	1.74 (0.97 to 3.11)
Dyspnoea	277	130 (26.9)	147 (20.2)	1.35 (1.01 to 1.79)*
Mild airflow obstruction	226	102 (21.1)	124 (17.0)	1.30 (0.96 to 1.76)
Moderate airflow obstruction	83	38 (7.9)	45 (6.2)	1.27 (0.80 to 2.00)
TLCO <80% predicted	153	62 (13.1)	91 (12.5)	1.04 (0.80 to 1.34)
Chronic obstructive bronchitis	22	15 (3.1)	7 (1.0)	3.19 (1.27 to 7.97)*
Emphysema (symptomatic)	29	19 (4.0)	10 (1.4)	3.18 (1.41 to 7.13)*
Emphysema (asymptomatic)	56	30 (6.2)	26 (3.6)	1.89 (1.07 to 3.34)*
COPD	42	26 (5.4)	16 (2.2)	2.70 (1.39 to 5.23)*
Mineral dust		n = 399	n = 814	
Morning cough	195	67 (16.8)	128 (15.7)	1.06 (0.75 to 1.49)
Chronic cough	120	42 (10.5)	78 (9.6)	1.08 (0.71 to 1.65)
Morning phlegm	90	40 (10.0)	50 (6.1)	1.44 (0.90 to 2.28)
Chronic bronchitis	49	21 (5.3)	28 (3.4)	1.32 (0.71 to 2.44)
Dyspnoea	277	92 (23.1)	185 (22.7)	1.22 (0.89 to 1.67)
Mild airflow obstruction	226	79 (19.8)	147 (18.1)	0.93 (0.67 to 1.29)
Moderate airflow obstruction	83	25 (6.3)	58 (7.1)	0.71 (0.42 to 1.19)
TLCO <80% predicted	153	50 (12.8)	102 (12.7)	0.85 (0.64 to 1.13)
Chronic obstructive bronchitis	22	9 (2.3)	13 (1.6)	1.40 (0.56 to 3.51)
Emphysema (symptomatic)	29	11 (2.8)	18 (2.3)	1.07 (0.46 to 2.45)
Emphysema (asymptomatic)	56	20 (5.0)	36 (4.4)	0.96 (0.52 to 1.79)
COPD	42	16 (4.1)	26 (3.3)	1.13 (0.57 to 2.27)
Gases and fumes		n = 663	n = 550	
Morning cough	195	116 (17.5)	79 (14.4)	1.27 (0.92 to 1.76)
Chronic cough	120	70 (10.6)	50 (9.1)	1.16 (0.79 to 1.72)
Morning phlegm	90	60 (9.1)	30 (5.5)	1.59 (1.00 to 2.53)*
Chronic bronchitis	49	31 (4.7)	18 (3.3)	1.31 (0.72 to 2.40)
Dyspnoea	277	154 (23.2)	123 (22.4)	1.09 (0.82 to 1.45)
Mild airflow obstruction	226	124 (18.7)	102 (18.6)	0.92 (0.67 to 1.24)
Moderate airflow obstruction	83	45 (6.8)	38 (6.9)	0.71 (0.42 to 1.19)
TLCO <80% predicted	153	84 (13.0)	68 (12.5)	1.03 (0.80 to 1.33)
Chronic obstructive bronchitis	22	17 (2.6)	5 (0.9)	2.81 (1.01 to 7.79)*
Emphysema (symptomatic)	29	18 (2.7)	11 (2.0)	1.26 (0.57 to 2.80)
Emphysema (asymptomatic)	56	32 (4.8)	24 (4.4)	0.96 (0.52 to 1.79)
COPD	42	28 (4.2)	14 (2.6)	1.63 (0.83 to 3.22)

TLCO, carbon monoxide lung transfer factor.
*$p<0.05$.
†Odds ratios (and 95% CI) were adjusted by age, sex, smoking status, and pack years. ‡Number of subjects with respiratory symptoms or conditions.
§Proportion of subjects with specific condition with and without exposure.

Effect of cumulative exposure

We also investigated if there was a dose-response relationship with any of the exposures. Cumulative exposure (years) was examined using two exposure subgroups, defined by the median of the weighted cumulative exposure, on the risk of developing chronic bronchitis, emphysema and COPD stratified by sex (table 5). In women we found an association between the shorter weighted cumulative exposure to biological dust and risk of chronic obstructive bronchitis, but not for the higher exposure group. For emphysema and COPD we found a significantly increased risk associated with each level of weighted cumulative exposure to biological dust. However, the risks did not increase with weighted duration of exposure for either emphysema or COPD. In men we did not observe any increased risk with more years of exposure to any of the exposures, except for biological dust where we found a significantly increased risk of emphysema only in the shorter exposure group. For cumulative exposure to biological dust, the p value for interaction with sex for the higher exposure group for COPD was significant ($p = 0.03$), and for emphysema was of borderline significance ($p = 0.06$).

