Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II)

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Summary

Background The role of exposure to substances in the workplace in new-onset asthma is not well characterised in population-based studies. We therefore aimed to estimate the relative and attributable risks of new-onset asthma in relation to occupations, work-related exposures, and inhalation accidents.

Methods We studied prospectively 6837 participants from 13 countries who previously took part in the European Community Respiratory Health Survey (1990–95) and did not report respiratory symptoms or a history of asthma at the time of the first study. Asthma was assessed by methacholine challenge test and by questionnaire data on asthma symptoms. Exposures were defined by high-risk occupations, an asthma-specific job exposure matrix with additional expert judgment, and through self-report of acute inhalation events. Relative risks for new onset asthma were calculated with log-binomial models adjusted for age, sex, smoking, and study centre.

Findings A significant excess asthma risk was seen after exposure to substances known to cause occupational asthma (Relative risk=1·6, 95% CI 1·1–2·3, p=0·017). Risks were highest for asthma defined by bronchial hyper-reactivity in addition to symptoms (2·4, 1·3–4·6, p=0·008). Of common occupations, a significant excess risk of asthma was seen for nursing (2·2, 1·3–4·0, p=0·007). Asthma risk was also increased in participants who reported an acute symptomatic inhalation event such as fire, mixing cleaning products, or chemical spills (RR=3·3, 95% CI 1·0–11·1, p=0·051). The population-attributable risk for adult asthma due to occupational exposures ranged from 10% to 25%, equivalent to an incidence of new-onset occupational asthma of 250–300 cases per million people per year.

Interpretation Occupational exposures account for a substantial proportion of adult asthma incidence. The increased risk of asthma after inhalation accidents suggests that workers who have such accidents should be monitored closely.

Introduction

Occupational asthma can be caused by more than 250 chemicals and about 15% of adult-onset asthma can be attributed to occupational exposure to pulmonary irritants.[1–4] Few such exposures have been assessed in prospective population-based studies designed to establish the incidence of asthma, rather than the cross-sectional prevalence.

Surveillance systems have played an important part in the identification of high-risk occupations and thus the prevention of occupational asthma. However the scope of these systems varies widely. Surveillance systems in the UK, USA, Australia, Belgium, and France each reported estimates of 20–40 new cases per million people every year, and higher estimates were recorded in British Columbia (Canada), Sweden, and Catalonia (Spain).[5–12] Finland has the highest estimate of all surveillance and reporting systems, at 174 cases per million people per year for 1989–95.[13]

Exposure-specific studies about occupational asthma have focused on substances, of high and low molecular-weight—eg, flour, enzymes, isocyanates, and latex.[3,14] Acute inhalation exposures are associated with reactive airways dysfunction syndrome.[15–17] The population distribution of irritant-induced asthma and of asthma symptoms after inhalation accidents has thus far been investigated poorly.

A cross-sectional analysis of data from the European Community Respiratory Health Survey (ECRHS),[18] an international population-based study done in 1990–95, noted increased odds ratios of asthma in several occupations, including farming, painting, and cleaning; the population attributable risk due to occupational factors was estimated as 9% of all cases of asthma in adults. Our follow-up ECRHS study was done about one decade later; we aimed to estimate the relative and attributable risks of new-onset asthma in relation to occupations, work-related exposures, and inhalation accidents.

Methods

Patients and procedures

Participants were 20–44 years of age at the time of ECRHS in 1990–95 and were randomly selected from the local populations of 28 centres in 13 countries. People who were included in ECRHS were recontacted and invited to take part in our follow-up survey (ECRHS-II) done in

1998–2003. Ethical approval was obtained for each centre from the appropriate institutional ethics committee, and written consent was obtained from each participant.

