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Increased asthma risk was associated with occupational exposure to moderate levels of irritants in a large Estonian study.

ABSTRACT

Occupational exposures importantly contribute to asthma morbidity. The role of low/moderate level irritants exposures remains unclear. We aimed to determine which occupational exposures are associated with asthma in an Eastern European country with low asthma prevalence.

The Estonian Genome Center collected data in 50,077 adults (2002-2011). Asthma was assessed through a questionnaire regarding diagnosed diseases, current health status, and medication. Exposures to 22 agents during the current and longest held jobs were estimated using an asthma-specific job-exposure matrix.

Analyses included 34,015 subjects (aged 18-65, 67.0% women), of which 1,209 (3.6%) reported asthma (608 with physician-confirmed diagnosis). After adjusting for age, sex, and smoking habits, lifetime occupational exposure to known asthmagens (20.4%) was significantly associated with physician-diagnosed asthma (OR(95% CI): 1.28(1.03-1.59)), especially high molecular weight agents (flour: 2.36(1.31-4.27), animals: 1.62(1.00-2.60)). Exposure to low/moderate level of irritants (17.4%) was associated with physician-diagnosed asthma (1.88(1.48-2.37)). More pronounced associations were observed in subjects reporting current treated asthma.

Beyond confirming the effect of known asthmagens (well-known mostly from observations in Western countries), the results evidenced a role of low/moderate exposure to irritants. This finding, observed in a country with a low prevalence of asthma and atopy, provides new insight in the understanding of asthma heterogeneity.

INTRODUCTION

There is a growing interest in asthma due to non-allergic mechanisms[1] in the context of the understanding of asthma heterogeneity.[2] Epidemiological studies have shown that less than one half of asthma cases would be related to atopy or attributable to allergen exposures,[1] consistently with findings from mechanistic or clinical approaches.[2, 3]

Occupational asthma is a good model to study asthma in general.[4] More than 400 agents have been recognized to cause occupational asthma, and new agents are reported each year.[5, 6] Occupational asthma is classified into two different types according to the causing agents and the underlying mechanisms. Most occupational asthmagens are low or high molecular weight sensitizers, inducing asthma through immunologic mechanisms.[5, 7] IgE-mediated mechanisms have been proven for most high and some low molecular weight agents.[5, 7] The second type of occupational asthma, referred to as "nonimmunologic occupational asthma"[5] or "irritant induced asthma",[8] has first been described in relation to a single exposure to high concentrations of irritants. The potential role of repeated low to moderate level of exposure to irritant in occupational asthma is receiving growing attention.[8]

As in other Eastern European countries formerly part of the Soviet Union,[9, 10] a lower prevalence of atopy and asthma was observed in Estonia compared to Western Europe in the 1990's.[11, 12] The degree of westernization, and associated environmental and lifestyle-related exposures,[9–11, 13] were suggested to explain these differences. However, in contradistinction with most other countries, the rate of asthma and allergy has remained low in Estonia.[14] Though the transition context in Eastern European countries provides interesting opportunities to improve understanding of asthma determinants and heterogeneity, few data have been reported in the last decade, especially in adults. Similarly, most - though

not all - epidemiological studies of work-related asthma have been conducted in populations of westernized countries,[15–17] while the development of a worldwide perspective in work-related lung disease is needed.[18]

In 2001, a large-scale (n~50,000) population-based study was set up by the Estonian Genome Center of University of Tartu (EGCUT).[19] The primary purpose of this project was genetic research for human health, but asthma and occupations were also investigated.

Taking advantage of the health and environmental data collected in EGCUT, we aimed to determine whether asthma is associated with occupational exposure to (1) well-known high and low molecular weight asthmagens and (2) irritants, in this Estonian population.

MATERIALS AND METHODS

Study population

The study participants come from the population-based biobank of EGCUT.[19, 20] Since 2002, the EGCUT collects genotypic, health and lifestyle data in adults living in Estonia. Participants were recruited by general practitioners or nurses/physicians in hospitals, with a random selection among regular visiting patients or individuals willing to join the cohort after hearing about it through a multimedia campaign. In October 2011, the cohort included 50,077 adults. Only the subjects aged 18-65 years old were included in the analyses (Figure 1). Subjects who had never worked, or with missing/imprecise job code were excluded.

The project is conducted in accordance to the Estonian Gene Research Act and all participants have signed an informed consent form.

Variables studied

A computer-assisted interview was conducted at the doctors' office by general practitioners or other medical personnel. Past diseases ("Which kind of disease have you been diagnosed with?") were classified according to the International Classification of Diseases (ICD-10). Diagnosis reliability level (confirmed by a physician, probable, or possible), current health status and medication (Anatomical Therapeutic Chemical (ATC))[21] used in the last two months were collected. The current and longest held jobs were recorded according to the International Standard Classification of Occupation 1988 (ISCO-88).

Asthma definitions

Ever asthma was determined by the report of a diagnosis of asthma (ICD-10: J45). Subjects with asthma diagnosis confirmed by a physician were classified as having *physician-diagnosed asthma*. Subjects with asthma who answered "yes" to the question "Do you have asthma now?" were classified as having *current asthma*. Among subjects with current asthma, those who reported asthma treatment (ATC: R03) in the last two months were classified as having *current treated asthma*.