DISCUSSION

While two previous studies have used an earlier version of this COPD specific JEM to investigate the role of workplace exposures,[17 28] our study is the first to use a community based sample of older adults who, because of their relatively advanced age, are more likely to have developed respiratory symptoms and airflow obstruction. The unique aspect of this JEM is the separation of biological and mineral dusts which have previously been found to be associated with different risks of COPD, using an earlier version of the ALOHA JEM and occupational titles to assess occupational exposure.[17 28 29]

We found significantly increased risks of respiratory symptoms and COPD associated with occupational exposure to biological dust. Biological dust exposures include substances of microbial, plant or animal origin such as bacteria, fungi, allergens, endotoxins, peptidoglycans, β(1→3)glucans, pollens, and plant fibres.[30] Generally, biological dust is a complex mixture of one or more of these substances, and any of these components could be responsible for initiating the inflammatory reaction seen in COPD.[31] Workforce based studies have found significant associations with respiratory symptoms and a decline in or reduced lung function among workers in occupations exposed to biological dust such as cotton textiles,[12] farmers,[13] grain handlers,[14] bakers, and saw mill workers.[15 16] However, these studies were based on specific occupational groups and hence may not be generalisable to the wider community. Our study has the advantage of investigating a community based sample of

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Table 4 Associations between occupational exposures, chronic obstructive bronchitis, emphysema, and COPD stratified by sex

	N†	Exposed n (%)‡	Not exposed n (%)‡	Adjusted OR (95% CI)§
Women (n=595)				
Biological dust		n=258	n=330	
Chronic obstructive bronchitis	11	9 (3.5)	2 (0.6)	5.83 (1.24 to 27.4)*
Emphysema	12	10 (3.9)	2 (0.6)	7.55 (1.58 to 36.0)*
COPD	18	15 (5.8)	3 (0.9)	7.43 (2.07 to 26.7)*
Mineral dust		n=115	n=473	
Chronic obstructive bronchitis	11	5 (4.4)	6 (1.3)	3.60 (1.06 to 12.3)*
Emphysema	12	2 (1.8)	10 (2.1)	0.90 (0.19 to 4.34)
COPD	18	5 (4.4)	13 (2.8)	1.79 (0.60 to 5.29)
Gases and fumes		n=289	n=299	
Chronic obstructive bronchitis	11	9 (3.1)	2 (0.67)	4.85 (1.03 to 22.9)*
Emphysema	12	7 (2.4)	5 (1.67)	1.65 (0.50 to 5.45)
COPD	18	12 (4.2)	6 (2.01)	2.37 (0.85 to 6.60)
Men (n=637)				
Biological dust		n=226	n=399	
Chronic obstructive bronchitis	11	6 (2.7)	5 (1.3)	2.02 (0.60 to 6.82)
Emphysema	17	9 (4.0)	8 (2.0)	1.99 (0.73 to 5.47)
COPD	24	11 (4.9)	13 (3.3)	1.49 (0.63 to 3.51)
Mineral dust		n=284	n=341	
Chronic obstructive bronchitis	11	4 (1.4)	7 (2.1)	0.59 (0.17 to 2.08)
Emphysema	17	9 (3.2)	8 (2.4)	1.14 (0.42 to 3.11)
COPD	24	11 (3.9)	13 (3.8)	0.88 (0.37 to 2.06)
Gases and fumes		n=374	n=251	
Chronic obstructive bronchitis	11	8 (2.1)	3 (1.2)	1.62 (0.42 to 6.26)
Emphysema	17	11 (3.0)	6 (2.4)	1.02 (0.36 to 2.90)
COPD	24	16 (4.3)	8 (3.2)	1.19 (0.49 to 2.92)

*$p<0.05$.
†Number of subjects with chronic bronchitis, emphysema and COPD.
‡Proportion of subjects with specific condition with and without exposure.
§Odds ratios (and 95% CI) were adjusted by age, smoking status, and pack years.

older adults for their entire work history. This took into account retirees and other workers who may have been forced to terminate work prematurely due to ill health.