Complete occupational history between ECRHS and ECRHS-II was obtained by a face-to-face interview for working participants. We excluded people who reported a history of asthma or respiratory symptoms (wheezing or whistling without a cold; ever having had asthma; having been woken by an attack of shortness of breath in the past 12 months) in ECRHS. These exclusions were intended to avoid confounding by baseline health status that could be associated with future risk of disease and risk factors.[19]

Asthma was defined by the participant either having an asthma attack or use of asthma medication in the 12 months before interview. Additionally, we tested bronchial hyper-reactivity by methacholine challenge in 4438 participants. Bronchial hyper-reactivity was defined as a reduction in forced expiratory volume in the first second (FEV_1) of 20% from the highest FEV_1. For a more specific definition of asthma, we combined the results of patient reports of asthma and bronchial hyper-reactivity test. Family history of asthma was defined as participants reporting either parent as having asthma. Patients with atopy in ECRHS were defined as those having specific serum IgE antibodies to at least one common inhalant allergen at concentrations of 0·35 U/mL or more as assessed by the Pharmacia CAP system (Pharmacia Diagnostics AB, Uppsala, Sweden).

	Population
Country	
Australia	299 (4 %)
Belgium	407 (6%)
Estonia	209 (3%)
France	910 (13%)
Germany	505 (7%)
Iceland	391 (6%)
Italy	429 (6 %)
Norway	473 (7%)
Spain	1082 (16%)
Sweden	1127 (17%)
Switzerland	334 (5%)
UK	520 (8%)
USA	151 (2 %)
Sex	
Male	3323 (49%)
Female	3514 (51 %)
Smoking status†	
Never smoked	2981 (44%)
Ex-smoker	1926 (28%)
Current smoker	1858 (27%)
Parental asthma	667 (10%)
Age (years)	42·83 (7·14)

Data are n (%) or mean (SD). *Participants in ECRHS who did not have asthma or other respiratory symptoms (n=6837). †Data missing for 72 participants.

Table 1: **Characteristics of the study population***

We assessed occupational exposures with a list of occupations that potentially have high risk of asthma, an asthma-specific job-exposure matrix incorporating an additional assessment of exposed jobs by experts, and participants' reports of inhalation accidents. Occupational history between surveys included all jobs done for at least 3 months. Occupations were classified[20] by experts in each country with a structured protocol. Participants who worked exclusively in professional, clerical, or administrative jobs between surveys were classified as having low-risk occupations and were the reference group.

Occupations were linked to an asthma-specific job-exposure matrix.[21] The asthma job-exposure matrix included 18 substances characterised as being high-risk. Seven of the substances were of high molecular-weight (eg, latex, flour) and contained proteins that caused IgE-mediated sensitisation. Six substances were low molecular-weight (eg, isocyanates, anhydrides, and sensitising drugs) that are linked to work-related asthma but have not been consistently associated with IgE-mediated allergy. The matrix also included bioaerosols (moulds, endotoxins) and four mixed environments (metalwork fluids, irritant gases or fumes, textiles, and agriculture with exposure to organic particles). The job-exposure matrix has higher specificity than sensitivity because occupations are classified as exposed only if the probability of exposure is high. The occupational history of all participants exposed to these substances was assessed by trained national experts who were blinded to case-control status.

Exposure to inhalation accidents was established by the question "Since the last survey have you been involved in an accident at home, work, or elsewhere that exposed you to high levels of vapours, gas, dust, or fumes?" Participants who had a positive response to this question were then asked further questions about symptoms and exposures.

Statistical analysis

Relative risks for asthma were calculated with log-binomial models adjusted for sex, age, smoking status, and study centre. In a stratified analysis we assessed relative risks by smoking status, presence of atopy, and bronchial hyper-response status at ECRHS, and sex and parental asthma status. We tested differences in relative risk between categories by introduction of an interaction term in regression models. We did a meta-analysis to test heterogeneity by region. For estimation of population-attributable risks we first applied Poisson regression with robust estimation of error to establish relative risks, and then calculated attributable risks.[22] For the estimation of asthma incidence we calculated person-years of observation for the participants who were free of respiratory symptoms at ECRHS. We multiplied the observed incidence by the estimated population attributable risk to calculate an occupation-attributable fraction. Statistical analyses were done with Stata SE 8.2 (Stata Corporation, College Station, TX, USA).

