Original research

Occupational exposures and incidence of asthma over two decades in the European Community Respiratory Health Survey

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ABSTRACT

Background While short-term occupational exposures to many agents are associated with increased risk of asthma, the long-term consequences of exposure have not been well understood. We investigated the effects of occupational exposures over two decades on the incidence of asthma.

Methods This population-based, multicentre cohort was assessed at baseline (European Community Respiratory Health Survey (ECRHS)1) and followed up twice over 20 years (ECRHS2 and ECRHS3). This analysis included data for 5591 participants with complete work histories and free of asthma at baseline. Incident adult-onset asthma was defined as either an asthma attack, woken by an attack of shortness of breath and/or current asthma medication in the last 12 months before each timepoint, without asthma at a previous survey. An updated asthma-specific job exposure matrix was used to estimate exposures to asthmagens. Adjusted Poisson models were fitted with generalised estimating equations to estimate asthma incidence.

Results Ever high exposure to high molecular weight *sensitisers* (rate ratio (RR)=1.31; 95% CI 1.15 to 1.63), *irritants* (RR=1.29; 1.09–1.54), biocides (RR=1.42; 1.12–1.79), only low exposure to low molecular weight *sensitisers* (RR=1.26; 1.08–1.47), mites (RR=1.48; 1.12–1.94) and reactive chemicals (RR=1.24; 1.06–1.45) were associated with increased incidence of asthma. Asthma incidence also increased with ever high or cumulative exposure to these exposures and for specific exposure to wood dust, cleaning agents and bleach. The population-attributable fraction for adult-onset asthma due to occupational exposures was 18% (16.9–19.4%).

Conclusion This strengthens the evidence that occupational exposures to sensitisers and chemical irritants contribute substantial risk and a substantive attributable fraction of adult-onset asthma. Control of implicated hazardous exposures and periodic screening of exposed workers should be considered.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recent studies have identified several novel occupational exposures associated with increased risk of asthma. However, longitudinal evidence from large-scale studies with repeated follow-up and work histories supporting such associations has been minimal.

WHAT THIS STUDY ADDS

⇒ Based on the large-scale prospective multicentre European Community Respiratory Health Survey cohort, we observed that ever and cumulative grouped exposures to high and low molecular weight sensitisers, microbial exposure and irritants, including specific exposures to wood dust, indoor cleaning agents and bleach, were associated with increased incidence of asthma over 20 years of follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ From a clinical perspective, we found that asthma incidence increased due to multiple relevant exposures from workplaces. From a public health perspective, policymakers and regulatory agencies should update and strengthen regulations related to known and new asthmagens to reduce the incidence of asthma.

INTRODUCTION

Asthma is a major contributor to the global burden of chronic non-malignant respiratory diseases. Asthma due to occupational exposure is defined as asthma developing de novo in someone who has no pre-existing asthma symptoms, due to workplace exposure to one or more harmful agents.[1] Most clinically identified cases of asthma developing in workplaces are allergic in nature and involve 'sensitisation', with a latent period between first occupational exposure to the agent(s) and the onset of symptoms.[2] Once sensitisation occurs, the worker may then react to much lower levels of the asthmagenic agent. While the Global Burden of Disease Study indicates a decline in asthma caused by occupational exposure,[3] region-specific data indicates an increase in asthmagens over the past decade.[2 4] However, overall trends may vary, with some reviews indicating a decline in incidence due to improved workplace controls and awareness.[5] Nonetheless, establishing the link between occupation and asthma still remains challenging, importantly due to difficulty in diagnosis and lack of prospective studies and under-reporting of cases.

Although there have been over 450 chemical and biological substances identified as potential causative agents for occupational asthma (OA), relatively few prospective population-based studies have documented the incidence rates of asthma associated with most of these agents.[6–8] Work-related asthma (WRA) includes various types of asthma that are triggered or made worse by exposures in the workplace. This includes immunological OA, which is characterised by a delay in symptoms after becoming sensitive to a specific substance in the workplace. On the other hand, non-immunological OA occurs after high exposure to irritants or after repeated exposure to moderate levels of irritants, but does not involve becoming sensitive to the substance.[1] Work-aggravated asthma refers to the worsening of pre-existing or concurrent asthma due to workplace exposures and is distinct from other asthma types. Occupational exposures that need further study are wheat flour, bioaerosols, latex, industrial cleaning agents, sterilising agents and wood dusts.[1]

Workplace-based studies have identified several specific occupational exposures, including isocyanates, flour, grain and wood dust, as responsible for the highest number of new cases of asthma, as highlighted in the previous report.[9] A recently published data linkage study from Canada confirmed increased risks of asthma among bakers, painters and decorators. Using a recently updated occupational asthma-specific job exposure matrix (OAsJEM),[10] they found increased risks of WRA for those exposed to flour, dust and isocyanates.[4]

Despite the evidence of the link between occupational exposures and asthma from workplace-[11 12] and population-based cross-sectional studies,[13–15] data from longitudinal studies using extended work histories have been limited.[7 8] Longitudinal analyses of asthma due to occupational exposure conducted in the last decade have identified novel or emerging exposures from entry to the workforce into adulthood.[16 17] A previous analysis using the first 13 years of follow-up of the European Community Respiratory Health Survey (ECRHS) found associations with isocyanates, latex and cleaning agents in a relatively young cohort middle-aged at enrolment.[7] An official review from the American Thoracic Society and the European Respiratory Society, based on data through 2017, reported an overall population attributable fraction (PAF) of 16% from all longitudinal studies with limited analysis stratified by gender and occupational agents.[18]

To address this knowledge gap, we aimed to estimate the incidence of OA and identify its risk factors using the updated OAsJEM to provide a more detailed analysis of the occupational burden of asthma using the large international ECRHS cohort with 20 years of follow-up.

