Occupational exposures and uncontrolled adult-onset asthma in the ECRHS II

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MATERIAL AND METHODS

Population

The European Community Respiratory Health Survey (ECRHS) is a multicentre study in the general population (http://www.ecrhs.org/) conducted among adults from 56 centres in 25 countries with a baseline survey as the first step. The aims were to evaluate variation in prevalence of asthma, asthma-like symptoms, atopic sensitization and bronchial reactivity among countries and how identified risk factors and treatment explain this variation. The baseline ECRHS study (ECRHS I) was conducted, from 1991 to 1993 among participants from 45 centres in 22 countries, as previously described [1, 2]. A random sample among at least 1500 men and 1500 women in each area, aged 20 to 44 years, was contacted to complete a short screening questionnaire on respiratory symptoms. Second, both a 20% random sample (participants from the screening questionnaire) and a respiratory symptom-enriched sub-group (those who reported asthma attacks, asthma medication, or 'wake up by shortness of breath' in the screening questionnaire but not selected in the random sample) were invited to participate in a clinical examination. Participants were asked to complete a second detailed questionnaire that included information on smoking habits, occupation, home environment, respiratory symptoms, asthma and treatment. In addition, lung function tests including methacholine challenge for non- specific bronchial reactivity were performed.

All participants from ECRHS I were invited to participate again in a follow-up survey (ECRHS II) conducted between 1998 to 2002, as previously described[3]. Participants were invited to complete a face-to-face administrated questionnaire (including detailed information on asthma, respiratory symptoms, and occupational history) and to participate in a clinical examination (lung function tests, blood samples). The information collected also included age, smoking status (never, former or current smoker), body mass index (BMI: ≥25 kg/m², Yes/no), age at full time education (< 17, 17-20, > 20 years old), an asthma symptom score, use of inhaled corticosteroids and sensitization. Participants classified 'with sensitization to common allergens' have specific serum Immunoglobuline E antibodies to at least one out of four common inhalant allergen (house dust mite, grass, cat and *Cladosporium herbarum*) at concentrations of 0·35 U/mL or more. Bronchial hyper-reactivity (BHR) was defined as a reduction in maximum FEV_1 of at least 20% of its postsaline value for a methacholine dose of 1 mg or less. According to baseline FEV_1 based on Quanjer et al. reference values, participants were classified as 'with' (< 80% of predicted values) or 'without' low FEV_1.

The response rate for the follow-up participation was approximately 65% overall. This analysis was limited to participants in ECRHSII from the 26 study centres in 12 countries[3, 4]. The information was used to evaluate both asthma control and occupational exposure among participants ever employed and with available data for sex, age, smoking habits, current asthma (n=9019). Among participants from the enriched sample, more prone to respiratory symptoms or diseases, only those with current asthma were included in the present analysis, as previously [5]. After excluding of 1942 participants, 796 participants from the enriched sample (all individuals without current asthma) and 1146 from the random sample (with past asthma (n=167)

or without current asthma but with asthma symptoms or treatment in ECRHSII (n=979)), analysis was performed on 7077 participants (1210 with 'current asthma'; 5867 with 'never asthma', Figure 1).

Four geographical areas were defined as previously[5]: English speaking (UK and USA), Northern (Estonia, Iceland, Norway, and Sweden), Central (Belgium, France, Germany, and Switzerland) and Southern (Italy and Spain) Europe areas.

As previously described by Sunyer et al and Pekkanen et al[6, 7], an asthma symptom score was calculated by the sum of positive answers to 5 items from a standardized questionnaire: 1) breathless while wheezing in the last 12 months, 2) woken up with a feeling of chest tightness in the last 12 months, 3) attack of shortness of breath at rest in the last 12 months, 4) attack of shortness of breath after exercise in the last 12 months, 5) woken by attack of shortness of breath in the last 12 months. A 3-level classification (0, 1, at least 2 symptoms) was considered.

Ethical approval to perform the study was obtained from the relevant ethic committee from each centre, and written informed consent was received from all participants.

Asthma phenotypes

Participants from the random sample were classified with '**never asthma**' (n=5867) if they never reported doctor-diagnosed asthma (never at ECRHSI and ECRHSII), and nor asthma-like symptoms (wheezing or whistling without a cold, woken by an attack of shortness of breath) nor use of asthma medications at ECRHS II.