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	Group total	Cases of asthma (%)	Relative risk*	95% CI	Population attributable risk	95% CI
Participant has had asthma attack or used asthma medication in past 12 months						
Occupation						
Reference group	4143	74 (1·8%)	1	n/a	n/a	n/a
High-risk occupations	1181	37 (3·1%)	1·69	(1·14–2·52)	14%	(2–24)
Job-exposure matrix						
Not exposed	5433	93 (1·7%)	1	n/a	n/a	n/a
Exposed	1355	40 (3·0%)	1·58	(1·09–2·29)	11%	(1–20)
Participant has had asthma attack or used asthma medication in the past 12 months and has had bronchial hyper-reactivity†						
Occupation						
Reference group	2433	19 (0·8%)	1	n/a	n/a	n/a
High-risk occupations	703	14 (2·0%)	2·55	(1·27–5·10)	26%	(2–44)
Job-exposure matrix						
Not exposed	3173	22 (0·7%)	1	n/a	n/a	n/a
Exposed	821	16 (2·0%)	2·40	(1·25–4·60)	23%	(1–40)

High-risk occupations=baking, plastics or rubber industries, printing, chemical processing, spray printing and other painting, nursing, hairdressing, electrical processing, welding, metal works, agriculture and forestry, cleaning and caretaking. Reference group=professional, clerical, and administrative jobs. Participants included in neither the reference or high-risk group were excluded. *Adjusted for age, sex, smoking status, and centre. †Data for bronchial hyper-reactivity and asthma available for 4438 participants, of whom 4001 are included in the analysis. Also excluded were 437 participants who had positive bronchial hyper-reactivity but no symptoms or vice versa.

Table 2: **Incidence of asthma and occupation**

Role of the funding source

No sponsor of the study had a role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

15716 people took part in the original ECRHS study, of those 9175 responded to our ECRHS-II questionnaire. No differences were seen in the prevalence of occupational exposure associated with asthma risk at baseline between eligible people who responded and those who did not respond (p=0·54). Median time between completion of ECRHS and ECRHS-II was 8·9 years. 8476 participants took part in face-to-face interviews about occupational history; of these, 1639 were excluded because they had reported symptoms of asthma in the first ECRHS study. Our analysis was therefore restricted to 6837 participants who reported neither respiratory symptoms nor a history of asthma in ECRHS (table 1).

Prevalence of smoking was higher in the 1639 ineligible people who were excluded (43% current smokers) compared with eligible participants (32% current smokers, p <0·0001).

Of participants reporting an asthma attack, 67% also reported use of medication. 1472 of 5742 (25·6%) tested participants had atopy.

The relative risk for new onset asthma associated with employment in any predefined high-risk occupation was 1·69 (95% CI 1·1–2·5). This relative risk was similar to that for the association of exposure to agents based on the job-exposure matrix analysis (table 2) . Relative risks were higher for asthma defined by a report of asthma symptoms with bronchial hyper-reactivity with significant (p=0·008) excess relative risk around 2·5 for both high-risk occupations and asthma-related exposures in the job-exposure matrix.

We also measured timing of exposure in relation to first asthma attack; exclusion of employment periods in a high-risk occupation after the first asthma symptoms gave nearly identical results to those shown in table 2. An analysis of participants who reported use of asthma medication only (relative risk [RR]=1·6, 95% CI 0·96–2·7, p=0·07 for high-risk occupations; 1·9, 1·2–2·9, p=0·008 for job-exposure matrix) also gave very similar results to those shown in table 2 for asthma attacks or asthma medication. Finally, an analysis limited to participants who reported asthma attacks or use of medication, but who did not have bronchial hyper-response gave lower relative risks than those in table 2 (1·5, 0·8–2·9, p=0·253 for high-risk occupations; 1·2, 0·6–2·4, p=0·552 for job-exposure matrix).

Table 3 shows analysis by subcategories of exposure in the job-exposure matrix and by occupational group. Exposure to high-molecular-weight agents was associated with a higher incidence of asthma compared with non-exposed participants, and an increase was also seen for exposure to low-molecular-weight agents. Among the most common specific exposures, cleaning agents, reactive chemicals (eg, isocyanates, anhydrides, reactive dyes, glues, and biocides), and exposure to latex were associated with a higher than 1·5 relative risk. Among major occupational groups, nurses and cleaners had the highest relative risks for new onset asthma. Relative risks higher than 1·5 were seen for occupational groups not shown in table 3 (bakers and spraypainters), but these estimates were based on small numbers, and thus might not be robust. Other occupations at high risk of new-onset asthma were all ones that have traditionally been identified in surveillance systems, including spray-painting, baking, and agriculture.