Previous population based studies have found similar associations between occupations with biological dust exposure and the risk of respiratory symptoms or COPD. The New Zealand population based study of the ECRHS also found increased risks of respiratory symptoms and airflow obstruction associated with a variety of occupations having biological dust exposure—specifically bakers, food process

Table 5 Associations between cumulative occupational exposure, chronic obstructive bronchitis, emphysema, and COPD

Cumulative exposure	Chronic obstructive bronchitis OR (95% CI)†	Emphysema OR (95% CI)†	COPD OR (95% CI)†
Women			
Biological dust			
0 years	1.0	1.0	1.0
1–12 years	7.38 (1.39 to 39.2)*	6.84 (1.18 to 39.7)*	8.24 (2.01 to 33.8)*
>12 years	4.65 (0.83 to 26.0)	8.15 (1.56 to 42.5)*	6.90 (1.75 to 27.2)*
Mineral dust			
0 years	1.0	1.0	1.0
1–11 years	4.23 (1.13 to 15.8)*	1.36 (0.28 to 6.64)	2.15 (0.65 to 7.07)
>11 years	2.48 (0.29 to 21.6)	N/A‡	1.16 (0.14 to 9.44)
Gases and fumes			
0 years	1.0	1.0	1.0
1–13 years	5.60 (1.10 to 28.4)	1.65 (0.42 to 6.51)	2.80 (0.92 to 8.51)
>13 years	3.91 (0.64 to 23.9)	1.68 (0.38 to 7.44)	1.85 (0.50 to 6.90)
Men			
Biological dust			
0 years	1.0	1.0	1.0
1–12 years	2.65 (0.68 to 10.3)	3.17 (1.06 to 9.49)*	2.23 (0.85 to 5.82)
>12 years	1.38 (0.26 to 7.30)	0.88 (0.18 to 4.36)	0.81 (0.22 to 2.97)
Mineral dust			
0 years	1.0	1.0	1.0
1–11 years	1.48 (0.41 to 5.26)	1.11 (0.31 to 3.93)	1.10 (0.39 to 3.11)
>11 years	N/A‡	1.18 (0.36 to 3.82)	0.71 (0.24 to 2.10)
Gases and fumes			
0 years	1.0	1.0	1.0
1–13 years	1.93 (0.42 to 8.89)	1.28 (0.39 to 4.22)	1.39 (0.49 to 3.94)
>13 years	1.39 (0.30 to 6.41)	0.82 (0.24 to 2.83)	1.03 (0.37 to 2.92)

*$p<0.05$.
†All odds ratios (95% confidence intervals) adjusted for age and smoking status.
‡N/A, insufficient subjects in stratum.

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workers, and hairdressers.[32] Zock *et al*,[28] using the complete data from 14 countries in the ECRHS, found an increased risk of respiratory symptoms associated with working in the agricultural, paper, cleaning, wood and food processing industries.

Two previous studies have looked at specific workplace exposures rather than occupational groups. The Spanish ECRHS study found an association between chronic cough, reduction in FEV_1 and biological dust exposure, but only investigated subjects aged between 20 and 45 years where the prevalence of COPD was rare.[17] An Italian case-control study found a ninefold increased risk of COPD in workers exposed to biological dust, but this study was restricted to men only.[29]

Our study found the highest risk of COPD in women with exposure to biological dust. Few studies of occupational exposure and risk of COPD have stratified by sex, and those that have found no difference in risk of respiratory symptoms or reduced lung function between the sexes.[4 7] These studies were not directly comparable as they did not differentiate between biological and mineral dust exposures, and used self-reported exposures. Furthermore, the reported prevalence of dust exposure was significantly lower than the prevalence of biological dust exposure in our female subjects. More recently, a study of women over 55 years of age found no association between self-reported doctor diagnosed chronic bronchitis or emphysema and either occupation or occupational exposure to dusts, gas, vapours, fumes or sensitisers.[33] Their study used expert assessment to assign exposure, they did not differentiate between biological and mineral dust exposure, and they assessed only the longest held occupation.

Our study is the first to show an association between biological dust exposure and risk of COPD predominantly in women. The women in our study with biological dust exposure were mainly nurses and other allied health workers, food and textile workers, artists, and cleaners. There is increasing evidence to suggest that female gender is an independent risk factor for COPD. This is based on some evidence that women are more susceptible to the effects of cigarette smoke, receiving a greater dose of smoke for a given number of pack years because of their smaller airway size.[34] Women also have a higher prevalence of BHR than men, which is a suspected risk factor for COPD.[35] Recent evidence has suggested that there is a preponderance of women with early onset COPD[36] and with COPD who are non-smokers.[37] Our data would suggest that women may also be more susceptible to the effects of biological dust. However, the exact mechanism by which this occurs needs to be determined.

