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Exposures and Asthma Outcomes using two different Job Exposure Matrices in a General Population Study in Northern Europe

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ABSTRACT

Objective: We have recently published a study on new-onset asthma in a large population in Northern Europe using a modified job-exposure matrix (N-JEM) to better reflect exposure assignment in these countries. The aim of this paper was to investigate how the N-JEM differ in exposure assignment and asthma risks from an already established JEM.

Method: The study comprised 6 253 men and 7 031 women from Northern Europe born 1945-73, who had answered both a screening (1989-1992) and a follow-up questionnaire 1999-2001. During the study period (1980-2000) there were 136 men and 293 women with new-onset asthma. Hazard ratios of new-onset asthma were calculated for both JEMs using Cox regression models. The analyses were made separately for men and women and were also stratified for atopy. Cohen's kappa (κ) was used to show agreements in exposure assignment (yes/no) between the JEMs. Population attributable risks (PARs) were calculated as well.

Results: The agreement in exposure assignment between the JEMs was substantial for the group 'any exposure' to asthma agents (κ=0.78). The agreement between comparable exposure groups in the JEMs varied from κ=1.00 (pharmaceutical product antigens, textile dust, cleaning agents) to 0.27 (low molecular weight agents). Significant increased asthma risks were seen for men exposed to isocyanates and accidental peak exposure with both JEMs. With the N- JEM increased asthma risks were seen for men exposed to plant associated antigens (all and non-atopic), epoxy compounds (all and non-atopic) and acrylates (non-atopic). With the other JEM increased asthma risks were seen in men and women exposed to 'possible exposure to irritants gases or fumes' (all and non-atopic), a group classified as having low asthma risk. Men and women exposed to cleaning agents also showed significant asthma risks with both JEMs. PAR with the N- JEM was 14.3% for men and 6.6% for women compared to 12.9% and 8.3% with the other JEM.

Conclusions: Acrylates, epoxy compounds and isocyanates are three exposure groups in the modified asthma JEM that might better reflect exposure situations in Northern Europe than the already established JEM. Exposure to 'possible exposure to irritants gases or fumes', a low asthma risk group in the established JEM, seems to be a group with high asthma risk in Northern Europe. It is important to continuously up-date JEMs, which are based only on occupational titles, in order to find new risk groups and to better reflect changes in work exposures when old risks disappear and new emerge.

Keywords: Asthma specific job exposure matrices, Cohen's kappa, exposure assignment, hazard ratios, new-onset asthma, occupational asthma, population attributable risk.

INTRODUCTION

Job-exposure matrices (JEMs) have become a common tool to assign exposure in epidemiological studies of occupational risks. The exposure assignments are based on occupational titles, and the primary use is in large population based studies. The first JEM using ISCO-88 (International Standard Classification of Occupations 1988), (ILO, 1991) four digit codes to assess exposure in a population based study of exposures groups and asthma risks, was developed by Kennedy *et al* (2000) during the late nineties. This JEM has been used in many other studies (Kogevinas et al., 2007; Le Moual et al., 2004; Zock *et al.*, 2004; Le Van *et al.,* 2006; Beach *et al*., 2012; Ghosh et al., 2013). We will refer to this JEM as the SK-JEM.

Recently we have published a paper on occupational exposure and new-onset asthma (Lillienberg *et al.,* 2013), using data from the RHINE (Respiratory Health in Northern Europe) study, a randomly selected sample from five countries in Northern Europe. We used a modified job-exposure matrix, here referred to as N-JEM. Asthma incidence was 1.3 cases/1000 person-years for men and 2.4 for women. Among men, an increased risk of new-onset asthma was found for exposures to (di)isocyanates, epoxy and acrylates. Exposure to cleaning agents increased the risks for both men and women. Non-atopics seemed to be at higher risks than atopics except for exposure to high molecular weight agents (HMW). The aim with the N-JEM was to develop an asthma-JEM, which will better reflect exposure conditions in northern Europe compared with the SK-JEM. As the SK-JEM has been widely used, it is also important to compare the new JEM with the existing one on the same study population.

A way to test how reliable a job-exposure matrix can predict risks is to compare with a JEM derived from expert assessments on the same study population (Offermans *et al*., 2012, Lavoué *et al*., 2012). These studies showed rather large variation in agreement between the JEM and the expert assessments in different occupational categories. Suarthana et al (2011) compared the SK-JEM with self-reports and investigator scores on job-training-related exposure in apprentices during their training in animal health technology, pastry making and dental hygiene. The agreement in exposure assignments varied from moderate to good after a

'verification step' and additional expert changes. Exposure misclassification of allergic asthma in the SK-JEM has been investigated by Beach *et al* (2012) comparing data from two provinces in Canada. Two JEMs can also be compared by examining differences in outcomes on the same study population. Van Tongeren *et al.* (2013) have done a study of brain tumours, where they compared different outcomes in the same study population, using exposure assignment from FINJEM (Finnish Job Exposure Matrix) and a modified version of it (INTERROC JEM). FINJEM is more complex than our N-JEM as it besides occupational titles includes agents, proportion of workers exposed as well as level of exposure during several time periods.