METHODS

ECRHS study design and population

The ECRHS is a multicentre longitudinal population-based study started as cross-sectional in 1991–1993 which enrolled general population samples aged 20–44 years in 55 centres from 23 countries (ECRHS1).[19] Each participant was first sent a brief screening questionnaire (stage 1). From those who responded, a random sample was selected for a detailed clinical examination in stage 2. The ECRHS2 Study followed up with participants from stage 2 of ECRHS1 between 1998 and 2002, repeating the same clinical examinations. Ten years later, in 2010–2012, the ECRHS3 Study was organised as another multicentre follow-up with the same group from ECRHS1 stage 2.

In ECRHS2 and 3 follow-ups, participants were asked to complete a detailed respiratory questionnaire, list their job titles and industries from jobs held since the previous study (ECRHS 1 and 2 stage 2, respectively) and undergo clinical testing. The detailed methods have been previously reported.[6 7] However, ECRHS1 only collected limited data on current job titles and job changes. The job titles and industries in ECRHS2 and 3 were collected as free text and occupations were subsequently coded according to the International Standard Classification of Occupations, 1988 (ISCO-88) four-digit job code, as described in the previous ECRHS paper.[20] Written informed consent was obtained from all participants.

Study population and definition of asthma

The population eligible for this study included participants with job history at baseline and who were followed up at ECRHS2 and/or ECRHS3 (n=5813). A total of 222 participants with current asthma (online supplemental file 1 for more detail) at the time of the baseline study (ECRHS1) were excluded from this analysis, leaving a total of 5591 as the final sample for this analysis with work history and clinical endpoint data.

Asthma was defined by the participant reporting: (1) An asthma attack, (2) Woken by an attack of shortness of breath and/or (3) Currently using asthma medication in the last 12 months before the follow-up interview .[6 7] Participants with incomplete job histories or missing exposure information (n=345) were also excluded (figure 1). Participants were defined as atopic if they had a positive skin prick test to any of *D. Pteronyssinus* (house dust mites, d1), Cat (e1), Timothy grass (g6), *Cladosporium* (m2), and Grass pollen (g6) common allergens at baseline and at the end of follow-up.

Occupational exposure

The job history at follow-up was collated and coded into ISCO-88 codes and linked to the OAsJEM.[10 20] OAsJEM is a two-dimensional table with the first axis listing the ISCO-88 codes and the second axis listing seven exposure groups: high molecular weight (HWM) sensitisers, mites (house dust mites, storage mites, plant mites), microbial exposures (mould/fungi, endotoxin, metal working fluids), low molecular weight (LMW) sensitisers, irritants, highly reactive chemicals (high level chemical disinfectants, aliphatic amines, isocyanates, acrylates, epoxy resin and persulfates/henna) and biocides (high level chemical disinfectants, herbicides, insecticides, fungicides

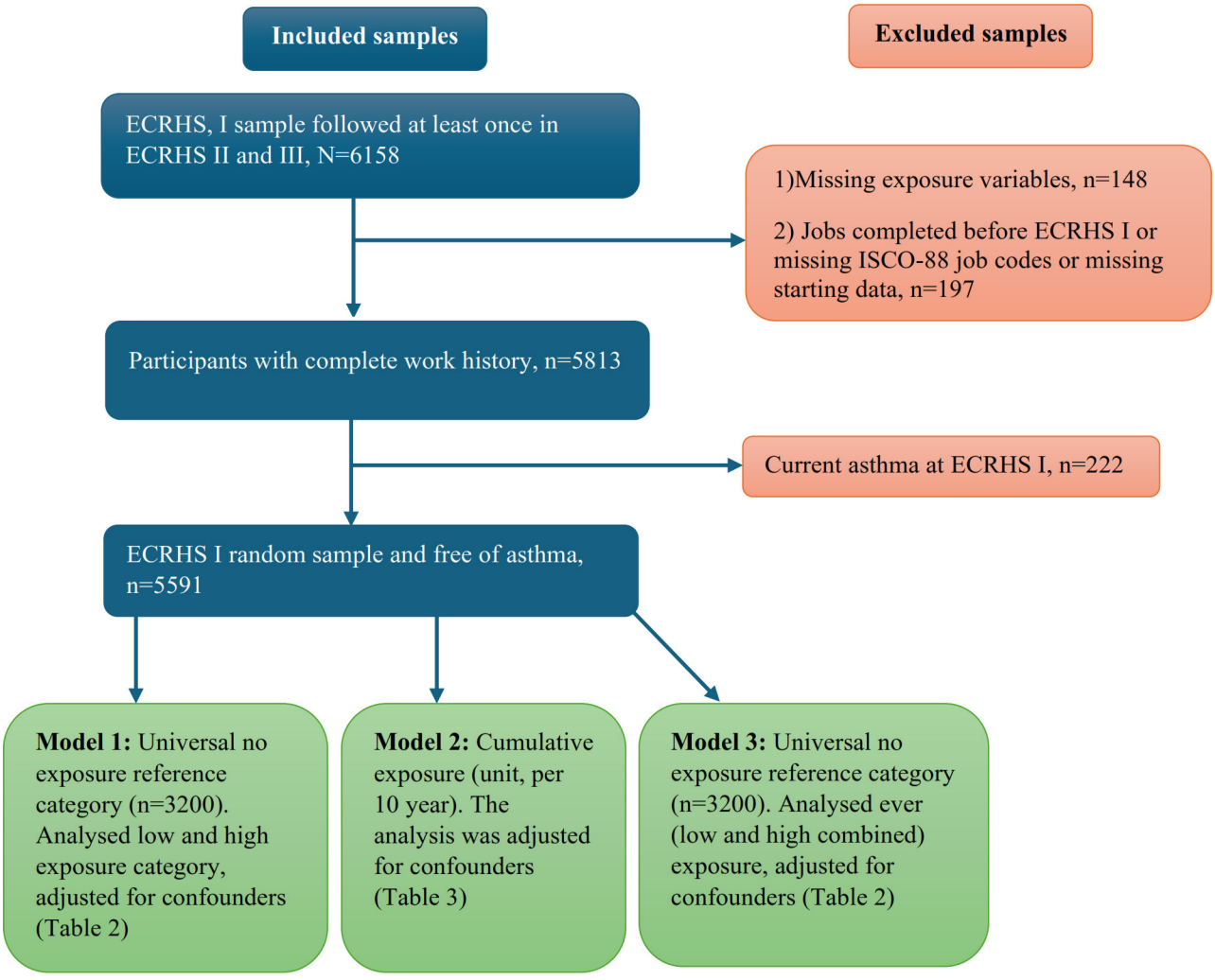

Figure 1 Flow chart of European Community Respiratory Health Survey (ECRHS) participants included in the analysis. ISCO-88, International Standard Classification of Occupations, 1988.