Occupational exposure

The job codes were linked to estimates of exposures to 22 agents using an asthma-specific Job-Exposure Matrix (JEM).[22] Exposures to (i) 18 known asthmagens, and (ii) 4 work environments with low/moderate level of exposure to irritants, or with low level of exposure to chemicals or allergens, were evaluated. The category "low/moderate level of exposure to irritants" refers to jobs unlikely to involve high concentration or "peak" exposure to irritants (known to induce asthma), but potentially involving repeated exposure to "common" levels of

irritants (not considered at risk for asthma when the JEM was set up [end of the 1990s]). The category “low level of exposure to chemicals or allergens” refers to jobs with potential exposure to know asthmagens, but at levels expected to be too low to cause occupational asthma. Exposure (yes/no) to each of the 22 agents was evaluated for the current and longest held jobs. The maximum exposure level over the current and longest held jobs was used to approximate lifetime exposure for each agent (for simplicity, it will be referred to as "lifetime exposure" in the next sections).

A list of occupations potentially at risk for asthma was also derived from previous classifications.[23] Current job titles were grouped into 58 categories and compared to a reference group of administrative and service jobs (see online supplement).

Statistical analyses

Associations with asthma outcomes were studied for (i) lifetime and current exposure using the broad categories of the asthma JEM (non-exposed, exposed to known asthmagens, only exposed to low level of irritants or chemicals/allergens), (ii) lifetime exposure to the specific agents of the asthma JEM, and (iii) the current job category. In all analyses, the exposure category “low level of irritants or chemicals/allergens” and its subcategories include only jobs not concurrently classified as exposed to known asthmagens. Analyses were performed for specific agents or job categories for which at least five subjects with asthma were exposed [22]. Associations were evaluated by logistic regressions, adjusted for age, sex, and smoking habits (never, ex- or current smokers), using SAS 9.1. Correction for multiple testing, using the False Discovery Rate approach (R package “p.adjust”), was applied to the analysis of job categories.

RESULTS

Demographic characteristics

Among the 34,015 subjects selected for the analyses (mean age: 41.5 years, 67.0% women, Table 1), asthma was reported by 1,209 subjects (3.6%). Among them, 50.3% (n=608) had physician-diagnosed asthma, 73.9% had current asthma and 51.9% reported use of asthma medication in the last 2 months. Subjects with asthma were less often employed at the interview (76.0%) than subjects without asthma (81.2%, $p<0.001$) and the difference remained significant after adjusting for age and sex. Among subjects not currently working, subjects with asthma were more often disability pensioners (35.2%) than subjects without asthma (24.0%, $p=0.01$ after adjusting for age and sex).

Exposure to asthmagens and irritants

Twenty percent of the subjects had ever been exposed to known asthmagens (most frequent exposures: latex (5.4%), highly reactive chemicals (4.3%), textile production (4.2%), agriculture (3.8%), see Figure E1 in the online supplement). Twenty-seven percent of the subjects had ever been exposed to low level of irritants or chemicals/allergens (and not to known asthmagens): 17.4% were exposed to low level irritant exposures (combustion particles or fumes, environmental tobacco smoke, or irritant gases or fumes) and 16.3% to low level of chemicals/allergens.

Women were significantly more often exposed to High Molecular Weight (HMW) agents and mixed environment than men (13.6% *vs.* 3.6% and 10.6% *vs.* 3.6% respectively), while men were more often exposed to irritant peaks (6.5% *vs.* 0.5%), low level irritant exposures (at least one of the three groups: 40.5% *vs.* 11.2%), and low level of exposure to chemicals/allergens (21.8% *vs.* 17.3%).

Occupational exposures and asthma outcomes

Lifetime exposure to known asthmagens overall was more frequent among subjects with asthma than among those without asthma, although the association did not reach significance (21.8% *vs.* 20.4%, p=0.08; adjusted OR=1.12 (0.97-1.30), Figure 2a). However, a significant positive association was observed with physician-diagnosed asthma (adjusted OR=1.28 (1.05-1.58)). Higher and significant ORs were observed for those with current physician-diagnosed asthma and current treated physician-diagnosed asthma.

Lifetime exposure to low level of irritants or chemicals/allergens was more frequent among subjects with asthma than among those without asthma (29.0% *vs.* 27.1%, p=0.06; adjusted OR=1.19 (1.03-1.37). More pronounced and significant associations were observed for physician-diagnosed asthma, current physician-diagnosed asthma and current treated physician-diagnosed asthma, with ORs increasing across asthma definitions from 1.76 to 1.99 (Figure 2b). Consistent results with higher ORs were observed in analyses of current occupational exposure.

A significant association between physician-diagnosed asthma and lifetime occupational exposure to known asthmagens was observed in women (1.33 (1.05-1.68)) and not in men (1.14 (0.68-1.91), p interaction=0.53). The associations observed for low level of exposure to irritants or chemicals/allergens were similar in men and women (see tables E2, E3 in the online supplement).

Exposure to known asthmagens and asthma outcomes

The main analysis evaluating the associations between exposure to each specific asthmagens and asthma was focused on lifetime occupational exposure and physician-diagnosed asthma

(Table 2). Among known asthmagens, significant associations were observed for three HMW agents (flour, enzymes, animals and bioaerosols) and two mixed environments (agriculture, textile production). For Low Molecular Weight (LMW) agents, ORs were close to or below the unity.

These results were confirmed using different definitions of occupational exposure and asthma outcomes. For the associations between current exposures and current treated physician-diagnosed asthma, higher ORs were observed: 1.82 (1.22-2.70) for exposure to HMW agents, and 2.52 (1.65-3.84) for mixed environment (ORs reaching 3.81 and 3.44 for exposure to animals and agriculture respectively). An additional significant association was observed for exposure to latex (1.67 (1.03-2.71)). Overall, ORs remained similar for exposure to LMW agents but a suggestive (non-significant) association was observed for exposure to industrial cleaning/disinfecting products (1.80 (0.83-3.91)).

In gender-stratified analyses (see Tables E2 and E3 in the online supplement), associations were observed for exposure to animal antigens in men, and for exposure to flour, enzymes, work in textile production and in agriculture in women.