From the 1980-ies and forward we were familiar with many asthma cases among workers handling epoxy compounds and acrylates in Sweden. We were also aware of that workers like fire-fighters, plumbers and welders in Scandinavia were exposed to isocyanates by thermal degradation of polyurethane but workers in these occupations are not considered to be exposed to isocyanates in the SK-JEM. This knowledge was an important reason, why we did not find the SK-JEM quite applicable for work situations in Northern Europe, and a motive to develop a modified JEM. Estimates of the population attributable risk (PAR) of occupational asthma have been inconsistent between studies (Blanc and Torén, 1999; Kogevinas et al., 2007; Torén and Blanc, 2009). The classification of exposures influences the estimates of the PAR, and therefore it is of interest to compare results using different JEMs. The purpose of this study was to investigate the differences in exposure assignments and subsequent risk analyses of the two JEMs.

METHODS

Study group

The randomly selected population in the RHINE study, which has been described elsewhere (Lillienberg *et al*., 2013), answered a screening questionnaire about asthma symptoms the last 12 months (1989-92) and an extensive follow-up questionnaire (1999-2001). The follow-up questionnaire included questions regarding occupational history, self-reported asthma symptoms, atopy and smoking habits. The response rate was 74%. After excluding those with asthma before 1980 and those with missing answers the study population ended up with 13 284 subjects, born 1945-73. New-onset asthma was defined as a positive answer to 'Do you have or have you ever had asthma after the age of 16?' and 'Have you ever had asthma

diagnosed by a physician?', (Torén *et al.*, 1993). Atopy was defined as a positive answer to 'Do you have hay fever or any other form of nasal allergy?

The occupational history included questions about all jobs (trade, work tasks/job title and start and stop year) with at least 6 months of employment. All jobs were classified according to ISCO-88 on a four digit level except for a few jobs classified on a three or two digit level. In the N-JEM, occupations were assigned exposure variables (yes or no) for being exposed, not exposed or 'uncertain or low exposed' by two occupational hygienists (LL, ADH). The assessments were discussed with two specialists in occupational medicine (KT, EA) until consensus was reached. To achieve a high specificity exposures were coded 'yes' for exposed only if there was a high probability of exposure relevant to work related asthma for at least half of the subjects with that code. Person-years (p-years) were calculated from 1980 or from the age of 16 years if they had not reached that age at 1980 up to year 2000 or until obtaining a diagnosis of asthma.

Job exposure matrices

In the SK-JEM we have used the classification of asthma agents in different risk groups according to Kennedy *et al.*, (2000) and the job-exposure matrix published on internet 2011 (Kennedy *et al.*, 2011) with the exception of the classification of the group 'cleaning agents'. In this group we have excluded three job codes (institution-based personal care workers, poultry producers, bleaching-, dyeing- and cleaning machine operators) by recommendation by J-P Zock (personal communication) as these workers are not working as cleaners or using ordinary cleaning agents.

The N-JEM has many similarities with the SK-JEM with e.g. exposure categories based on exposure to high molecular weight (HMW) asthma agents and low molecular weight (LMW) asthma agents. The N-JEM can be described as a two dimensional matrix with the four digit job codes on one axis and 17 risk groups (including accidental peak exposures) on the other based on known risk factors for occupational asthma with 1 for exposed, 0 for non-exposed and Z for uncertain or low exposed. The risk groups are gathered together into six exposure categories depending on type of asthma agents. The categories besides HMW and LMW agents are 'irritating agents', 'accidental peak exposure to irritants', 'uncertain or low exposed to asthma agents' and a reference group unexposed to asthma agents. The first four groups are comparable with the three high risk categories in the SK-JEM (HMW allergens, LMW allergens, high probability of accidental peak exposure to irritants) and a low risk group called 'other exposure – asthma risk low'. Irritating agents in the N-JEM includes the risk groups

exposed to vehicle/motor exhausts and environmental tobacco smoke (ETS), which are risk groups included in 'Other exposure – asthma risk low' in the SK-JEM. The SK-JEM has a risk category called 'mixed environments – asthma risk high', which is not included in the N-JEM. Some of the HMW groups in SK-JEM have been merged into a larger group in N-JEM to increase the number of exposed subjects in the group. The groups 'flour associated antigens', 'plant (other) associated antigens' together with some occupations from the subgroup 'agricultural antigens (mixed exposure)' in the SK-JEM are merged to one HMW group in N-JEM. In the same way we have merged arthropods, mites, bio-aerosols and enzymes in SK-JEM into one group in N-JEM. Cleaning agents is a subgroup of LMW agents in SK-JEM, while in the N-JEM it is a subgroup of irritating agents. Another LMW subgroup in SK-JEM is 'antigenic wood dust', where you should have clear evidence of exposure to antigenic wood dust e.g. cedar dust or other exotic hardwoods to be regarded as exposed. In N-JEM we have chosen to have wood and paper dust in a group called 'organic dust, wood, paper' within the risk category of irritating agents as Type 1 allergy is not suspected to be a major cause of wood dust induced asthma in Nordic countries (Jacobsen G *et al*., 2010), Table 1. The occupations within groups with similar or identical names differ for most of the groups and for some rather substantially. Besides exposure categories and risk groups for both JEMs, Table 1 also shows the number of exposed subjects in different groups together with values of Cohen's kappa between comparable groups.