and bleach). Out of these substances, 11 were HMW, including 3 mites as a subcategory, 8 were LMW sensitisers (such as isocyanates, acrylates and aliphatic amines), 3 were microbial exposures (such as moulds and textiles defined as HMW sensitisers), and 7 were chronic exposures to irritants, including a few LMW agents.

In each cell, exposure to a group of agents and to a specific agent is coded as no, low or high.[10] OAsJEM prefers specificity over sensitivity given the relatively low prevalence of occupational exposure in the general population, so jobs were only classified as highly exposed if the probability and intensity of exposure was high.[10] Any exposure was calculated by considering exposures to all (groups of) agents over all jobs for each participant. In the case of participants who had concurrent employment in two different jobs, exposures from both jobs were averaged and rounded up to the nearest integer. The OAsJEM method was employed to determine cumulative exposure in arbitrary intensity-years for each participant by multiplying the years worked in each job with the corresponding exposure intensity (ie, 1 for low or 4 for high exposure) and then summed over the entire working life.[21] Cumulative exposure was estimated for all asthmagens and scaled as a continuous variable of cumulative exposure per 10 years.

Confounders

The minimum set of confounders was identified from Directed Acyclic Graph (DAG) using DAGitty software (online supplemental figure S1). Based on the DAG: age, sex, lifetime smoking, pack-years among ever smokers, socioeconomic status, weight change and atopy were included as confounders (see online supplemental material for more detail).

Statistical analyses

The associations between occupational exposures and incidence of asthma during the entire 20 years follow-up were assessed using multivariable Poisson regression models fitted using generalised estimating equations (GEEs) with an exchangeable correlation matrix and robust error variance. This model provided population-averaged rate ratio estimation over the follow-up period of a longitudinal study, taking into consideration clustering by ECRHS Study centre and country. The GEE model also accounted for correlations between multiple observations from the same participant (that is ECRHS2 and ECRHS3). The final models adjusted for age, sex, lifetime smoking, pack-years, socioeconomic status, weight change and atopy were also considered.

In the main exposure analysis, a universal 'no exposure' to any asthmagen was used to allow comparison across all asthmagens. The analyses were conducted for only low and ever high exposure categories during the work history separately. We also analysed the 'ever exposure' group, where we combined only low and/or ever high exposure categories to define ever exposure, because the small number of participants in some groups limited the statistical power (see online supplemental material). An interaction term was included in the models between occupational exposure with sex, smoking and atopy to explore effect modification, and interaction p values were reported.

The PAF[18] for any occupational exposure was calculated from the Poisson regression models with robust estimation of the error, within a single model that included adjustment for covariates. Several sensitivity analyses were performed to test the robustness of our findings. The final models were adjusted for: (1) Body mass index (instead of weight change), doctor diagnosed (2) Chronic bronchitis, (3) Chronic obstructive pulmonary disease and (4) Other lung diseases. All statistical analyses were conducted using Stata V.18.0 (Stata Corporation, College Station, Texas, USA) and a conservative two-sided value of $p<0.01$ was used as cut-off for statistical significance to address multiple comparison issues. The reported value of p was also corrected using the Benjamini-Hochberg FDR correction method to account for multiple comparisons.

RESULTS

The descriptive characteristics of study participants are summarised in table 1. The median age at last follow-up (ECRHS3) was 53.5 years, and the mean (±SD) weight of participants increased at follow-up (from 69.5±13.6 kg to 78.3±16.2 kg). The proportion of current smokers decreased over time (from 32.7% to 19.4%). Of participants with clinical data, 1184 (21.2%) had incident asthma from ECRHS1 to ECRHS3 and 964 (20.5%) in ECRHS2, giving an overall incidence rate of asthma at ECRHS3 of 15 per 1000 person-years. The annual incidence proportion of asthma was highest in Spain, Estonia, the UK and Norway (1.3%–1.4% per year), and lowest in Switzerland and Italy (0.73%–0.77% per year) (figure 2) (online supplemental file 1 for more details).

Table 2 summarises the results from the adjusted GEE models. In table 2, the risk estimates are presented for the seven main exposure groups and for the underlying specific agents, and a universal 'no exposure' reference category was used to estimate the effect estimates. We observed an increased incidence of asthma with ever-higher exposures to *HMW sensitisers, irritants and biocides. We also found that only low exposure to LMW sensitisers*, mites and reactive chemicals was linked to a statistically higher incidence of asthma over time. When we looked at specific agents, we found that consistent ever-high exposures to the substances wood dust, indoor cleaning agents and bleach were also associated with a higher incidence of asthma. The population-attributable risk for the incidence of asthma associated with occupational exposure was 18.2% (95% CI 16.9% to 19.5%) for only low or ever-high occupational exposure to any agent.

When we combined the groups with ever-high and only low exposure to define 'ever exposure', a similar pattern was observed. We observed that ever exposures to all main exposure groups, except for the group microbial exposures, were associated with a higher incidence of asthma. For specific agents, such as wood dust, indoor cleaning agents, bleach and organic solvents, there was also an association between ever-exposure and increased incidence of asthma (table 2).