Low level of exposure to irritants or to chemicals/allergens (and no exposure to known asthmagens) and asthma outcomes

A significantly increased risk of physician-diagnosed asthma was observed in subjects ever exposed to low level of chemicals/allergens, and to combustion particles/fumes and irritant gases/fumes (Table 2). Similar results were observed in men and women (see Tables E2 and E3 in the online supplement). ORs greater than 2 were observed considering current exposures and current treated physician-diagnosed asthma: 2.63 (1.96-3.53) for low level of

chemicals/allergens, 2.86 (1.73-4.73) for combustion particles/fumes and 2.83 (1.96-4.09) for irritant gases/fumes.

Associations between asthma and low level of exposure to irritants (combustion particles/fumes, irritant gases/fumes or environmental tobacco smoke) were examined specifically. The ORs were respectively 1.88 (1.48-2.37) and 2.86 (2.08-3.94) for the associations between lifetime exposure and physician-diagnosed asthma, and between current exposure and current treated physician-diagnosed asthma. After excluding those with concurrent exposure to low level of chemicals/allergens, ORs remained high and significant (respectively 1.82 (1.34-2.45) and 2.44 (1.57-3.80)). The most frequent occupations with low level of exposure to irritants were: building workers, heavy truck/lorry/car/bus drivers, carpenters/joiners and cabinet makers, machinery mechanics (jobs with >90% male workers); cleaning workers in offices or hotels (job with >90% female workers) and waiters/bartenders (~60% female workers).

Job categories

Among the 58 job categories classified as potentially at risk for asthma, 20 jobs categories were analyzed (≥5 subjects with asthma exposed). Significant and positive associations (Table 3) were observed with current physician-diagnosed asthma for 13 job categories (all remained significant after correction for multiple comparisons). Among the job categories associated with asthma, six were in large majority held by women (>80%), including cleaning and health-related occupations, textile workers, hand packers and dairy/livestock producers; while five job categories were mostly held by men (>90%), including mechanical workers, electricians, motor vehicle drivers, and building workers. A positive association was also

observed for wood treaters and for "other craft and trade workers" (~45% female workers). A significant negative association with asthma was observed for teaching professionals.

Population-attributable risk

The results from the current study yield a Population-Attributable Risk (PAR) estimate of 4.7% for known asthmagens and physician-diagnosed asthma (using the formula [(OR-1)/OR*exposure frequency$_{cases}$]). For low level of exposure to irritants or chemicals/allergens and physician-diagnosed asthma, the estimated PAR was 15.8%. Considering exposure to any of the three categories of low level exposure to irritants only, the PAR was 6.7%.

DISCUSSION

In this large study conducted in subjects from Estonia, the role of known occupational asthmagens, mainly HMW and mixed environment was evidenced, extending observations mostly from Western countries of occupational determinants of asthma. Importantly, the still-disputed role of moderate exposure to irritants was clearly evidenced in subjects living in a country with a low prevalence of asthma and atopy.

The EGCUT cohort was not specifically designed for research on respiratory health, and asthma definition was based on a general health questionnaire. It has been suggested that differences in diagnostic practices in relation to the influence of the former Soviet Union partly explains the lower prevalence of physician-diagnosed asthma in Estonia compared to western European countries.[24] However, economic, environmental and lifestyle conditions are evolving rapidly in Estonia since the fall of the socialist system [25]. Increased asthma awareness and changes in diagnostic procedures have been emphasized, and an increase in the

prevalence of physician-diagnosed asthma has already been observed in children in 2001-2002.[25] The EGCUT started in 2002, and nearly three-quarters of the participants were recruited after 2008, i.e. more than 15 years after the end of the Soviet era and after the entry of Estonia into the European Union (2004). Nonetheless, asthma may remain under-diagnosed in our population,[24] leading to a potential misclassification bias. On the other hand, one strength of the current study was the relatively precise data on asthma (diagnosis confirmation by a physician, current disease status, use of asthma medication) for such a large population. Our results were systematically confirmed, with increasing ORs, when using more stringent definitions of asthma outcomes. Finally, women, younger/middle-aged and highly educated subjects were over-represented in this cohort compared to the Estonian population. However, the EGCUT main objective being known as the study of genetic determinants of health, it is unlikely that occupational health had influence on participation leading to major bias.

Occupational exposures were evaluated using an asthma-specific JEM, designed based on experts' knowledge at the end of the 1990s, to link job codes to exposure to agents potentially at risk for asthma or respiratory health, and already used in several previous studies and populations.[26] This JEM was not specifically designed for Estonia and an expert re-evaluation step, recommended to improve exposure assessment (but likely to be more important in small studies), could not be applied here as information on jobs was limited. However, the JEM has already been used in a large study without the expert step.[23] The elevated ORs observed for well-known HMW allergens and for work environments with multiple hazardous exposures (agriculture, textile production) confirm the relevance of the JEM in this population. On the other hand, no association was suggested for exposure to LMW agents. Studying job categories is a more sensitive and exploratory approach,

complementing the JEM. For instance, for exposures to cleaning/disinfecting products and to wood dust, no associations were observed with the JEM, while increased asthma risks - consistent with existing literature[7, 27, 28] - were suggested through the analysis of job categories. For mechanics, electricians or hand packers, the observed associations were similar to previous studies[16, 28], though the specific hazardous agent(s) remain unknown. A refined exposure assessment taking into account the specificities of exposure conditions in Estonia, and considering relevant exposure windows in relation to the historical context, may be useful in future studies.