As a part of the SK-JEM a verification step (expert judgement) is recommended, which includes ISCO codes that should be checked for exposure assignment during a re-evaluation step. The verification step also includes suggestions to check and recode 2 or 4 digit ISCO codes to 4 digit levels. In our study population there were very few subjects only coded with two or three digits and these were checked and changed to 4 digit level where possible. In the follow-up questionnaire we asked about trade but not what the firm/company produced or what services they provided, and therefore the verification step would not add much new information. Instead we have introduced a new group in the SK-JEM called 'verification variables (check exposures and ISCO)',

Statistical analyses

All statistical analyses were performed with SAS version 9.2. Cox regression analyses were performed using the counting process style of input to handle the time dependent exposure status . Cox regression analyses were performed separate for men and women and the analysis

were also stratified for atopy. Hazard ratios (HRs) with 95% confidence intervals (CIs) were adjusted for age and atopy. Additional analyses adjusted for smoking were performed but notified in the tables only where the significances were changed. Hazard ratios are not shown with less than three cases of new-onset asthma. HRs for N-JEM have previously been presented in Lillienberg *et al* (2013). Population attributable risk (PAR) for new-onset asthma induced by exposure to agents at the workplace causing asthma was calculated together with 95% CIs according to Nataranjan *et al.* (2007) using the Bonferroni inequality, where PAR=Pd*(HR-1/HR) and Pd is the proportion of exposed asthma cases. Cohen's kappa (κ) was calculated to measure to which degree the two JEMs agreed regarding the exposure assignments in comparable groups.

RESULTS

Agreements, measured as Cohen's kappa, between the JEMs in comparable groups are shown in Table 1. The lowest kappa values, or comparable groups with largest differences, were seen for assigned exposure to LMW agents and within this category in (highly) reactive chemicals and in isocyanates. Groups exposed to environmental tobacco smoke, vehicle motor exhaust and latex in the two JEMs showed substantial agreement (κ = 0.63-0.85). In the groups classified as exposed to 'any exposure' category (except uncertain or low exposed in N-JEM and low probability of enough exposure for OA in SK-JEM) there was also a substantial agreement (κ = 0.78). The merged group exposed to 'plant associated antigens' in N-JEM showed a kappa value of 0.61 compared with the group exposed to 'flour associated antigens' in SK-JEM and if exposure to 'flour antigens' was merged with exposure to 'plant (other) associated antigens' in SK-JEM the kappa value increased to 0.81.

The risk of new-onset asthma for 'any exposure' for men was similar with both JEMs but significant only for non-atopic men with SK-JEM (HR=1.7; 95% CI =1.0-2.8). The only HMW subgroup with a significant increase in new-onset asthma was 'plant associated antigens' in men (all and non-atopics) with N-JEM. There was a significant asthma risk in men exposed to LMW agents with SK-JEM (HR=1.6; 95% CI =1.0-2.6) and in N-JEM it was significant for non-atopic men (HR=2.0; 95% CI =1.0-4.1). The risk groups of LMW agents in N-JEM showed significant asthma risks for men exposed to isocyanates (all and non-atopic), epoxy compounds (all and non-atopic) and acrylates (non-atopic).There was also a significant asthma risk in men exposed to isocyanates with SK-JEM, but the numbers of asthma cases were too few to calculate the risks when stratified for atopy. The group exposed

to ’possible exposure to irritants gases or fumes’, classified as having a low asthma risk with SK-JEM, showed a significant increased asthma risk in men (all HR=1.9; 95% CI =1.2-3.0 and non-atopic HR=2.3; 95% CI =1.2-4.4), Table 2.

There was a significant asthma risk in women exposed to ‘any exposure’ with SK-JEM (HR=1.3; 95% CI =1.0-1.7), while the risk was not significant with N-JEM (HR=1.2; 95% CI =0.95-1.6). Atopic women exposed to HMW agents showed a significant asthma risk with the SK-JEM (HR=1.5; 95% CI =1.1-2.2), which was also shown for atopic women exposed to latex protein with both JEMs. Women exposed to LMW agents had a significant asthma risk with SK-JEM (HR=1.4; 95% CI =1.0-1.9) and those exposed in the subgroup, reactive chemicals, showed a significant asthma risk for non-atopic with N-JEM (HR=2.7; 95% CI =1.2-6.2). Those women exposed to ‘possible exposure to irritants gases or fumes’, classified as a low asthma risk group, also showed a significant asthma risk (all HR=1.8; 95% CI =1.1-2.8 and non-atopics HR=2.5; 95% CI =1.4-4.7) with SK-JEM, Table 3.

Those assigned exposure in ‘verification variables’ in the SK-JEM showed no increased asthma risk for men or women, while there was an increased, but not significant, asthma risk in non-atopic men and women assigned exposure in the group ‘relevant exposures remain uncertain after check´. Subjects classified as exposed in the group ‘uncertain or low exposed’ with N-JEM showed no increased asthma risk for men or women, Table 2 and 3.

The number of p-years for men and women in the reference populations were about the same in N-JEM and SK-JEM. In N-JEM we considered more occupations at risk of work-related asthma than in the SK-JEM. If in the group ‘any exposure’ in SK-JEM the group ‘low probability of enough exposure for occupational asthma (OA)’ was excluded, there were 26% more exposed p-years in men and 23% more p-years in women with N-JEM, Tables 2 and 3.