Cumulative exposures to the main groups HMW sensitisers, irritants, biocides as well as cumulative exposure to the specific indoor cleaning agents and bleach were associated with increased asthma incidence (table 3). However, no increase was observed for the specific agents such as latex, organic solvents and herbicides or fungicides. Cumulative exposures to microbial agents like moulds, fungi and endotoxin were also associated with increased incidence of asthma. The interaction analysis is presented by sex in online supplemental table S1 and by smoking in online supplemental table S2. We did not observe any interaction between sex and smoking and the considered asthmagens.

Table 1 Characteristics of the study participants (n=5591)

Study characteristics	ECRHS1	ECRHS3
Median age at follow-up (range) years	33.5 (28–40)	53.5 (48–60)
Men; n (%)	2743 (49.1)	
Weight (kg); mean±SD	69.5±13.3	78.3±16.2
Smoking status		
Never smokers; n (%)	2381 (42.6)	2442 (43.7)
Former smokers; n (%)	1190 (21.3)	2039 (36.5)
Former smokers pack-years; median (IQR)	7 (2.4–14)	12.9 (5–24.8)
Current smokers; n (%)	1831 (32.8)	1082 (19.4)
Current smokers pack-years; median (IQR)	11.3 (5.6–19)	24.1 (14–36.3)
Clinical endpoints; n/N (%)		
Atopic *	967/4926 (19.6)	1133/5135 (22.1)
Asthma †	----	1184/5591 (21.2)
Incident asthma		15 per 1000 person-years
Doctor diagnosed other lung diseases	----	408/5094 (8)
Doctor diagnosed COPD	----	49/5184 (1)
Country and study centre; n (%)		
Australia—Melbourne	----	212 (3.8)
Belgium—Antwerp South, Antwerp City	----	321 (5.7)
Denmark—Aarhus	----	188 (3.4)
Estonia—Tartu	----	127 (2.3)
France—Bordeaux, Grenoble, Montpellier, Paris	----	998 (18.0)
Germany—Hamburg, Erfurt	----	600 (10.8)
Iceland—Reykjavik	----	373 (6.7)
Italy—Pavia, Turin, Verona	----	208 (3.7)
Norway—Bergen	----	343 (6.1)
Spain—Barcelona, Galdakao, Albacete, Oviedo, Huelva	----	803 (14.3)
Sweden—Göteborg, Umeå, Uppsala	----	771 (13.8)
Switzerland—Basel	----	388 (6.9)
The UK—Ipswich, Norwich	----	259 (4.6)

Positive responses from the following questions: 'Have you been woken by an attack of shortness of breath at any time in the last 12 months?' or 'Have you had an attack of asthma in the last 12 months?', or 'Are you currently taking any medications for asthma in the last 12 months?' from ECRHS3 was coded as current asthma.
*Participants were defined as atopic if they had the presence of allergen-specific IgE antibody (as defined by positive skin prick test of weal of 3 mm or greater).
†The endpoint asthma was defined as having current asthma among those who did not have asthma at baseline.
COPD, Chronic Obstructive Pulmonary Disease; ECRHS, European Community Respiratory Health Survey.

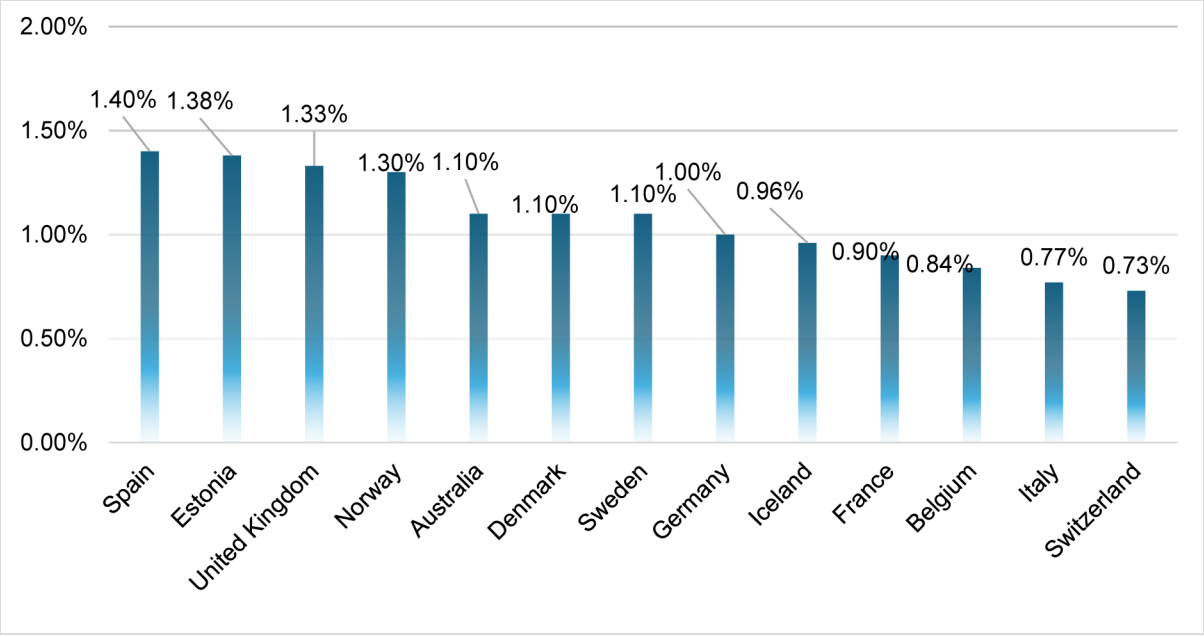

Figure 2 Estimated annual asthma incidence proportion for countries participating in ECRHS1 and ECRHS3. ECRHS, European Community Respiratory Health Survey.