In the current analysis, we also observed pronounced associations for irritants, whose role in asthma is less established. For the associations between asthma outcomes and low/moderate occupational exposure to irritants only, we found ORs as high as for well-known HMW asthmagens. While the role of irritants in work-exacerbated-asthma is established,[29, 30] whether repeated low dose exposures to irritants may induce new-onset asthma remains discussed.[8] In clinical studies, the lack of objective test (specific inhalation challenges) for irritants hampers the diagnosis of low-dose irritant-induced occupational asthma cases, who may be misclassified as having work-exacerbated asthma.[30] Results of epidemiological studies are thus of particular interest. In the current study, the cross-sectional design and the lack of reliable information on the age at asthma onset prevent strong conclusion on the effect of irritants on new-onset asthma. However, the associations between irritant exposures and asthma were relatively strong, with increased ORs for more specific definitions of asthma outcome. In a recent longitudinal study of Norwegian smelters, dust exposure was associated with incidence of work-related asthma-like symptoms,[31] while exposure level was low to moderate and further exposure to sensitizers was unlikely. In a British longitudinal study,[16]

occupational exposure to environmental tobacco smoke (evaluated by the same asthma JEM [22]) was associated with adult-onset asthma. In a Taiwanese case-control study [17] also using this asthma JEM,[22] associations were observed between exposure to irritant peaks and asthma without atopy, but results for lower level of exposure to irritants were not reported. Finally, the growing amount of literature on the relationship between cleaning exposures and asthma suggests a prominent role of irritants.[16, 27, 32]

Studies in European populations using the same JEM have not consistently found elevated risks of asthma associated with the same categories of irritant exposures.[16, 23] A healthy worker effect, potentially more pronounced for irritant exposures,[33] may partly prevent the evidence for their role. In the current study, the ORs were relatively elevated and generally higher for current exposure, suggesting that the results are not strongly affected by a healthy worker effect.

The population historical context has to be considered to interpret the current results regarding the role of exposure to low/moderate level of irritants. Almost all subjects (99.8%) were born before 1991 i.e. under Soviet conditions, and were thus exposed in their first years of life (and for a large majority, during all childhood) to an environment and lifestyle likely to be protective against the development of allergic diseases in childhood, and potentially later in life.[9–11, 13] In studies conducted in children, wheezing was less associated with atopy in Estonia and in Russian Karelia compared to Sweden or Finland.[9, 34] Precise data are lacking in the literature (especially in adults), and no allergy marker was available in the current study. Despite this, indirect arguments suggest that non-allergic asthma might play a more prominent role than allergic asthma in this Estonian cohort compared to western European populations. This might partly explain the pronounced associations between asthma

and occupational exposure to low/moderate level of irritants in this Estonian cohort, while results were more contrasted in other populations.

The mechanisms of irritant-induced asthma remain poorly understood. Irritant exposures can provoke injuries of the bronchial epithelium, which would lose its protective properties.[5] An increased airway permeability caused by irritant exposures may facilitate epithelium crossing by allergens.[5, 18] Concomitant workplace exposure to irritants and allergens would thus be associated with higher risk of asthma. In the current study, when considering jobs exposed to low level of irritants only, ORs remained high and significant. Occupational asthma is a good model for the understanding of asthma in general. Genes expressed in the epithelium have been found associated with asthma following agnostic approaches. [35] It is of interest to observe that results of occupational studies on irritants are consistent with the increasing emphasis of the defect in epithelial barrier hypothesis in asthma.

In conclusion, findings contribute to increasing evidence of a role of repeated low to moderate exposures to irritants in asthma onset, which has implication in clinical practice as irritants should more largely be considered as potential causing agents. Moreover, by showing high risk of asthma associated with irritant exposures in this Estonian population with a low prevalence of asthma and atopy, the current analysis provides new insight in the understanding of asthma and its heterogeneity. In that respect, our results support the conduction of more studies of work-related asthma in various population contexts.

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Competing interests

None

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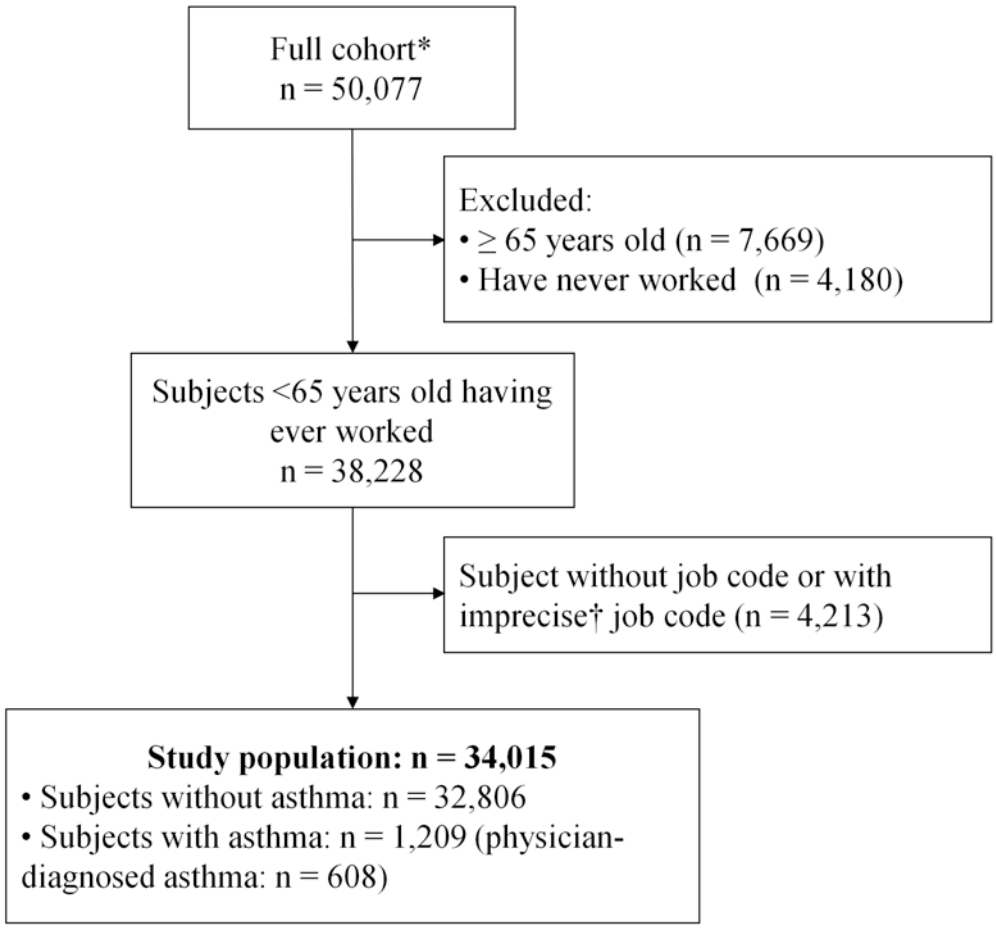