Participants were classified with '**current asthma**' at follow-up (n=1210), as previously described by de Marco et al [8] and Cazzoletti et al [4, 9], if they had reported doctor-diagnosed asthma and if, in the last 12 months, they had reported respiratory symptoms (wheezing, nocturnal chest tightness, attack of breathlessness following activity, at rest or at night time, at least 1 asthma attack) or had used asthma medications.

Participants without current asthma at ECRHSII and who reported a history of ever asthma at ECRHSI or ECRHSII (asthma in remission, n=167) or asthma-like symptoms or asthma medication at ECRHSII (n=979) were excluded from the present analyses (Figure 1), as previously performed[3].

Among participants with current asthma, **asthma control** was defined, as previously described by Cazzoletti et al[4], combining diurnal and nocturnal respiratory symptoms, asthma attacks, activity limitations, lung function, hospitalization for asthma and use of treatment for asthma. Participants with 'current asthma' were classified as: (i) ***'Controlled asthma'*** if all the following features were present: diurnal symptoms less than once a week *(see online supplement, question Q14.9)*, no nocturnal symptoms *(Q14.8)*, no asthma attacks *(Q14.7)*, short-acting β2-agonists twice or less per week in the past 3 months; no activity (work, other

activities) limitations *(Q90.1, Q91)* and no use of oral steroids in the past 12 months, and FEV1 ≥ 80% predicted. (ii) ***'Partly-controlled asthma'*** when 1 or 2 of the above features were absent. (iii) ***'Uncontrolled asthma'*** when asthma, shortness of breath or wheezing had caused hospital/emergency admissions in the past 12 months *(Q84.1, Q85.1)*; or oral corticosteroids were used on short courses or continuously in the past 12 months *(Q77.3.3)*; or the participant had more than 12 asthma attacks (>1/week) in the past 3 months; or > 3 of the above features were absent.

It has been suggested that exacerbations should be considered separately from 'current clinical control' because they may occur even if the patient has adequate current control of symptoms and few activity limitations[10]. Therefore, further analysis was conducted without including the exacerbation domain in the asthma control definition ('current clinical control' domain). 'Current clinical control' domain was defined as previously for ***'Controlled asthma'*** and ***'Partly-controlled asthma'*** whereas participants with 'current asthma' were classified as ***'Uncontrolled asthma'*** when the participant had more than 12 asthma attacks (>1/week) in the past 3 months; or > 3 of the above features were absent (exacerbations not taken into account to defined uncontrolled asthma).

Age at asthma onset (childhood, adult), reported to be a key factor in asthma phenotype [11], should be considered, especially in work-related asthma studies. Information collected at follow-up and at baseline was used to evaluate the age at asthma onset. Participants with asthma, and without inconsistent responses regarding age at asthma onset, were classified as 'adult-onset asthma' when the age at asthma onset was greater than 16 years old and as 'childhood-onset asthma' when age of atshma was lower than 16, as previously defined [12, 13]. Studying the "healthy worker hire effect" in ECRHS[14], completion of fulltime education and age of 16-years old have been used to define childhood and adulthood -onset asthma. Whatever the cut-off used for asthma onset (age of 16 years; completion of fulltime education) the results were similar. Among participants with current asthma, 91 were excluded from some analyses due to missing values or inconsistent responses at the two surveys for the age at asthma onset.

Occupational exposure

All occupations held for at least three months during the follow-up between the ECRHS I and II (evaluated retrospectively at ECRHS II) were recorded in a face-to-face interview. Jobs were coded using the International Standard Classification of Occupations (ISCO-88) system[15]. Both past 12-month and 10-year (between ECRHS I and II; evaluated retrospectively at ECRHS II) occupational exposures were evaluated through an asthma job-exposure matrix (Asthma-specific JEM) [16] designed to give correspondence between jobs and exposures after translation of job descriptions into International Standard Classification of Occupations (ISCO88) codes [15]. The asthma-specific JEM is a two-dimensional table with the first axis listing international job codes. The second axis contains 22 exposure estimates coded as yes or no in the cells. Among the 22 exposure estimates, 18 categories of asthmagens were classified at high risk for asthma