DISCUSSION

In this longitudinal analysis using 20-year follow-up data from the ECRHS cohort showed that occupational exposures to HMW sensitisers, LMW sensitisers, irritants, mites, reactive chemicals and biocides were associated with increased incidence of asthma. A similar pattern was also observed for exposure to several specific agents like low exposure to chemical disinfectants and high exposure to wood dust, indoor cleaning agents and bleach. The incidence of asthma was also increased for cumulative exposures to specific agents like mould, fungi, endotoxins, wood dust, indoor cleaning and bleach. These findings augment previous evidence regarding the role of several occupational exposures in the incidence of asthma and identify new exposures, such as bleach and wood dust, which did not exhibit a significant impact in previous longitudinal studies.

A significant association was observed between the LMW sensitiser wood dust and incidence of asthma. The association with cumulative exposure to wood dust was also increased, although the value of p=0.035 was above the 0.01 threshold for significance we applied in this analysis. The associations between wood dust and respiratory symptoms, reduced lung function and asthma have been documented in systematic reviews and meta-analyses.[22] However, only a limited number of population-based studies have investigated the relationship between wood dust and asthma incidence,[23] including the ECRHS2 Study.[7]

The biological mechanism responsible for the effect of wood dust has been explained in some studies finding that abietic acid contained in the resin of certain trees may damage bronchial epithelial cells. Additionally, terpenes in coniferous trees may cause an increase in bronchial responsiveness along with IgE-mediated sensitisation.[24] It is plausible that the inhalation of dust particles from diverse wood types, such as pine, western red cedar and obeche, can induce IgE-mediated sensitisation.[24] A meta-analysis pooled the associations between asthma and exposure to wood dust, revealing a higher relative risk of asthma among woodworkers compared with the general population.[25] Nonetheless, the precise pathological mechanisms responsible for this phenomenon have not yet been fully described.[26] Apprentices who demonstrate a specific sensitivity to wood dust have also exhibited sensitisation to common aeroallergens, resulting in rhinitis or other allergic symptoms.[27]

We observed that ever-high and cumulative exposures to the microbial agents like moulds, fungi and endotoxins were associated with increased incidence of asthma. Exposure to mould has many deleterious effects on respiratory health. Inhalation of mould spores, fungal toxins and volatile organic compounds upon release into the atmosphere can incite respiratory symptoms, particularly in those individuals with asthma.[28] Moulds, a variety of fungi that thrive in damp and humid environments, are frequently encountered in selected occupational settings.[29] However, previous ECRHS studies have not investigated these associations.[6 7]

Similar to this analysis, the previous ECRHS2 Study reported only a slightly increased incidence of asthma due to natural rubber latex exposure.[7] We did not find a significant association with latex exposure. Another ECRHS analysis did not find a significant association between latex exposure and uncontrolled asthma.[30] The evidence for this relationship from prospective studies was also very limited. In the last century, nurses were sensitised to latex through widespread use of powdered latex gloves, a practice that was consequently phased out in most European countries by the late 2000s.[31]

Similar to latex, we did not find an association with flour dust, previously identified as a risk factor for asthma in ECRHS1.[32] However, the previous study conducted a cross-sectional analysis while we performed a longitudinal analysis using multiple follow-up data. Another reason for the difference in results could be because the JEM itself assigned some exposures, such as bakery workers, to the HMW agent enzymes, which limited the identification of associations with this exposure category, as well as ended up with a healthy survivor population.

Our analysis confirmed that occupations with exposure to cleaning are high-risk occupations for developing asthma, as identified in other cohorts of professional cleaners using chemical disinfectants, cleaning agents and bleach.[33 34] A possible mechanism is the repetitive low levels of exposures over time, causing