The figure shows relative risks for new-onset asthma due to exposure to substances in the workplace as assessed by the job-exposure matrix and stratified by key risk factors. Men and women had similar relative risk of new-onset asthma; people with atopy at ECRHS had a higher relative risk than those who did not; people who had never smoked had a higher relative risk than those who were ex-smokers or still smoking at ECRHS; a parental history of asthma was associated with a far higher relative risk than no parental history of asthma; and bronchial hyper-reactivity at ECRHS was associated with a slightly higher risk than no bronchial hyper-response. A significant difference was seen only between people with atopy and those without (p=0·019).

Relative risks of asthma associated with exposures assessed by the job-exposure matrix were highest in southern Europe (Italy, Spain, 25 cases of new-onset

asthma in total; RR 2·3, 95% CI 1–15·1;), low in countries in the central latitudes of Europe (Belgium, Germany, France, Switzerland, Estonia, and the UK, 51 cases of new-onset asthma in total; 1·8, 1·0–3·3;), and lowest in northern countries (Norway, Sweden, and Iceland, 49 cases of new-onset asthma in total; 1·3, 0·7–2·3;) and the two non-European countries (USA, Australia, 8 cases of new-onset asthma in total; 1·2, 0·2–9·0;). However, the differences in risk between geographical regions were not significant (p=0·66).

Table 4 shows details of inhalation accidents, in the time between ECRHS and this study, that were associated with an increased relative risk of incident asthma. Notably, the relative risk of asthma was increased in participants who had an inhalation accident, irrespective of whether they had immediate symptoms. Many different accidents were reported including fire at docks with smoke inhalation, ammonia leak from tanks in factory, mixing two household cleaners, inhalation of pure nitrogen through a fume cupboard for 4 or 5 seconds. Of 112 participants who provided detailed descriptions of the exposure event, 18 events were due to fires (RR for asthma=3·1, 95% CI 1·1–8·7), 11 to mixing cleaning products (2·5, 0·7–9·0), and 83 to spills, explosions, or other exposures to irritants (2·0, 0·9–4·2).

The population attributable risk for occupational exposures ranged from 10% to 25% of cases of new-onset asthma and was highest for asthma defined by symptoms or medication use, and bronchial hyper-reactivity testing (table 2). The highest population attributable risk was seen in southern Europe (23%, 95% CI 0– 43), with lower risk in central (12%, 0–25) and northern Europe (6%, 0–22).

134 participants in all had new asthma symptoms, giving an overall estimate for incidence of asthma of 2·2 per 1000 person-years. Of 4438 participants who had complete bronchial hyper-reactivity (at ECRHS-II) and questionnaire data, 426 had bronchial hyper-reactivity. Of those, 38 reported new asthma symptoms, a rate of 0·99 cases per 1000 person-years. Application of these rates to the corresponding attributable risks for each of the two definitions, results in an estimated 248–303 new cases of asthma per million people per year, attributable to occupational exposures.

Discussion

Our incidence data suggest that exposure to substances in the workplace causes more than 10% of all cases of adult-onset asthma. Occupations with the highest risk include nursing and cleaning. The highest risks were recorded for high-molecular-weight agents, but exposure to low-molecular-weight agents and irritants such as isocyanates, latex, and cleaning products also contribute substantially to the occurrence of occupational asthma.

Participants who had atopy at ECRHS and parental history of asthma were at highest risk of occupational asthma. Analysis by geographical region showed that