and four categories of products *a priori* 'non-asthmagenic' agents were classified at low risk for asthma) at the set-up of the Asthma JEM. As explained previously [16, 17] and updated on the Asthma-specific JEM's website (http://cesp.vjf.inserm.fr/asthmajem/), individuals were classified exposed to *a priori* 'non-asthmagenic agents' or 'at low risk for asthma' when they may be exposed to (a) 3 categories of respiratory hazards not likely associated with occupational asthma (vehicle or motor exhaust fumes; high probability of exposure to environmental tobacco smoke; possible exposure to irritant gasses or fumes) or (b) to 'asthmagens' but with low probability of enough exposure to induce occupational asthma. We agree that this classification of *a priori* 'non-asthmagenic' agents may be discussed according to current knowledge, especially for low to moderate exposures to irritants. The JEM was first applied to job codes, followed by a second step where expert re-evaluation was undertaken, as previously described in the ECRHSII survey [3]. Participants were classified as 'exposed to asthmagens' (HMW, LMW, mixed environment (which could involve combined exposures to irritants, HMW and LMW agents), or high peak irritants), exposed to *a priori* 'non-asthmagenic' agents only (participants exposed to both 'asthmagens' and 'non-asthmagenic' agents were classified only exposed to' asthmagens' for the present analysis) or 'non exposed'. Occupational exposure to cleaning agents (LMW agents) was also assessed by this method.

Statistical analysis

Analyses were stratified by BMI, smoking habits, gender, and sensitization as previously suggested[3, 18]. A meta-analysis by geographical areas was also performed. Further analysis was conducted without including the exacerbation domain in the asthma control definition ('current clinical control' domain; see methods and Table 3).

Population attributable risks (PAR) were calculated for occupational contribution to uncontrolled asthma, considering past 12-month and 10-year exposure to asthmagens (proportion exposed): "proportion exposed × (odds ratio – 1)" divided by "(proportion exposed × (odds ratio – 1)) + 1", as previously described[19, 20].

ADDITIONAL RESULTS

Additional analyses were performed among participants with adult-onset asthma. Similar but non significant associations were observed between 12-month occupational exposure to asthmagens in general (1.5[0.8-2.7]), HMW (1.6[0.8-3.5]), LMW (1.4[0.7-2.7]), cleaning agents (1.6[0.7-3.8]) and uncontrolled asthma compared to participants with controlled asthma. The ORs for 10-year occupational exposure were similar or slightly lower. ORs lower than one were observed for partly-controlled asthma. According to asthma control dimensions, similar associations were observed for exacerbations, with lower associations for 10-year than for 12-month occupational exposure. For lung function, no significant associations were

observed. However an OR greater than 2 was observed between 12-month exposure to LMW agents and FEV < 80% compared to participants with controlled asthma. Increased risks were observed for 10-year occupational exposures to all asthmagens (1.5 to 2.7). No association was observed for the symptoms and activity limitations domains. Association between 10-year occupational exposure and uncontrolled asthma was stratified on BMI, smoking status, sensitization and gender. No significant associations were observed between exposure and uncontrolled asthma (*vs* controlled) except for HMW agents (2.5[1.0-6.2) among smokers. Higher ORs (from 1.4 to 2.0) were observed among non-smokers with OR lower than one for smokers. Higher ORs were observed among non-overweight participants with a stronger association for HMW agents. Higher ORs was observed in non-atopic participants. ORs were higher in men than in women for exposure to asthmagens in general whereas higher ORs were observed in women for LMW agents including cleaning agents.

Population attributable risks for uncontrolled adult-onset asthma were calculated for 12-month and 10-year occupational exposure to asthmagens and were found to be 9.4% and 12.6%, respectively.