Table 2 Associations between any occupational exposures and incidence of asthma

Exposure group	Specific agent n=3200 used as a reference category	Low exposure *No asthma/asthma 2583/617 (Ref.)*	RR (95% CI)*	P value	High exposure *No asthma/asthma 2583/617 (Ref.)*	RR (95% CI)	P value	Ever exposure	RR (95% CI)	P value
Any exposure	All exposures	1186/338	1.13 (0.97 to 1.31)	0.118	638/229	**1.27 (1.08 to 1.51)**	**0.005**	1824/567	**1.18 (1.09 to 1.34)**	**0.008**
HMW sensitisers	All HMW sensitisers	446/140	1.23 (1.01 to 1.51)	0.042	360/113	**1.31 (1.15 to 1.63)**	**0.008**	806/253	**1.27 (1.08 to 1.49)**	**0.005**
	Animals	42/15	1.49 (0.92 to 2.44)	0.108	22/11	1.96 (0.99 to 3.87)	0.052	64/26	**1.62 (1.10 to 1.83)**	**0.009**
	Fish/shellfish	99/32	1.14 (0.77 to 1.69)	0.517	7/2	----	----	106/34	1.11 (0.76 to 1.62)	0.584
	Flour	54/19	1.03 (0.6 to 1.77)	0.922	25/9	1.15 (0.55 to 2.38)	0.712	79/28	1.07 (0.69 to 1.66)	0.774
	Foods (milk, eggs)	81/30	1.17 (0.77 to 1.77)	0.487	----	----	----	81/30	1.16 (0.76 to 1.77)	0.487
	Plant-related dusts	29/19	**1.92 (1.17 to 3.13)**	**0.009**	43/12	1.10 (0.58 to 2.07)	0.768	72/31	1.51 (1.02 to 2.24)	0.041
	House dust mites	72/31	1.41 (0.96 to 2.06)	0.082	49/18	1.23 (0.69 to 2.16)	0.48	121/49	1.35 (0.97 to 1.87)	0.077
	Storage mites	66/31	1.53 (1.03 to 2.27)	0.034	----	----	----	66/31	1.53 (1.03 to 2.27)	0.034
	Plant mites	28/17	1.75 (1.04 to 2.95)	0.036	42/12	1.10 (0.59 to 2.07)	0.769	70/29	1.42 (0.94 to 2.14)	0.096
	Enzymes	81/30	1.16 (0.76 to 1.76)	0.495	----	----	----	81/30	1.16 (0.76 to 1.76)	0.495
	Latex	301/79	1.22 (0.94 to 1.58)	0.135	225/65	1.30 (0.98 to 1.73)	0.071	526/144	1.25 (1.02 to 1.54)	0.030
	Textiles	28/13	1.12 (0.56 to 2.23)	0.748	2/1	----	----	30/14	1.20 (0.62 to 2.30)	0.526
LMW sensitisers	All LMW sensitisers	933/305	**1.26 (1.08 to 1.47)**	**0.003**	211/69	1.25 (0.96 to 1.64)	0.097	1144/374	**1.26 (1.1 to 1.45)**	**0.002**
	Chemical disinfectants	597/198	**1.32 (1.10 to 1.57)**	**0.003**	29/14	1.7 (0.99 to 2.91)	0.056	626/212	**1.34 (1.13 to 1.60)**	**0.001**
	Aliphatic amines	98/25	0.89 (0.55 to 1.42)	0.618	12/6	1.15 (0.51 to 2.61)	0.736	110/31	0.94 (0.62 to 1.43)	0.766
	Isocyanates	71/27	1.37 (0.9 to 2.1)	0.145	7/2	----	----	78/29	1.33 (0.89 to 1.99)	0.166
	Acrylates	105/36	1.30 (0.91 to 1.85)	0.792	----	----	----	105/36	1.30 (0.91 to 1.85)	0.15
	Epoxy resins	36/18	1.73 (1.07 to 2.83)	0.028	97/26	1.15 (0.75 to 1.74)	0.533	133/44	1.33 (0.96 to 1.85)	0.091
	Persulfate and henna	31/6	0.75 (0.27 to 2.1)	0.578	----	----		31/6	0.75 (0.27 to 2.10)	0.578
	Wood dusts	67/33	1.48 (1.01 to 2.15)	0.043	27/13	**1.94 (1.11 to 3.39)**	**0.008**	94/46	**1.59 (1.15 to 2.20)**	**0.005**
	Metal and metal fumes	352/115	1.22 (0.97 to 1.55)	0.092	54/15	1.10 (0.63 to 1.91)	0.746	406/130	1.21 (0.96 to 1.51)	0.102
Irritants	All irritants	1011/302	1.16 (0.99 to 1.36)	0.056	596/218	**1.29 (1.09 to 1.54)**	**0.003**	1607/520	**1.21 (1.06 to 1.38)**	**0.004**
	Herbicides	46/19	1.54 (0.95 to 2.51)	0.083	26/12	1.48 (0.8 to 2.78)	0.215	72/31	**1.52 (1.02 to 2.25)**	0.038
	Insecticides	53/21	1.20 (0.74 to 1.96)	0.472	64/25	1.43 (0.93 to 2.21)	0.109	117/46	1.32 (0.94 to 1.84)	0.107
	Fungicides	64/29	1.55 (1.02 to 2.37)	0.046	59/21	1.3 (0.81 to 2.1)	0.282	123/50	**1.42 (1.02 to 1.99)**	0.035
	Indoor cleaning	472/148	1.22 (1.00 to 1.48)	0.046	291/121	**1.41 (1.13 to 1.78)**	**0.003**	763/269	**1.30 (1.09 to 1.53)**	**0.002**
	Bleach	372/144	**1.39 (1.14 to 1.71)**	**0.001**	179/62	**1.41 (1.09 to 1.89)**	**0.009**	551/206	**1.40 (1.16 to 1.67)**	**<0.001**
	Organic solvents	690/238	**1.28 (1.08 to 1.52)**	**0.005**	100/31	1.13 (0.77 to 1.65)	0.537	790/269	**1.26 (1.07 to 1.49)**	**0.006**
	Exhaust fumes	252/76	0.99 (0.74 to 1.31)	0.922	173/55	1.18 (0.86 to 1.61)	0.323	425/131	1.06 (0.84 to 1.34)	0.624