Figure 1. Selection of the study population.

* The EGCUT has been designed to approach the structure of the adult (≥18 years old) population in Estonia, though participation rates were higher in women, younger/middle-aged and highly educated subjects.[20]

† ≤3-digit code, excluded because of potential increased exposure misclassification when applying the JEM.[22] We investigated a potential bias due to their exclusion by comparing them to the subjects included (see Table E1 in the online supplement).

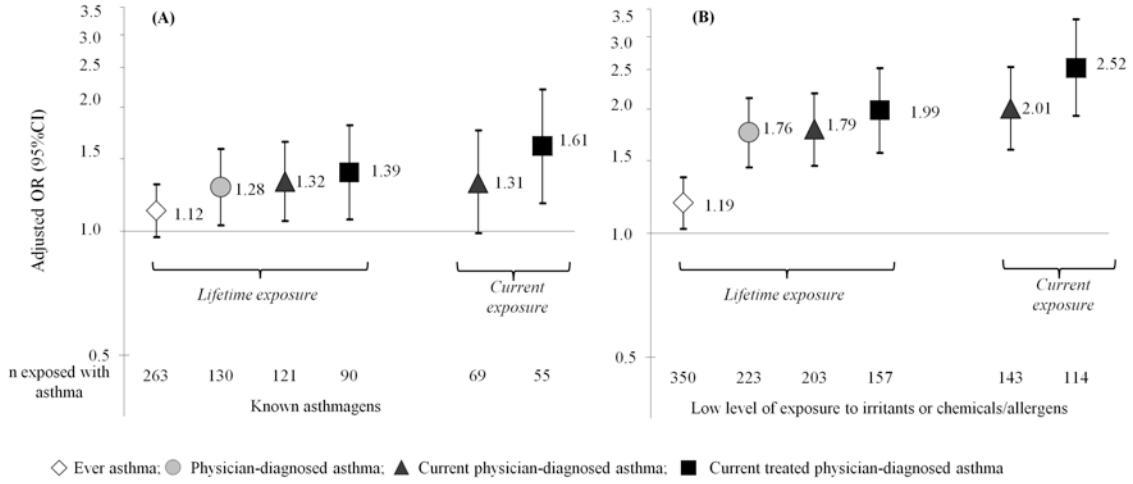

Figure 2. Associations between "lifetime" occupational exposure (i.e. during the longest held job or during the current job) and current occupational exposure to (A) known asthmagens and (B) low level of irritants or chemicals/allergens (and not known asthmagens), and asthma according to asthma definition. OR adjusted for age, sex and smoking habits.

Table 1. Description of the study population according to asthma diagnosis

	Total (n=34,015)	No asthma (n=32,806)	Asthma (n=1,209)	p*	Physician-diagnosed asthma (n=608)	p*
Age, years, mean (SD)	41.5 (12.7)	41.4 (12.6)	42.8 (13.2)	<0.001	45.9 (12.6)	<0.001
Women, %	67.0	66.9	69.5	0.06	67.8	0.6
Smoking habits †, %						
Never smokers	54.2	54.3	52.0		51.5	
Ex-smokers	13.9	13.8	16.4	0.07	17.3	0.1
Current smokers	31.8	31.8	31.6		31.3	
Current asthma, %		-	73.9	-	91.1	-
Current treated asthma, %		-	51.9		67.1	
Currently working, %	81.0	81.2	76.0	<0.001	75.2	<0.001

JEM, Job Exposure Matrix; SD, Standard Deviation. * p for comparison (Chi-2 or t Student tests) between subject without asthma and subjects with asthma and physician-diagnosed asthma respectively. † Missing for n=13 subjects.

Table 2. Associations between lifetime* specific occupational exposures and physician-diagnosed asthma (n=33,414)