Table E1 - Description of the ECRHS II population according to asthma status

	All participants				Current asthma		
	All	**Never asthma**	**Current asthma**	***p value***	**Childhood onset**	**Adult onset**	***p value***
	n=7,077	**n=5,867**	**n=1,210**		**n=503**	**n=616**	
Women,%	51.8	50.6	57.7	**	46.3	66.7	**
Age, mean (SD)	42.8 (7.2)	42.9 (7.1)	42.1 (7.2)	*0.001*	40.2 (7.0)	43.9 (6.8)	**
Body mass index, %	n=6,071	n=5,033	n=1,038	**	n=419	n=539	*0.05*
< 25 kg/m^2	52.5	53.6	47.0		51.1	44.3	
25-30 kg/m^2	35.2	35.1	35.6		34.8	36.4	
≥ 30 kg/m^2	12.3	11.3	17.4		14.1	19.3	
Smoking habits, %				*0.08*			*0.03*
Non smokers	45.2	44.6	48.1		52.3	45.8	
Ex-smokers	27.9	28.3	26.0		26.4	26.5	
Current smokers	26.9	27.1	25.9		21.3	27.7	
Age finishing full-time education , %				**			*0.07*
< 17 years old	18.1	17.0	23.1		20.7	24.8	
17 – 20	35.1	36.2	30.1		28.2	30.7	
> 20	46.8	46.8	46.8		51.1	44.5	
Asthma job exposure matrix*, %							
Men				*ns*			*ns*
Low risk for asthma	27.2	27.4	26.3		26.4	27.2	
High risk, Asthmagens	13.4	13.5	12.7		11.2	15.4	
Women				*0.03*			*ns*
Low risk for asthma	6.7	6.2	8.9		9.4	8.1	
High risk, Asthmagens	21.1	20.8	22.6		19.3	24.6	
Used of inhaled corticosteroids, past 12 months %	7.1	0.0	42.3	-	39.6	44.7	*0.09*
Sensitization	n=5,731	n=4,736	n=995	**	n=401	n=516	**
	30.0	23.2	62.3		76.8	50.6	
FEV_1% predicted, mean (SD)	n=6,046	n=5012	n=1034	**	n=418	n=536	*ns*
	99.4 (14.1)	101.2 (12.9)	90.9 (16.1)		90.7 (16.4)	91.0 (16.1)	
BHR, %	n=4,571	n=3,905	n=666	**	n=270	n=343	*0.004*
	14.4	8.0	52.1		59.6	47.8	

** p< *0.001*

* Past 12-month occupational exposures were evaluated through an asthma-specific job-exposure matrix (Kennedy et al, OEM 2000) which allowed estimation of exposure to 4 *a priori* 'non-asthmagenic agents' at ***low risk for asthma*** (low probability of exposure to asthmagens, exhaust fumes, high probability of exposure to environmental tobacco smoke, possible exposure to irritants) and exposure to 18 asthmagens at ***high risk for asthma*** (classified in 4 large categories: high molecular, low molecular weight agents, mixed environments, irritants peaks) including cleaning agents. For the present analysis, participants were classified as exposed to *a priori* 'non-asthmagenic' agents (considered at low risk for asthma when the asthma JEM was set up) only if they are not considered in addition as exposed to 'asthmagens' (see online supplement).

Sensitization was defined as a specific serum Immunoglobuline E antibodies to at least one out of four common inhalant allergen (house dust mite, cat, timothy grass or *Cladosporium herbarum*) at concentrations of 0.35 U/mL or more. According to baseline forced expiratory volume in the first second (FEV_1) based on Quanjer et al. reference values[17], participants were classified as 'with' (< 80% of predicted values) or 'without' low FEV_1. Bronchial hyper-reactivity (BHR) was defined as a reduction in maximum FEV_1 of at least 20% of its postsaline value for a methacholine dose of 1 mg or less.

Table E2-Description of ECRHS II population with asthma according to asthma control CHILDHOOD ONSET*