Continued

Table 2 Continued

Exposure group	Specific agent n=3200 used as a reference category	Low exposure *No asthma/asthma 2583/617 (Ref.)*	RR (95% CI)*	P value	High exposure *No asthma/asthma 2583/617 (Ref.)*	RR (95% CI)	P value	Ever exposure	RR (95% CI)	P value
Microbial exposures	All Microbial exposure	100/39	1.42 (0.99 to 2.01)	0.054	95/37	1.3 (0.89 to 1.89)	0.173	195/76	1.36 (1.03 to 1.79)	0.028
	Moulds, fungi	99/39	1.42 (1.01 to 2.02)	0.048	7/7	**2.26 (1.12 to 3.06)**	**0.006**	106/46	1.51 (1.09 to 2.09)	0.014
	Endotoxin	78/26	1.20 (0.78 to 1.85)	0.413	31/18	**2.02 (1.22 to 3.32)**	**0.006**	109/44	1.45 (1.04 to 2.03)	0.030
	Metal working fluids	17/8	2.00 (0.96 to 4.2)	0.068	64/21	0.99 (0.6 to 1.67)	0.986	81/29	1.19 (0.76 to 1.84)	0.452
Mites	All mites	148/67	**1.48 (1.12 to 1.94)**	**0.005**	89/29	1.18 (0.77 to 1.79)	0.448	237/96	**1.38 (1.09 to 1.75)**	**0.008**
	House dust mites	72/31	1.41 (0.96 to 2.06)	0.082	49/18	1.23 (0.69 to 2.16)	0.48	121/49	1.35 (0.97 to 1.87)	0.077
	Storage mites	66/31	1.53 (1.03 to 2.27)	0.034	----	----	----	66/31	1.53 (1.03 to 2.27)	0.034
	Plant mites	28/17	1.75 (1.04 to 2.95)	0.036	42/12	1.10 (0.59 to 2.07)	0.769	70/29	1.42 (0.94 to 2.14)	0.096
Highly reactive chemicals	All highly reactive chemicals	904/284	**1.24 (1.06 to 1.45)**	**0.007**	401/128	1.23 (1.00 to 1.52)	0.047	1305/412	**1.24 (1.08 to 1.42)**	**0.003**
	High level chemical	597/198	**1.32 (1.10 to 1.57)**	**0.003**	29/14	1.7 (0.99 to 2.91)	0.056	626/212	**1.34 (1.13 to 1.60)**	**0.001**
	Aliphatic amines	98/25	0.89 (0.55 to 1.42)	0.618	12/6	1.15 (0.51 to 2.61)	0.736	110/31	0.94 (0.62 to 1.43)	0.766
	Isocyanates	71/27	1.37 (0.9 to 2.1)	0.145	7/2	----	----	78/29	1.33 (0.89 to 1.99)	0.166
	Acrylates	105/36	1.30 (0.91 to 1.85)	0.792	----	----	----	105/36	1.30 (0.91 to 1.85)	0.15
	Epoxy resins	36/18	1.73 (1.07 to 2.83)	0.028	97/26	1.15 (0.75 to 1.74)	0.533	133/44	1.33 (0.96 to 1.85)	0.091
	Persulfate and henna	31/6	0.75 (0.27 to 2.1)	0.578	----	----		31/6	0.75 (0.27 to 2.10)	0.578
	Bleach	372/144	**1.39 (1.14 to 1.71)**	**0.001**	179/62	**1.41 (1.09 to 1.89)**	**0.009**	551/206	**1.40 (1.16 to 1.67)**	**<0.001**
	Organic solvents	690/238	**1.28 (1.08 to 1.52)**	**0.005**	100/31	1.13 (0.77 to 1.65)	0.537	790/269	**1.26 (1.07 to 1.49)**	**0.006**
Biocides	All biocides	559/185	1.21 (1.01 to 1.45)	0.039	267/98	**1.42 (1.12 to 1.79)**	**0.004**	826/283	**1.28 (1.09 to 1.49)**	**0.003**
	High level chemical	597/198	**1.32 (1.10 to 1.57)**	**0.003**	29/14	1.7 (0.99 to 2.91)	0.056	626/212	**1.34 (1.13 to 1.60)**	**0.001**
	Herbicides	46/19	1.54 (0.95 to 2.51)	0.083	26/12	1.48 (0.8 to 2.78)	0.215	72/31	**1.52 (1.02 to 2.25)**	0.038
	Insecticides	53/21	1.20 (0.74 to 1.96)	0.472	64/25	1.43 (0.93 to 2.21)	0.109	117/46	1.32 (0.94 to 1.84)	0.107
	Fungicides	64/29	1.55 (1.02 to 2.37)	0.046	59/21	1.3 (0.81 to 2.1)	0.282	123/50	**1.42 (1.02 to 1.99)**	0.035
	PAF† for any exposure	18.2% (16.9-19.5%)								

*Analyses were adjusted for age, sex, lifetime smoking, pack-years, socioeconomic status, weight change and atopy.
†For estimation of population-attributable fraction in this study sample, we first applied Poisson regression with robust estimation of error to establish relative risks, and then calculated attributable fractions using 'punaf' command in Stata (log (PUF)=log(1−PAF)). The value of p was generated using the Benjamini-Hochberg FDR correction method.
HMW, high molecular weight; LMW, low molecular weight; PAF, population attributable fraction; RR, rate ratio.

Table 3 Associations between cumulative occupational exposures and incidence of asthma

Cumulative exposure (units, per 10 years)	RR (95% CI)	P value
HMW sensitisers		
All HMW sensitisers	**1.11 (1.08 to 1.42)**	**0.009**
Animals	1.12 (0.96 to 1.29)	0.14
Fish/shellfish	0.92 (0.7 to 1.23)	0.56
Flour	0.96 (0.81 to 1.15)	0.67
Foods (milk, eggs)	1.06 (0.75 to 1.51)	0.74
Plants-related dusts	1.05 (0.91 to 1.22)	0.53
House dust mites	1.05 (0.91 to 1.23)	0.49
Storage mites	1.32 (0.91 to 1.89)	0.14
Plant mites	1.05 (0.90 to 1.21)	0.57
Enzymes	0.93 (0.62 to 1.40)	0.73
Latex	1.03 (0.98 to 1.07)	0.33
Textiles	0.89 (0.52 to 1.52)	0.66
LMW sensitisers		
All LMW sensitisers	1.05 (0.96 to 1.24)	0.091
Chemical disinfectants	1.07 (0.98 to 1.17)	0.15
Aliphatic amines	0.95 (0.77 to 1.18)	0.63
Isocyanates	1.00 (0,8 to 1.26)	0.97
Acrylates	1.05 (0.79 to 1.4)	0.74
Epoxy resins	0.98 (0.89 to 1.08)	0.71
Persulfate and henna	0.86 (0.67 to 1.10)	0.23
Wood dusts	1.13 (1.01 to 1.26)	0.035
Metal and metal fumes	1.05 (0.96 to 1.15)	0.26
Irritants		
All irritants	**1.19 (1.1 to 1.44)**	**0.003**
Herbicides	1.06 (0.90 to 1.25)	0.48
Insecticides	1.08 (0.98 to 1.19)	0.12
Fungicides	1.05 (0.94 to 1.18)	0.38
Indoor cleaning	**1.13 (1.08 to 1.29)**	**0.008**
Bleach	**1.05 (1.02 to 1.39)**	**0.01**
Organic solvents	1.01 (0.95 to 1.08)	0.66
Exhaust fumes	1.01 (0.96 to 1.06)	0.71
Microbial exposures		
Microbial exposure	1.03 (0.89 to 1.89)	0.193
Moulds, fungi	**1.07 (1.02 to 1.30)**	**0.007**
Endotoxin	**1.16 (1.05 to 1.28)**	**0.003**
Metal working fluids	1.00 (0.89 to 1.13)	0.94
Mites		
All mites	1.18 (0.77 to 1.79)	0.448
House dust mites	1.05 (0.91 to 1.23)	0.49
Storage mites	1.32 (0.91 to 1.89)	0.14
Plant mites	1.05 (0.90 to 1.21)	0.57
Highly reactive chemicals		
All highly reactive chemicals	1.13 (1.00 to 1.42)	0.047
High level chemical	1.07 (0.98 to 1.17)	0.15
Aliphatic amines	0.95 (0.77 to 1.18)	0.63
Isocyanates	1.00 (0,8 to 1.26)	0.97
Acrylates	1.05 (0.79 to 1.4)	0.74
Epoxy resins	0.98 (0.89 to 1.08)	0.71
Persulfate and henna	0.86 (0.67 to 1.10)	0.23
Bleach	**1.05 (1.02 to 1.39)**	**0.01**
Organic solvents	1.01 (0.95 to 1.08)	0.66
Biocides		
All biocides	**1.22 (1.12 to 1.59)**	**0.008**
High level chemical	1.07 (0.98 to 1.17)	0.15
Herbicides	1.06 (0.90 to 1.25)	0.48
Insecticides	1.08 (0.98 to 1.19)	0.12
Fungicides	1.05 (0.94 to 1.18)	0.38