In the general population PAR for ‘any exposure’ was 14.3% (95% CI=-4.5-32.4) in men and 6.6% (95% CI=-2.9-16.7) in women with N-JEM and 12.9% (95% CI=-4.0-28.2) and 8.3% (95% CI=-0.4-17.6) with SK-JEM (excluding the group with low probability for OA). None of these values were statistically significant. PARs were in general higher for men with N-JEM but lower for women. The only exposure category with statistically significant PAR was accidental peak exposure in men with N-JEM (PAR=9.3%; 95% CI= 0.8-20.5) and SK-JEM (PAR=8.0%; 95% CI= 0.2-17.6).

In the sub groups, the risks of adult-onset asthma attributed to occupational exposure were highest for 'possible exposure to irritants gases or fumes' in men with SK-JEM (PAR=13.2%; 95% CI=1.3-25.2), isocyanates with N-JEM (PAR=9.9%; 95% CI= 0.5-22.2) and epoxy compounds with N-JEM (PAR=9.1%; 95% CI=0.7-20.3). Significant PARs were also seen in men exposed to 'plant associated antigens' with N-JEM and isocyanates with SK-JEM (PAR=4.1%; 95% CI=0.0-11.1), Figure 1. Significant PARs (around 5%) were seen for women exposed to cleaning agents with both JEMs and for women exposed to 'possible exposure to irritants gases or fumes' with SK-JEM (PAR=4.8%; 95% CI=0.4-10.6), Figure 2.

DISCUSSION

We have shown how differences in exposure assignment between the two JEMs will affect the estimates of risks of new-onset asthma and the PARs. Epoxy and acrylates are two new groups in N-JEM. The highest increase in risk of new-onset asthma was seen in men exposed to plant associated antigens, acrylates, epoxy compounds, isocyanates and peak exposure to irritants with N-JEM and isocyanates with SK-JEM. High asthma risks were also seen for men and women exposed to cleaning agents with both JEMs. The group 'possible exposure to irritants gases or fumes' in the SK-JEM was classified as a group with low asthma risk, but in this study population the group showed high asthma risk for both men and women.

There was a substantial agreement (κ=0.85) between the JEMs for subjects exposed to latex protein but a somewhat higher asthma risk for atopic women with SK-JEM (1.6 compared with 1.4, both significant). In N-JEM we have assigned latex exposure to more occupations than in SK-JEM and some of the women assigned latex exposure might have had too low exposure to be at risk for asthma. We could only show a fair agreement (κ = 0.27) between those exposed to LMW agents in the two JEMs, which to some extent depends on the group exposed to 'cleaning agents', which in SK-JEM is included in LMW agents but within 'irritating agents' in N-JEM. In N-JEM there was an increased asthma risk for non-atopic women exposed to reactive chemicals, which was not seen in women exposed to highly reactive chemicals in SK-JEM. The latter group includes exposure to 'institution-based personal care workers', which is a group with many women in this study. In N-JEM, this group is only assigned exposure to latex, which might be the reason why non-atopic women

exposed to reactive chemicals only showed increased asthma risk with N-JEM (exposure to latex is associated with increased asthma risk among atopic subjects).

In N-JEM we have introduced two new LMW risk groups, exposure to acrylates and epoxy compounds, which both showed increased asthma risks for men, with the highest risk for non-atopic men. In Finland, Jaakkola *et al* (2003) have shown increased asthma risks in electrical and electronic production workers, jobs that we classified as exposed to acrylates in N-JEM. Sensitisation to acrylates is well known e.g. in work with artificial acrylic nails (Roch *et al.*, 2008). Artificial nail work is an occupation included in the hairdressers ISCO code. In our study we have not considered this job code as exposed to acrylates, as the percentage working with artificial nails during the period 1980-2000 most likely was very low. Karjalainen *et al* (2002) have shown increased asthma risks among Finish construction workers like floor layers, plumbers and pipe fitters, spray painters and machine and metal product assemblers, which are occupations that we classified as exposed to epoxy compounds in N-JEM.

The number of p-years exposed to isocyanates in men is much higher in N-JEM, which shows that more ISCO codes are classified as exposed to isocyanates compared with SK-JEM. In the Nordic countries we consider fire fighters, plumbers and pipe fitters and welders and flame cutters exposed to isocyanates, which are groups not included in the isocyanate group in the SK-JEM. Motor vehicle mechanics is a group classified as exposed to isocyanates in the N-JEM but in SK-JEM it is a group that should be considered to be exposed to isocyanates in the verification step and recoded as exposed only if it is very clear that the person works in an auto body repair shop. An increased asthma risk was shown for men exposed to isocyanates with both JEMs but it was only in N-JEM that we could show that non-atopic men were at highest risk, as the number of asthma cases was too low in the SK-JEM if stratified for atopy.

Those classified as exposed in the group ‘possible exposure to irritants gases or fumes’ is regarded as a low asthma risk group in SK-JEM, but in this study population the group turned out to be a group with high asthma risk for both men and women. The group is rather heterogenic and includes some high risk occupations like many of the occupations in the group ‘cleaning agents’ and e.g. poultry producers and ‘plumbers and pipe fitters’.