	n	Physician-diagnosed asthma, n (%)	OR	Adjusted† OR	95% CI*
Non-exposed (ref.) ‡	17,503	255 (1.5)	1	1	
Known asthmagens					
High molecular weight (HMW) agents	3,442	73 (2.1)	**1.47**	**1.40**	**1.07-1.82**
Animals	699	19 (2.7)	**1.89**	**1.62**	**1.00-2.60**
Flour	351	12 (3.4)	**2.39**	**2.36**	**1.31-4.27**
Enzymes	287	9 (3.1)	**2.19**	**2.14**	**1.08-4.22**
Latex	1,791	30 (1.7)	1.15	1.15	0.78-1.69
Bioaerosols	1,042	26 (2.5)	**1.73**	**1.51**	**1.00-2.28**
Drugs¶	741	9 (1.2)	0.83	0.85	0.43-1.66
Low molecular weight (LMW) agents	2,125	26 (1.2)	0.84	0.84	0.56-1.26
Highly reactive chemicals	1,417	20 (1.4)	0.97	0.97	0.61-1.53
Cleaning/disinfecting products	559	9 (1.6)	1.11	1.02	0.52-2.01
Metals	801	6 (0.7)	0.51	0.51	0.22-1.16
Mixed environment	2,767	64 (2.3)	**1.60**	**1.48**	**1.12-1.96**
Textile production	1,388	30 (2.2)	**1.49**	**1.47**	**1.00-2.17**
Agriculture	1,259	34 (2.7)	**1.88**	**1.63**	**1.13-2.35**
High irritants peaks	837	8 (1.0)	0.65	0.72	0.34-1.50
Low level of exposure to irritants or to chemicals/allergens only					
Low level of exposure to chemicals/allergens	5,454	132 (2.4)	**1.68**	**1.72**	**1.39-2.14**
Combustion particles/fumes	2,371	62 (2.6)	**1.82**	**1.77**	**1.26-2.48**
Environmental tobacco smoke	514	5 (1.0)	0.66	0.94	0.38-2.31
Irritant gases/fumes	3,096	81 (2.6)	**1.82**	**2.04**	**1.55-2.68**
Low level of exposure to irritants *only*§	3,651	91 (2.5)	**1.73**	**1.82**	**1.34-2.45**

OR – Odds Ratio; CI – Confidence Interval. * Exposure during the longest held job or current job. † Evaluated by logistic regressions, adjusted for age, sex and smoking habits. ‡ Reference group: not exposed to any of the 22 agents of the JEM during the longest held job and current job. ¶ Pharmaceutical products may include both HMW and LMW antigens. § Irritants (combustion particles/fumes, irritant gases/fumes or environmental tobacco smoke), after excluding those further exposed to low level of chemicals/allergens. Analyses were performed for specific agents for which at least five subjects with asthma were exposed, i.e. 15 out of the 22 agents of the asthma JEM.

Table 3. Associations between current job categories and current physician diagnosed asthma

Current job category	ISCO-88 codes	n	Women, %	Current asthma*, n (%)	OR	Adjusted OR†	95% CI†	p†	q‡
Professionals, administrative or services workers (ref.)	*See online supplement*	12,024	68.9	139 (1.2)	1	1	-		
Cleaners (offices, hotels…)	9132	600	97.2	19 (3.2)	**2.80**	**2.07**	**1.25 - 3.42**	**0.005**	**0.02**
Healthcare professionals, any	*5 following categories*	*1925*	*93.9*	*43 (2.2)*	***1.95***	***1.77***	***1.24 – 2.53***	***0.002***	-
Nursing	3230 - 3232	533	96.8	8 (1.5)	1.30	1.30	0.63 - 2.68	0.48	0.48
Medical doctors / Health professionals	2221, 2229	482	85.9	9 (1.9)	1.63	1.38	0.70 - 2.73	0.36	0.40
Medical assistants	3221	159	94.3	7 (4.4)	**3.94**	**3.62**	**1.65 - 7.91**	**0.001**	**0.01**
Personal care workers	5132	372	95.7	7 (1.9)	1.64	1.40	0.65 - 3.05	0.39	0.41
Health associate professionals not elsewhere classified	3229	379	98.2	12 (3.2)	**2.80**	**2.47**	**1.34 - 4.53**	**0.004**	**0.02**
Dairy and livestock producers	6121	153	81.1	6 (3.9)	**3.49**	**3.03**	**1.31 - 7.02**	**0.01**	**0.02**
Building workers	7120-7123, 7129,7133,9313	627	4.5	12 (1.9)	**1.67**	**2.54**	**1.31 - 4.93**	**0.01**	**0.02**
Wood treaters	7421	199	47.2	6 (3.0)	**2.66**	**3.20**	**1.38 - 7.40**	**0.01**	**0.02**
Wood industry machine operators	7423, 8141, 8240	292	33.6	6 (2.1)	1.79	2.22	0.96 - 5.15	0.06	0.08
Textile workers	7332, 7430 - 7437	735	98.0	18 (2.4)	**2.15**	**2.12**	**1.27 - 3.52**	**0.004**	**0.02**
Machinery mechanics	7230 - 7233	254	0.0	9 (3.5)	**3.14**	**3.89**	**1.84 - 8.24**	**0.0004**	**0.01**
Mechanical engineers / technicians	2145, 3115	167	11.4	5 (3.0)	**2.64**	**2.76**	**1.08 - 7.05**	**0.03**	**0.05**
Electricians	7137, 7241, 7245	213	7.0	8 (3.8)	**3.38**	**3.43**	**1.58 - 7.41**	**0.002**	**0.01**
Motor vehicle drivers	8320 - 8323	345	5.2	10 (2.9)	**2.55**	**2.57**	**1.27 - 5.23**	**0.01**	**0.02**
Stock clerks	4131	223	71.8	5 (2.2)	1.96	1.87	0.76 - 4.62	0.18	0.22
Teaching professionals	2330 - 2332	1,181	98.6	7 (0.6)	**0.51**	**0.42**	**0.19 - 0.90**	**0.03**	**0.04**
Cooks	5122	485	93.6	9 (1.9)	1.62	1.49	0.75 - 2.97	0.26	0.30
Hand packers	9322	155	89.7	5 (3.2)	**2.85**	**2.76**	**1.10 - 6.91**	**0.03**	**0.05**
Other craft and trade workers	*See online supplement*	1,587	44.9	31 (2.0)	**1.70**	**1.72**	**1.15 - 2.57**	**0.01**	**0.02**

* Subjects with physician-diagnosed asthma who answered “yes” to the question “Do you have asthma now?”. † Evaluated by logistic regressions, adjusted for age, sex and smoking habits, with reference group: professional, administrative or service jobs. Analyses were performed for job categories for which at least five subjects with asthma were exposed, i.e. 20 out of the 58 job categories. ‡ q-values correspond to p-value corrected for multiple testing using the False Discovery Rate approach (calculated with the R package “p.adjust”).