*Analyses were adjusted for age, sex, lifetime smoking, pack-years, socioeconomic status, weight change and atopy. P-value was generated using the Benjamini-Hochberg FDR Correction method.
HMW, high molecular weight; LMW, low molecular weight; RR, rate ratio.

the release of various inflammatory substances, such as histamines and leukotrienes, leading to airway remodelling, responsible for asthmatic reactions.[35] Earlier studies have also found an increased risk of asthma due to cleaning agents.[7 33] A recent study also found irritant-induced asthma was more common in occupations where workers were exposed to ammonia released from sludge pipes, which may be attributed to subacute or long-term exposures.[36]

In our study, we observed a borderline association between low exposure to house dust mites, storage mites, plant mites, and ever exposure to storage mites with asthma incidence. This finding suggests that even low levels of exposure to these mites in work environments may contribute to asthma risk, particularly among sensitised individuals. While high exposure levels are more commonly associated with respiratory symptoms, studies also indicate that long-term, low exposure may stimulate immune responses leading to asthma, especially in susceptible individuals.[2 14] Occupations such as agriculture, food storage and textiles, where workers frequently come into contact with organic dust and plant materials, can harbour mites and promote their proliferation, leading to repeated exposure even at lower levels.[4] Moreover, storage mites have been increasingly recognised as occupational allergens, with sensitisation reported among agricultural and food processing workers.[23] These findings highlight the importance of addressing even low-level mite exposure in work environments and implementing preventive measures to minimise the risk of asthma.

The association between occupational exposure to irritants and asthma incidence might be related to distinct asthma phenotypes. The asthma phenotypes included clinical characteristics over the last 12 months, which reflected current exposure, rather than past history of exposures.[37] Therefore, stronger associations would be expected with more recent exposures compared with more distant exposures. However, a more comprehensive asthma definition, including inflammatory biomarkers and lung function, would be needed to study the temporal relationship between occupational exposures and asthma phenotypes. In addition, we could not distinguish asthma incidence due to occupational exposure from work-exacerbated asthma, and any observed associations may reflect both types of WRA. The diagnosis of WRA is complex and requires careful consideration of work history and clinical diagnostic methods.

The specific inhalation challenge (SIC) is often considered the gold standard for diagnosing occupational asthma, as it allows for controlled exposure to suspected asthmagens and can help differentiate between sensitiser-induced and irritant-induced asthma.[38] Sensitiser-induced asthma, triggered by allergens like flour dust and isocyanates, typically involves an immunological response with a latency period. Whereas irritant-induced asthma can occur immediately following high exposure to irritants, resulting in proinflammatory responses, increased lung permeability and remodelling of airway epithelium.[38 39] The use of diagnostic approaches is crucial in identifying WRA, as failure to distinguish between sensitiser and irritant-induced asthma accurately could impact the effectiveness of management strategies and prevention efforts. Improved diagnostic accuracy through SIC and other methods also facilitates earlier diagnosis and minimises long-term complications for affected workers.

Strengths and limitations

Strengths of our study included the use of a large general population-based sample from 13 industrialised countries using work histories, which enabled the calculation of cumulative exposures, which were not studied in earlier analyses of asthma incidence within ECRHS.[6 7] We also obtained detailed information about respiratory symptoms and estimated asthma in a cohort of people who had no previous history of diagnosed asthma.

One limitation is that asthma was based solely on questionnaire data rather than on an objective definition, such as bronchial hyperresponsiveness in a previous ECRHS2 analysis. Unfortunately, bronchial hyperresponsiveness was not measured in the ECRHS3 follow-up, limiting our analysis. There is a scarcity of empirical evidence supporting the validity of the definitions of asthma used in epidemiological research in comparison to those used in clinical practice.

We have attempted to minimise recall bias by using an updated general population-based OAsJEM with a high specificity to estimate exposures across all jobs. However, JEMs are susceptible to non-differential misclassification of exposures, which often arises due to the diversity of exposures present in each occupation, but this will only lead to imprecision but not bias the risk estimates.[40] Our modelling approach does lead to the limitation of multiple comparisons. We addressed this in part by setting the significance level of $p<0.01$ rather than a conventional $p<0.05$ cut-off, but we acknowledge that this is only a partial corrective. We also reported the corrected value of p using the Benjamini-Hochberg false discovery rate (FDR) correction method to account for multiple comparisons.

In conclusion, our study has shown that long-term occupational exposures to HMW sensitisers, LMW sensitisers, biocides, specific microbial exposures and irritants, including specific exposures such as wood dust, indoor cleaning agents and bleach were associated with an increased incidence of asthma. These exposures are still currently highly relevant, and some exposures are likely to become more prevalent and at higher exposure levels. Avoidance, reduction and control of exposures, early and complete identification of workers with symptoms, and accurate diagnosis of WRA is essential to prevent disease and manage it in those who do develop asthma.

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