In the general population, adult onset asthma attributed to occupational exposure, was 14% in men with N-JEM and 13% with SK-JEM and in women 7% with N-JEM and 8% with SK-

JEM. None of these values were statistically significant indicating a rather high uncertainty. At the same time the values were rather equal between the JEMs. The risk groups, where we have shown significant asthma risks, the PARs were also significant. Exposure to isocyanates in men showed a PAR of 10% in N-JEM, while it was only 4% in SK-JEM indicating a higher asthma risk in the group assigned exposure to isocyanates in N-JEM. At the same time some of those occupations assigned exposure to isocyanates were also assigned exposure to epoxy compounds (PAR 9%), and we might overestimate the PARs, caused by these agents, as we have two asthma inducing agents for several of the asthma cases.

Suarthana *et al* (2009) compared the outcomes of occupational allergies using SK-JEM with self-reports and investigator scores in a follow-up of 375 apprentices trained in animal health technology, pastry making and dental hygiene technology. The agreements in Cohen's kappa between self-reported and investigator scoring HMW allergens compared with the SK-JEM were moderate (κ=0.56 and 0.52 respectively). The results indicate that there are some misclassifications in the SK-JEM and that the exposure classifications could be improved. All pastry makers might not be exposed to enzymes and some of the life science technicians might be exposed to laboratory animals and latex. Suarthana *et al* (2011) also showed that after the verification step and several additional exposure corrections, the kappa values increased substantially (κ=0.80 and 0.79 respectively). The HRs also increased, after the corrections, but only one out of four groups changed from not significant to significant asthma risk. As we did not do a comparison with self-reports or investigator scores in our study we cannot say, which of the JEMs that is most correct in assigning exposure to HMW agents. Our study showed that the agreement in exposure assignment between the HMW agents was substantial (κ=0.82) and a conclusion is that both JEMs probably can estimate most asthma risks without the verification step and additional corrections, considering HMW agents. The study by Suarthana *et al* (2009) was done in Canada, where the exposure situations might differ from northern Europe, and thus it is difficult to know if the results are quite applicable to our study population

In a study by Zock *et al.* (2004) the SK-JEM was used in the Spanish population of the ECRHS II. In this study they tested differences in outcomes before and after the expert judgement steps. Prevalence ratios (PRs) were used to evaluate associations between exposure groups and symptoms of asthma. Major changes in PRs, after the verification step, were only seen for a few occupational categories. Only exposure to sensitizing drugs and asthma

changed from statistical significant before expert judgement to not significant after the verification step. The conclusion was that despite the labour-intensive expert judgement steps and relevant modifications, substantial changes were only made in a few categories. In our study the asthma risk for those exposed in the group 'verification variables' is the same or lower than in the reference group for both men and women indicating that most of these subjects are not at risk of OA. However, we found that non-atopic men and women exposed in the group 'relevant exposures remain uncertain after check' had an increased but not significant asthma risk, which indicate that the verification step will not give sufficient information to recode many of the occupations that might have an increased asthma risk and that the verification step might not be worth the effort to carry out.

A limitation with a JEM based only on occupational titles is that exposure profiles change over time, and is not taken into account in contrast to e.g. in FINJEM, which have agent, occupation, time period, prevalence and exposure estimates. Known changes in exposure profiles are e.g. exposure to environmental tobacco smoke and latex, where the exposures have decreased substantially during the last years. There might also be regional differences and differences between countries in how the work is performed. It is therefore important to continuously update and revise JEMs based only on occupational titles.

CONCLUSIONS

Compared with the SK-JEM there were in general slightly higher asthma risks for men and slightly lower for women with N-JEM. The two new risk groups introduced in the N-JEM, epoxy compounds and acrylates both showed increased asthma risks in men. There were more occupational titles included in the group assigned exposure to isocyanates in N-JEM and the PAR was also higher (10%) compared with SK-JEM (4%). The two new exposure groups in N-JEM together with the more expanded isocyanate group might better reflect the exposure situations in Northern Europe at least during the study period 1980-2000. The group 'possible exposure to irritants gases or fumes', which in SK-JEM was considered as a group with low asthma risk, showed high asthma risk in our study population. It is important to continuously update and revise JEMs, which are based only on occupational titles, as work-life situations change and old risks disappear and new emerge.

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Table 1. Number of exposed subjects in exposure groups in N-JEM and SK-JEM and agreement in exposure assignments in comparable groups using Cohen's kappa (κ)