	Cases of asthma†	Relative risk‡ (95% CI)
Exposures (grouped)§		
High-molecular-weight	23/628 (3·7%)	1·75 (1·09–2·80)
Low-molecular-weight	27/913 (3·0%)	1·58 (1·03–2·43)
Mixed exposures	5/209 (2·4%)	1·43 (0·58–3·54)
Not exposed	93/5433 (1·7%)	1 (n/a)
Exposures (specific)§		
Bioaerosols	3/72 (4·1%)	2·91 (0·91–9·26)
Mites	4/81 (4·9%)	2·52 (0·91–6·99)
Agricultural	4/118 (3·4%)	1·93 (0·71–5·24)
Cleaning products	15/410 (3·7%)	1·80 (1·01–3·18)
Reactive chemicals	15/436 (3·4%)	1·72 (0·99–3·01)
Latex	17/489 (3·5%)	1·53 (0·90–2·61)
Not exposed	93/5433 (1·7%)	1 (n/a)
Occupations§		
Printing	2/56 (3·6%)	2·37 (0·59–9·46)
Woodworking	3/77 (3·9%)	2·22 (0·69–7·17)
Nursing	14/291 (4·8%)	2·22 (1·25–3·96)
Agriculture and forestry	4/131 (3·1%)	1·85 (0·67–5·12)
Cleaning and caretaking	12/358 (3·4%)	1·71 (0·92–3·17)
Electrical processors	4/153 (2·6%)	1·56 (0·56–4·33)
Reference¶	74/4143 (1·8%)	1 (n/a)

*Risky occupations and specific exposures are those with a relative risk greater than 1·5. †Asthma defined as having had an asthma attack or taking asthma medication in the past 12 months. ‡RRs adjusted for age, sex, smoking status, and centre. §Participants can have been exposed to more than one agent and employed in more than one occupation. ¶Reference group includes professional, clerical, and administrative occupations.

Table 3: **Occupations and exposures* at high risk of asthma**

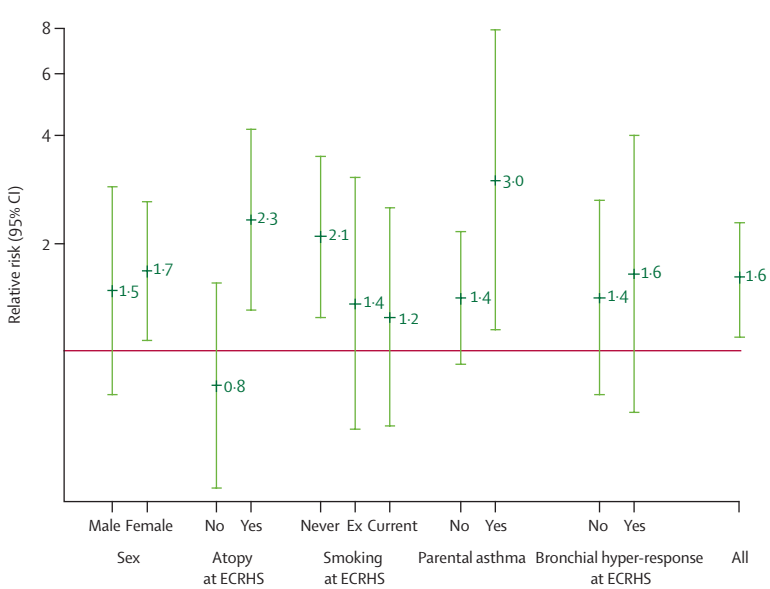

Figure: **Relative risks for new-onset asthma in people exposed to substances in the workplace**
Participants with any job-exposure matrix exposures compared with unexposed individuals, overall and grouped by sex, atopy, smoking status, parental asthma history, and bronchial hyper-reactivity. Relative risks were calculated for each group and were adjusted for age, study centre, sex (in analyses other than those grouped by sex), and smoking status (in analyses other than those grouped by smoking status).

occupational asthma is present in all regions, with highest risks in southern European countries. Finally, we showed that inhalation accidents, in both occupational and environmental scenarios, contribute substantially to new-onset asthma.

Our estimate of occurrence of new-onset asthma of 250–300 cases per million people is higher than estimates of the incidence of occupational asthma derived from traditional surveillance systems. Estimates from these systems range from 20–30 cases per million people in countries such as France, the UK, and the USA,[5] to around 200 cases per million people in Finland, which probably has the most complete surveillance scheme available for detection of occupational asthma.[13] Our results suggest that the true incidence of new-onset asthma in many industrialised societies is probably higher than is detected at present. Differences in estimates from surveillance programmes are probably also due to variation in the causes of occupational asthma and safety controls on these causes. These differences were also documented in ECRHS in the geographical analysis of relative risks of occupational asthma.