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Online supplement

Occupational irritants and asthma: an Estonian cross-sectional study of 34,000 adults

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Table E1. Comparison of the subjects included in the analyses and subjects without occupational data (excluded from the analyses)

	Selected population (n=34,015)	Subjects who have never worked* (n = 4,180)	p†	Subject without job code or with imprecise‡ job code (n = 4,213)	p†
Age, years (mean (sd))	41.5 (12.7)	21.3 (5.7)	<0.001	38.9 (12.8)	<0.001
Women (%)	67.0	58.6	<0.001	63.8	<0.001
Smoking habits (%)					
Never smokers	54.2	64.4	<0.001	52.2	<0.001
Ex-smokers	13.9	4.9		11.0	
Current smokers	31.8	30.6		36.7	
Highest education level (%)					
No or elementary education	0.89	2.7	<0.001	0.88	<0.001
Basic or secondary education	36.2	83.5		42.0	
Professional education	40.5	10.2		40.9	
University or research degree	22.5	3.5		16.3	
Asthma (%)	3.6	3.8	0.4	3.1	0.05§
Physician-diagnosed asthma (%)	1.8	1.2	0.01	1.4	0.1

* Most of the subjects who had never worked were students (58%) or members of the armed forces (11%). The reason for not working was unknown in 16%.

† Compared to the selected population.

‡ Imprecise job code: 1-, 2-, or 3- digit job code (complete ISCO-88 codes are 4-digits codes).

§ Non-significant after adjusting for age, sex and education level

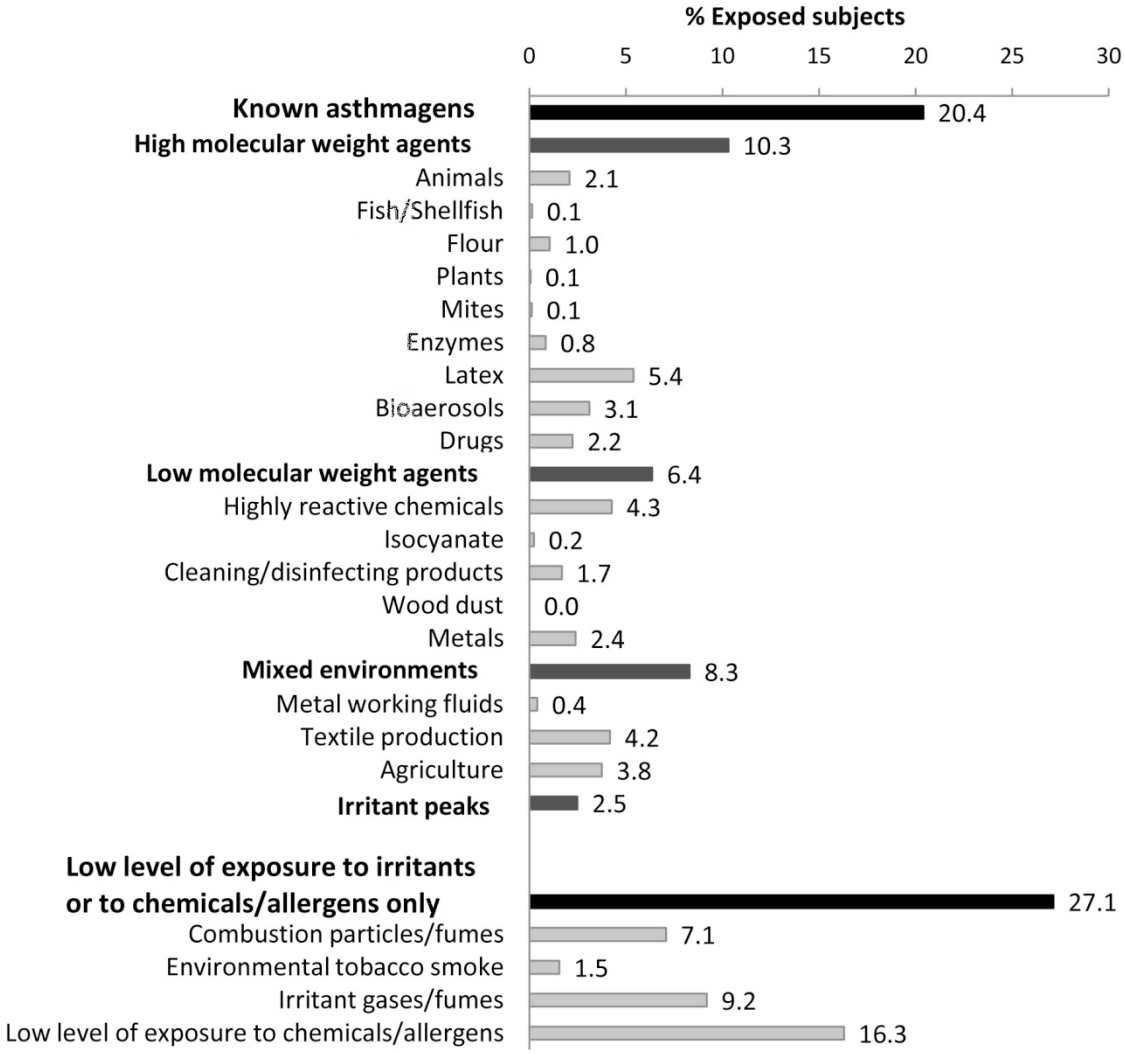

Figure E1. Frequency of lifetime occupational exposures in the study population (n=34,015)