N-JEM	N1[a]	Kappa	N2[b]	**SK-JEM**
Any exposure groups 1-4	6907	0.78	5459	**Any exposure groups 1-5** (except low probability group)
1. **HMW agents**	2889	0.82	2176	1. **HMW asthmagen exposure variables - asthma risk high**
Animal derived antigens including fish	334	0.54	125	Animal antigens including fish
			28	Fish/shellfish antigens
Plant associated antigens from cereal, tobacco, brewery	216	0.61	114	Flour associated antigens
together with mixed agriculture			35	Plant (other) associated antigens
Arthropod, mite, bioaerosol antigens, antigenic enzyme	561	0.75	338	Bioaerosol antigens
			97	Antigenic enzymes
			48	Mite and insect antigens
Latex protein	2076	0.85	1590	Latex antigens
Pharmaceutical product antigens	416	1.00	418	Pharmaceutical product antigens
2. LMW agents	1397	0.27	2810	**2. LMW asthmagen exposure variables - asthma risk high**
Reactive chemicals (e.g. amines, aldehydes, anhydrides)	525	0.29	1445	Highly reactive chemicals
(Di)isocyanates	616	0.32	121	Reactive chemicals - isocyanates
Acrylates	493		832	Cleaning/disinfecting products
Epoxy compounds	429		0	Antigenic wood dusts (only if evidence of antigenic wood dust)
			696	Metal and metal fume antigens
3. Accidental peak exposures	415	0.99	420	**3. High probability of accidental peak exposures to irritants**
4. Irritating agents	4119		513	**4. Mixed environments - asthma risk high**
Organic dust, textile industry	146	1.00	146	Textile production
Metal working fluids, MWF	399	0.40	101	Metal working fluids, MWF
Organic dust, wood, paper	563		271	Agricultural antigens (mixed exposures)
Inorganic dust and fumes	1528			
Cleaning agents	832	1.00[c]		
		0.68[d]	4303	**5. Other exposure – asthma risk low**
			1725	Possible exposure to irritants gases or fumes
Vehicle/motor exhaust	1515	0.81	1084	Combustion particles/fumes: vehicle/motor exhaust
Environmental tobacco smoke	505	0.63	230	High probability of exposure. to environmental tobacco smoke
			2416	Low probability of enough exposure for occupational asthma
5. Uncertain or low exposed	1424	0.43	1561	**6. Relevant exposures remain uncertain after checking**
			3113	**7. Verification variables (check exposure, check ISCO)**
6. Reference group	6302		5505	**8. Reference group (unlikely to be exposed to asthmagens)**

[a]Number of exposed subjects in N-JEM, [b] Number of exposed subjects in SK-JEM [c]with SK-JEM group 2; Cleaning products, [d]with N-JEM group 4; Irritating agents.

Table 2. HR and 95% CI of new-onset asthma in men exposed to any exposure and different exposure groups with N-JEM and SK-JEM.

Job exposure group	Person-years all	Asthma cases all/atopic/nonatopic	All exposed[a] HR (95% CI)	Atopics[b] HR (95% CI)	Non-atopics[b] HR (95% CI)
N-JEM men					
Referents	51541	59/33/26	1	1	1
Any exposure (groups 1-4)	48430	70/34/36	1.4 (0.96-1.9)	1.3 (0.8-2.1)	1.5 (0.9-2.4)
1. HMW agents	8770	15/7/8	1.5 (0.9-2.7)	1.3 (0.6-3.0)	1.8 (0.8-3.9)
Plant associated antigens, cereal etc.	1352	5/2/3	**3.6 (1.4-9.0)**	NA[c]	**4.1 (1.2-13.6)**
Arthropods mites bioaerosols enzyme	3948	6/3/3	1.3 (0.6-3.1)	1.2 (0.4-3.9)	1.5 (0.4-4.8)
Latex protein	2618	5/3/2	1.7 (0.7-4.2)	1.8 (0.6-7.0)	NA[c]
2. LMW agents	11249	17/5/12	1.4 (0.8-2.3)	0.8 (0.3-2.0)	**2.0 (1.0-4.1)**
Reactive chemicals	2764	3/1/2	1.0 (0.3-3.1)	NA	NA
Acrylates	4078	8/1/7	1.8 (0.8-3.7)	NA	**3.3 (1.4-7.5)**
Epoxy compounds	4249	11/3/8	**2.4 (1.3-4.5)**	1.3 (0.4-4.3)	**3.6 (1.6-7.9)**
(Di)isocyanates	6158	14/5/9	**2.1 (1.2-3.7)**	1.5 (0.6-3.8)	**2.8 (1.3-6.0)**
3. Peak exposure to irritants	3945	11/5/6	**2.4 (1.3-4.7)**	2.0 (0.8-5.2)	**3.0 (1.2-7.2)**
4. Irritating agents	35272	53/27/26	1.4 (0.96-2.0)[d]	1.3 (0.8-2.3)	1.5 (0.9-2.6)
Cleaning agents	1749	6/2/4	**2.6 (1.1-6.1)**[d]	NA	**4.1 (1.4-12.1)**
Inorganic dusts and fumes	16517	26/12/14	1.5 (0.9-2.3)	1.3 (0.7-2.6)	1.6 (0.9-3.1)
Vehicle/motor exhaust	13319	15/6/9	1.0 (0.6-1.8)	0.7 (0.3-1.8)	1.3 (0.6-2.8)
5. Uncertain or low exposed	7565	7/2/5	0.8 (0.4-1.8)	NA	1.4 (0.5-3.6)
SK-JEM men					
Referents	51195	64/36/28	1	1	1
Any exposure (groups 1-5 except low exposed)	35876	57/24/33	1.4 (0.95-2.0)	1.1 (0.7-1.9)	**1.7 (1.0-2.8)**
1. HMW agents - asthma risk high	5423	8/5/3	1.2 (0.6-2.4)	1.3 (0.5-3.4)	1.0 (0.3-3.3)
Latex protein	1776	3/2/1	1.4 (0.4-4.4)	NA	NA
2. LMW agents - asthma risk high	11312	23/11/12	**1.6 (1.0-2.6)**	1.5 (0.7-2.9)	1.8 (0.9-3.6)
Highly reactive chemicals	3035	8/4/4	2.1 (0.99-4.3)	1.9 (0.7-5.3)	2.4 (0.8-6.7)
Isocyanates	899	4/2/2	**3.2 (1.2-8.9)**	NA	NA
Cleaning agents	1749	6/2/4	**2.3 (1.0-5.4)**[d]	1.4 (0.3-5.8)	**3.5 (1.2-10.4)**
Metal and metal fume antigens	5798	9/5/4	1.3 (0.6-2.6)	1.4 (0.5-3.5)	1.2 (0.4-3.5)
3. Peak exposure to irritants (RADS)	3977	11/5/6	**2.2 (1.2-4.2)**	1.8 (0.7-4.6)	**2.7 (1.1-6.5)**
4. Mixed environments - asthma risk high	2771	3/1/2	0.9 (0.3-2.7)	NA	NA
Mixed agriculture agents	1675	3/1/2	1.3 (0.4-4.2)	NA	NA
5. Other exposure - asthma risk low	37837	47/21/26	1.1 (0.7-1.5)	0.9 (0,5-1.5)	1.3 (0.8-2.2)
Possible exposure to irritants gases or fumes	11150	25/11/14	**1.9 (1.2-3.0)**	1.6 (0.8-3.1)	**2.3 (1.2-4.4)**
Vehicle/motor exhaust	11288	12/4/8	0.9 (0.5-1.6)	0.6 (0.2-1.6)	1.3 (0.6-2.8)
Relevant exposures remain uncertain after check	5981	9/2/7	1.2 (0.6-2.4)	NA	2.1 (0.94-4.7)
Verification variables (check exp. and ISCO)	17602	20/10/10	0.9 (0.6-1.5)	0.8 (0.4-1.6)	1.0 (0.5-2.1)