Cleaning was identified as a high-risk occupation in ECRHS[18] and a high risk of occupational asthma in cleaners has been noted in several populations.[13,16,17,23] Additionally, nursing and exposure to latex were associated with occupational asthma in the 1990s. Several cross-sectional studies have reported sensitisation to latex and increased risk of asthma in nurses.[24] However, evidence from prospective investigations is inconsistent.[25] Nurses could be exposed to sensitising substances, respiratory allergens, and irritants including sterilisers and disinfectants such as glutaradelhyde or bleach. In the early 1990s nurses' exposure to latex increased through use of gloves and other protective equipment, although this exposure was probably reduced in some countries in the late 1990s due to reductions in the amount of latex used in these items.

	Cases of asthma (%)	Relative risk* (95% CI)
Participant has had asthma attack or used asthma medication in past 12 months		
No inhalation event	114/5977 (1·9%)	1 (n/a)
Inhalation event	10/323 (3·1%)	1·60 (0·82–3·14)
No inhalation event or asymptomatic inhalation event	118/6121 (1·9%)	1 (n/a)
Symptomatic inhalation event	4/136 (2·9%)	1·56 (0·58–4·19)
Participant has had asthma attack or used asthma medication in past 12 months and has bronchial hyper-reactivity		
No inhalation event	33/3600 (0·9%)	1 (n/a)
Inhalation event	3/201 (1·5%)	1·31 (0·38–4·53)
No inhalation event or asymptomatic inhalation event	33/3692 (0·9%)	1 (n/a)
Symptomatic inhalation event	3/78 (3·8%)	3·33 (1·00–11·13)

*Adjusted for age, sex, smoking status, occupational exposure (job-exposure matrix), and centre.

Table 4: **New-onset asthma and inhalation events**

Inhalation accidents were associated with increased risk of new-onset asthma but no widely applied guidelines exist for the follow-up of people who have an inhalation accident. These findings suggest a need for follow-up that accounts for the increased risk of developing asthma. Several studies assessed high-intensity inhalation accidents and unequivocally associated them with irritant-induced asthma. Evidence is accumulating about the effects of irritant exposures on occurrence of asthma through studies in specific occupations such as cleaning or pulp and paper industries. Additionally, evidence is growing for the importance of repeated moderate exposures to irritants in the development of asthma.[26]

Strengths of our study include that we assessed new-onset occupational asthma in a large randomly selected population in 13 industrialised countries. We also obtained detailed information about respiratory symptoms, and our estimates were made with data from a cohort of people who participated in ECRHS and had no respiratory symptoms or history of asthma at that time.

ECRHS is a large prospective population-based study, but even in this study, analyses of specific occupations and exposures are based on small numbers and do not allow assessment of duration of exposure for most agents. The inadequate power does not affect worldwide assessment of grouped exposures, such as high-molecular-weight agents, or investigation of the most common occupations at risk, such as nursing, but does affect the precision of more specific exposures and uncommon occupations. A second limitation of our study is that the application of the job-exposure matrix might result in some degree of non-differential misclassification that would attenuate any effect.[21] To some extent this bias has been controlled because of the specificity of the asthma job-exposure matrix further revision of exposure estimates by national experts.

In industrialised populations, occupational asthma is the most frequently reported occupational resipratory disease. Findings from this large international study suggest that the frequency of this disease is systematically underestimated. The heightened asthma risk after inhalation accidents suggests that workers having such accidents should be monitored closely. Reduction of exposure, early and complete identification of workers with symptoms suggestive of asthma, would help prevent disease and effectively manage workers who develop occupational asthma.[27]

Contributors

MK, J-PZ, DJ, HK, LL, KR, KT, GB, PDB, AD-H, NK, BL, MCM, NM, DN, MO, FP, SV, MvS, IU, GW, JS, and JMA designed the study. DJ, KT, GB, NK, BL, NM, FP, MvS, IU, and JS were responsible for data collection in local centres. SK, J-PZ, LL, KR, GB, AA, AD, and MH were responsible for exposure assessments. EP managed and analysed the data. All authors participated in the interpretation and presentation of the results.

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Conflict of interest statement

We declare that we have no conflict of interest.

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