Previous studies have found dose-response relationships between duration or cumulative exposure and respiratory symptoms such as wheeze, chronic phlegm, and shortness of breath.[4 8] We did not find an increasing risk with weighted duration of exposure for COPD. However, we did find a significantly increased risk associated with each level of weighted duration of exposure to biological dust in women only. This may suggest a threshold effect for biological dust exposure—that is, once someone has had a sufficient amount of exposure, further exposure may not influence the occurrence of COPD. The most likely reason for the lack of exposure response is inaccurate assessment of exposure by application of a general population JEM. To determine the threshold effect, a more accurate estimate of exposure would have been necessary which was not possible in our large general population study.

We did not find any association between mineral dust exposure and respiratory symptoms or COPD, which agrees with the findings of Sunyer *et al*.[17] They attributed this to the small number of miners in their sample and the young age of their subjects. A limitation of previous studies of dust exposure which have grouped dusts into one category[4 8] is the potential for exposure misclassification.[38] Like Sunyer and colleagues,[17] we found quite different results for biological and mineral dusts, further emphasising the need to consider these exposures independently.

The risk of COPD with biological dust exposure in our overall analyses was similar to the risk found in ever smokers only. However, when we further stratified by intensity of smoking using pack years, we were unable to show any evidence of effect modification due to duration of exposure (results not shown). The statistical significance we observed for the ever smokers is most likely due to the larger number of subjects with chronic bronchitis, emphysema, and COPD in the ever smokers group compared with never smokers.

We found a higher prevalence of exposure to biological dusts and mineral dust than other population based studies. Previous community based studies in other countries have found the prevalence of dust exposure to be around 30%.[4 8] Sunyer *et al*[17] found a much lower prevalence of biological dust exposure in their Spanish population using the ad hoc JEM. However, their prevalence of mineral dust exposure was similar to ours. The prevalence of exposure to gases/fumes in our study was significantly higher than in all other reported studies. This may be explained by our assessment of lifetime occupational exposures (for example, ever exposed), while most previous studies have only assessed current or most recent job. International differences in occupational exposures may also explain the higher exposure in our study than in other studies. Zock *et al*[28] found significant differences between countries in the ECRHS for their analyses of occupational exposures.

The main limitations of our study are the small number of cases (especially for the subgroup analyses), possible misclassification, non-response bias, and multiple comparisons. We aimed to investigate a wide range of possible risk factors for COPD, not just occupational exposures. It was therefore unlikely that people with occupational exposure were selectively invited to participate. More likely was self-selection due to concern over respiratory symptoms. To examine this we compared the prevalence of self-reported respiratory symptoms between participants in the laboratory phase of the study and those in the initial screening questionnaire phase only. A significantly higher prevalence of wheeze was seen in those who attended the laboratory, but not in other respiratory symptoms and self-reported COPD. There were significantly more current smokers among the non-participants and slightly more men (data not shown). However, this bias towards symptomatic non-smokers is unlikely to have affected the associations between occupational exposures and COPD.

JEMs are affected by non-differential misclassification of exposure, which occurs when there is heterogeneity of exposure in a given job or occupation. However, this generally results in misclassification towards the null, leading to an underestimation of the effect of the exposure on risk of the disease.[39] Therefore, if this study was affected by non-differential misclassification, the results are likely to be an underestimation of the true effect. Because of the multiple comparisons performed in this study, it might be argued that adjustment for multiple comparisons was necessary. However, for each exposure there was an a priori hypothesis of an association with respiratory symptoms and/or COPD, based on previous workplace and community based studies. Also, the associations with biological dust exposure were consistent across several traits, suggesting a genuine association. The analyses are therefore presented as they were performed and the results should be viewed as hypothesis

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generating rather than proof that biological dust is a true risk factor.

In conclusion, occupational exposure to biological dusts was associated with increased risk of COPD in this general population sample of middle aged and older adults, particularly in women. Future studies need to consider the independent effects of different occupational exposures and to determine the underlying biological mechanisms. From a clinical perspective, occupational exposures need to be considered when assessing patients with respiratory symptoms and reduced lung function, particularly in women who previously may not have had an occupational history taken. Patients with known occupational exposure should have routine lung function measurement to detect any decline in lung function. Preventive strategies should reduce exposure to these noxious agents in the workplace, especially biological dusts. This may involve new technologies to reduce exposures and better workplace monitoring to ensure levels remain within recommended standards.

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