[a] Adjusted for age and atopy, [b] adjusted for age, [c] NA=not applicable (< 3 asthma cases), [d] not significant when adjusted also for smoking.

Table 3. HR and 95% CI of new-onset asthma in women exposed to any exposure and different exposure groups with N-JEM and SK-JEM.

Job exposure group	Person-years all	Asthma cases all/atopic/non atopic	All exposed[a] HR (95% CI)	Atopic[b] HR (95% CI)	Non-atopic[b] HR (95% CI)
N-JEM women					
Referents	75564	174/107/67	1	1	1
Any exposure (groups 1-4)	38718	107/66/41	1.2 (0.95-1.6)	1.2 (0.9-1.7)	1.2 (0.8-1.7)
1. HMW agents Latex protein Pharmaceutical product antigens	23554 21258 4223	63/42/21 59/40/19 13/11/2	1.2 (0.9-1.6) 1.3 (0.9-1.7) 1.3 (0.8-2.3)	1.4 (0.94-1.9) **1.4 (1.0-2.1)** 1.9 (0.99-3.4)	1.0 (0.6-1.6) 1.0 (0.6-1.6) NA[c]
2. LMW agents Reactive chemicals	3889 2557	10/4/6 10/4/6	1.1 (0.6-2.1) 1.6 (0.9-3.2)	0.7 (0.3-1.8) 1.0 (0.4-2.6)	1.7 (0.8-4.0) **2.7 (1.2-6.2)**[d]
4. Irritating agents Cleaning agents Vehicle/motor exhaust	12383 4752 2836	37/20/17 21/10/11 7/5/2	1.3 (0.9-1.9) **2.0 (1.2-3.0)** 1.1 (0.5-2.3)	1.1 (0.7-1.8) 1.5 (0.8-2.9) 1.3 (0.5-3.2)	1.5 (0.9-2.6) **2.6 (1.4-5.0)** NA
5. Uncertain or low exposed	6351	12/7/5	0.8 (0.5-1.5)	0.8 (0.4-1.8)	0.8 (0.3-2.1)
SK-JEM women					
Referents	75338	176/112/64	1	1	1
Any exposure (groups 1-5 except low exposed) Any exposure (groups 1-5)	29942 34388	90/57/33 97/61/36	**1.3 (1.0-1.7)** [d] 1.2 (0.96-1.6)	1.4 (0.99-1.9) 1.3 (0.9-1.7)	1.2 (0.8-1.9) 1.3 (0.8-1.9)
1. HMW agents – asthma risk high Latex protein Pharmaceutical product antigens	18661 16510 4255	54/38/16 49/35/14 13/11/2	1.3 (0.96-1.8) 1.3 (0.98-1.8) 1.3 (0.7-2.3)	**1.5 (1.1-2.2)** **1.6 (1.1-2.3)** 1.8 (0.94-3.3)	1.0 (0.6-1.7) 1.0 (0.5-1.7) NA
2. LMW agents – asthma risk high Highly reactive chemicals Cleaning agents	17290 11349 4752	55/31/24 35/21/14 21/10/11	**1.4 (1.0-1.9)** [d] 1.4 (0.96-2.0) **2.0 (1.2-3.1)**	1.3 (0.9-1.9) 1.4 (0.9-2.2) 1.5 (0.8-2.8)	1.6 (0.99-2.5) 1.4 (0.8-2.5) **2.8 (1.5-5.3)**
4. Mixed environments – asthma risk high	2008	3/1/2	0.6 (0.2-2.0)	NA	NA
5. Other exposure - asthma risk low Possible exposure to irritants gases or fumes Vehicle/motor exhaust	12358 5527 711	38/21/17 22/10/12 3/2/1	1.3 (0.94-1.9) **1.8 (1.1-2.8)** [d] 1.9 (0.6-6.1)	1.2 (0.7-1.9) 1.3 (0.7-2.5) NA	1.6 (0.9-2.7) **2.5 (1.4-4.7)** NA
Relevant exposures remain uncertain after checking **Verification variables (check exposures and ISCO)**	8483 15816	25/12/13 41/28/13	1.3 (0.9-2.0) 1.1 (0.8-1.6)	1.1 (0.6-2.0) 1.3 (0.8-1.9)	1.7 (0.93-3.1) 0.9 (0.5-1.7)