Table E2. Associations between lifetime occupational exposures and physician-diagnosed asthma in men (n=11,065)

	n	Physician-diagnosed asthma, n (%)	Adjusted OR	95% CI
Non-exposed	4,255	53 (1.2)		
Known asthmagens	1,442	21 (1.5)	1.14	0.68-1.91
High molecular weight agents	397	12 (3.0)	**2.43**	**1.28-4.63**
Animals	111	5 (4.5)	**3.52**	**1.37-9.09**
Bioaerosols	232	5 (2.2)	1.66	0.65-4.25
Low molecular weight agents	695	7 (1.0)	0.80	0.36-1.78
Metals	544	5 (0.9)	0.70	0.28-1.79
Mixed environment	397	8 (2.0)	1.57	0.73-3.36
Agriculture	253	7 (2.8)	2.15	0.96-4.83
High irritants peaks	719	5 (0.7)	0.51	0.20-1.30
Low level of exposure to irritants or to chemicals/allergens only	5,368	122 (2.3)	**1.80**	**1.29-2.50**
Combustion particles/fumes	2,035	52 (2.6)	**1.96**	**1.30-2.96**
Irritant gases/fumes	2,048	45 (2.2)	**1.75**	**1.16-2.65**
Low level of exposure to chemicals/allergens	2,198	45 (2.0)	**1.67**	**1.12-2.51**

OR – Odds Ratio; CI – Confidence Interval.* Odds-ratio adjusted for age and smoking habits

Table E3. Associations between lifetime occupational exposures and physician-diagnosed asthma in women (n=22,349)

	n	Physician-diagnosed asthma, n (%)	Adjusted OR	95% CI
Non-exposed	13,248	202 (1.5)		
Known asthmagens	5,364	109 (2.0)	**1.33**	**1.05-1.68**
High molecular weight agents	3,045	61 (2.0)	1.26	0.95-1.69
Animals	588	14 (2.4)	1.31	0.76-2.28
Flour	322	11 (3.4)	**2.29**	**1.23-4.26**
Enzymes	269	9 (3.3)	**2.22**	**1.12-4.40**
Latex	1,690	27 (1.6)	1.07	0.72-1.61
Bioaerosols	810	21 (2.6)	1.45	0.91-2.29
Drugs	713	8 (1.1)	0.78	0.38-1.59
Low molecular weight agents	1,430	19 (1.3)	0.87	0.54-1.40
Highly reactive chemicals	1,239	18 (1.5)	0.96	0.59-1.57
Cleaning/disinfecting products	535	8 (1.5)	0.93	0.45-1.89
Mixed environment	2,370	56 (2.4)	**1.48**	**1.10-2.00**
Textile production	1,357	30 (2.2)	**1.53**	**1.04-2.26**
Agriculture	1,006	27 (2.7)	**1.51**	**1.00-2.28**
Low level of exposure to irritants or to chemicals/allergens only	3,737	101 (2.7)	**1.76**	**1.38-2.24**
Combustion particles/fumes	336	10 (3.0)	1.86	0.97-3.56
Environmental tobacco smoke	426	5 (1.2)	1.25	0.51-3.11
Irritant gases/fumes	1,048	36 (3.4)	**2.15**	**1.50-3.10**
Low level of exposure to chemicals/allergens	3,256	87 (2.7)	**1.77**	**1.37-2.29**

OR – Odds Ratio; CI – Confidence Interval.* Odds-ratio adjusted for age and smoking habits

Detail of job categories ISCO88 codes (Table 3)

Professionals, administrative or services workers (ref.):
110, 1100, 1110, 1120, 1130, 1140 - 1143; 1200, 1210, 1220 - 1237, 1239; 1300, 1310 – 1319;

2100, 2110 - 2112, 2114, 2141, 2142, 2144, 2147 - 2149, 2120 - 2122; 2200, 2210 - 2213, 2220; 2310, 2320, 2340, 2350 - 2352, 2359; 2400, 2410 - 2412, 2419 - 2422, 2429, 2440 - 2446, 2450 - 2453 - 2455, 2460, 2470;

3100, 3110, 3112, 3114, 3117, 3119, 3123, 3130 - 3133, 3139, 3140 - 3145, 3150 - 3152; 3200, 3210, 3212, 3213, 3220, 3222 - 3224, 3240 - 3242;

3300, 3330, 3340; 3400, 3410 - 3417, 3419 - 3423, 3429 - 3434, 3439, 3440 - 3444, 3449, 3450, 3460, 3470, 3472 - 3475, 3480;

4100, 4110 - 4115, 4120 - 4122, 4130, 4132, 4133, 4140, 4143, 4144, 4190; 4200, 4210 - 4215, 4220 - 4223;

5100, 5111- 5113, 5120, 5121, 5130, 5139, 5140, 5142, 5143, 5149, 5150 - 5152, 5160 - 5163, 5169, 5200, 5210, 5220, 5230;

9113, 9133;

Other craft and trade workers:

6100, 6110 - 6114, 6142;

7100, 7110 - 7113, 7130 - 7132, 7134 - 7136; 7140, 7143; 7200, 7215, 7216, 7223, 7240, 7242 - 7244; 7300, 7310 - 7313, 7320 - 7323, 7330, 7331, 7340 - 7346; 7400, 7410, 7416, 7420, 7424;

8100, 8110 - 8113, 8120 - 8124, 8130, 8131, 8139, 8140, 8142, 8143, 8150 - 8155, 8159 - 8163, 8170 - 8172; 8200, 8210 - 8212, 8220 - 8224, 8229 - 8232, 8250 - 8253, 8260, 8264 - 8266, 8269, 8280 - 8287, 8290; 8300, 8310 - 8312, 8330, 8331, 8334, 8340;

9100, 9110, 9111, 9112, 9120, 9150 - 9153, 9160 - 9162; 9200, 9210, 9213; 9310 - 9312, 9332.