[a]Adjusted for age and atopy, [b]adjusted for age, [c] NA=not applicable (< 3 asthma cases), [d]not significant when adjusted also for smoking.

Figure 1. Population attributable risk and 95% CIs for risk groups in men with N-JEM

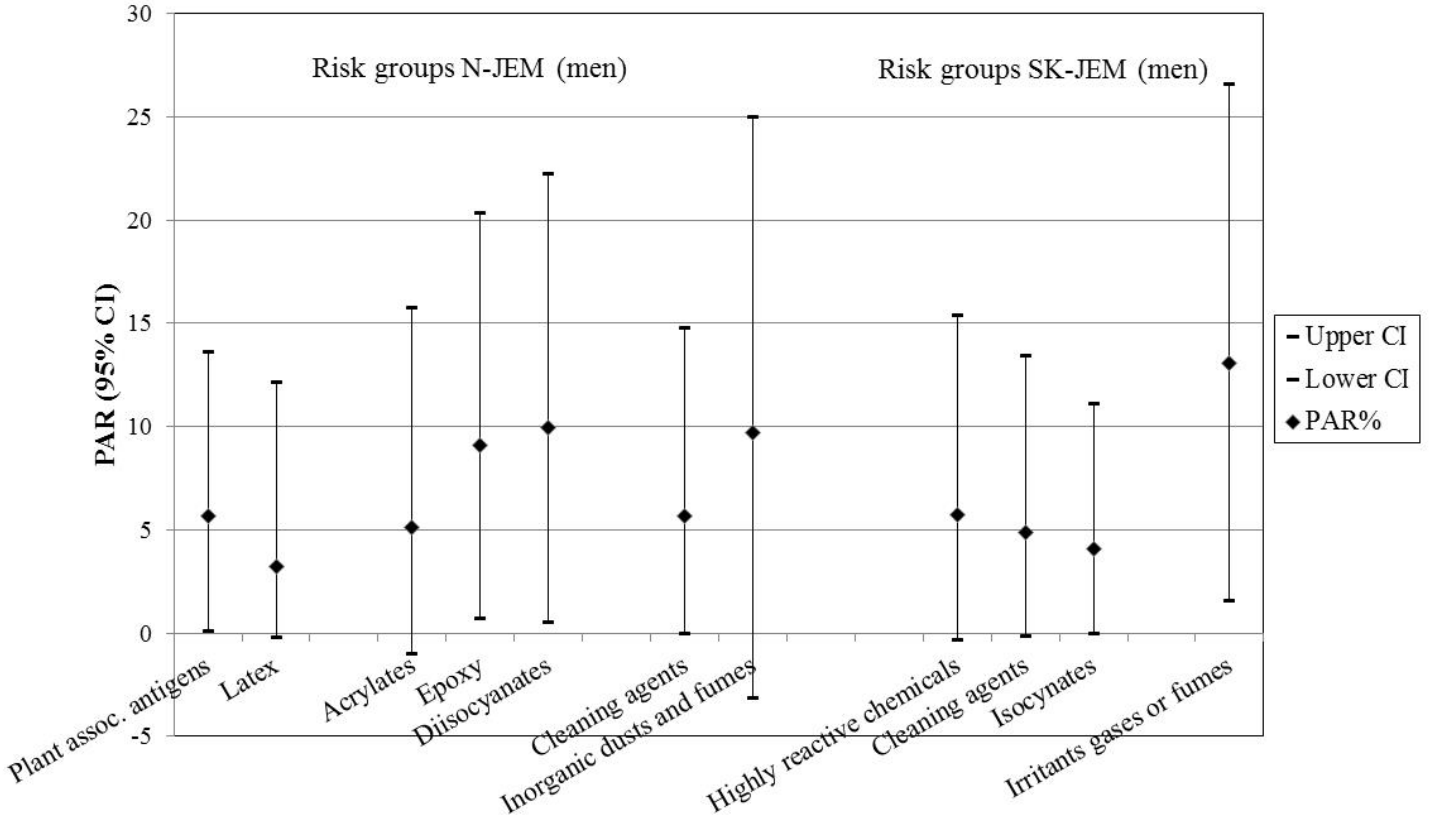

Figure 2. Population attributable risk and 95% CIs for risk groups in women with N-JEM