	Controlled asthma n=132	Partly controlled n=135	Uncontrolled asthma n=143	p value
Women,%	43.2	44.4	51.8	ns
Age, mean (SD)	40.3 (6.7)	40.5 (7.1)	40.3 (7.2)	ns
Sensitization to common allergens	n=119 74.0	n=118 78.0	n=113 80.5	ns
Total IgE > 100 kU/L, %	n=120 47.5	n=118 55.9	n=114 62.3	0.07
BHR, %	n=99 48.5	n=84 66.7	n=57 82.5	< 0.001
Used of inhaled corticosteroids, last 12 months %	n=131 16.8	n=131 40.5	n=142 68.3	< 0.001
Oral corticosteroids, past 12 months#	0.0	3.7	20.4	< 0.001
Asthma symptom score, %	n=131	n=130	n=143	< 0.001
0	22.1	11.5	0.7	
1	38.2	20.0	4.9	
2	23.7	30.0	18.2	
3	9.2	19.3	18.9	
4	3.8	11.5	30.8	
5	3.0	7.7	26.5	
Four domains of asthma control, %	n=132	n=135	n=143	
Lung function (Quanjer), FEV1 < 80%	0.0	14.3	37.8	< 0.001
Symptoms, past 3 months	0.0	51.1	91.6	< 0.001
Exacerbations, past 12 months	0.0	0.0	30.1	< 0.001
Activity limitation, past 12 months	0.0	24.4	44.1	< 0.001
Smoking habits, %	n=132	n=135	n=143	ns
Non smokers	49.2	53.3	52.5	
Ex-smokers	27.3	28.2	27.3	
Current smokers	23.5	18.5	20.3	
Age finishing full-time education , %	n=132	n=135	n=143	ns
< 17 years old	19.0	21.5	19.6	
17 – 20	28.0	27.4	33.6	
> 20	53.0	51.1	46.8	
Body mass index, mean (SD),%	n=130	n=124	n=121	0.10
< 25 kg/m^2	56.9	54.8	47.1	
25-30 kg/m^2	36.2	30.7	35.5	
$\geq$ 30 kg/m^2	6.9	14.5	17.4	
"Have you had to leave jobs (during follow-up) because it affected your breathing?"	n=131 6.1	n=132 6.1	n=137 8.8	ns
Asthma-specific job exposure matrix, %	n=132	n=135	n=143	ns
Non-asthmagenic irritants, in life	21.2	21.5	18.2	
Asthmagens, in life	17.4	17.8	17.5	

*** Out of 503 participants with childhood-onset asthma, 410 were classified as controlled, partly or uncontrolled asthma (n=93 missing values for asthma control)**

use of oral corticosteroids 'when needed', 'continuously', 'in short courses'(see Question 3, annex 1)

Sensitization to common allergens was defined as a specific serum Immunoglobuline E antibodies to at least one out of four common inhalant allergen (house dust mite, cat, timothy grass or *Cladosporium herbarum*) at concentrations of 0.35 U/mL or more.

According to baseline forced expiratory volume in the first second (FEV_1) based on Quanjer et al. reference values[17], participants were classified as 'with' (< 80% of predicted values) or 'without' low FEV_1.

Bronchial hyper-reactivity (BHR) was defined as a reduction in maximum FEV_1 of at least 20% of its postsaline value for a methacholine dose of 1 mg or less.

Table E3– Relationship between 12-month and 10-year occupational exposure to asthmagens and asthma in ECRHS II

	12-month occupational exposure, Asthma JEM*					10-year occupational exposure, Asthma JEM*				
	All **A/HMW/LMW/C** Exposed, n	Asthmagen, all	HMW, any	LMW, any	Cleaning agents	All **A/HMW/LMW/C** Exposed, n	Asthmagen all	HMW, any	LMW, any	Cleaning agents
Never asthma (reference)	4424 910/471/567/243	1.0	1.0	1.0	1.0	4771 1172/607/748/345	1.0	1.0	1.0	1.0
Current asthma	879 191/111/116/65	1.0 [0.8-1.2]	1.0 [0.8-1.3]	0.9 [0.7-1.2]	1.1 [0.8-1.4]	999 270/161/177/112	1.0 [0.9-1.2]	1.1 [0.9-1.3]	1.0 [0.8-1.2]	1.2 [0.9-1.5]
Age at asthma onset#										
Childhood-onset	364 66/35/41/17	0.8 [0.6-1.1]	0.8 [0.6-1.2]	0.8 [0.6-1.1]	0.8 [0.5-1.4]	400 90/50/58/26	0.8 [0.6-1.0]	0.8 [0.6-1.1]	0.8 [0.6-1.0]	0.7 [0.5-1.1]
Adult-onset	449 112/67/66/42	1.2 [0.9-1.5]	1.2 [0.9-1.6]	1.0 [0.8-1.4]	1.3 [0.9-1.8]	522 163/100/107/78	**1.3** **[1.1-1.6]**	**1.3** **[1.0-1.7]**	**1.3** **[1.0-1.6]**	**1.6** **[1.2-2.2]**

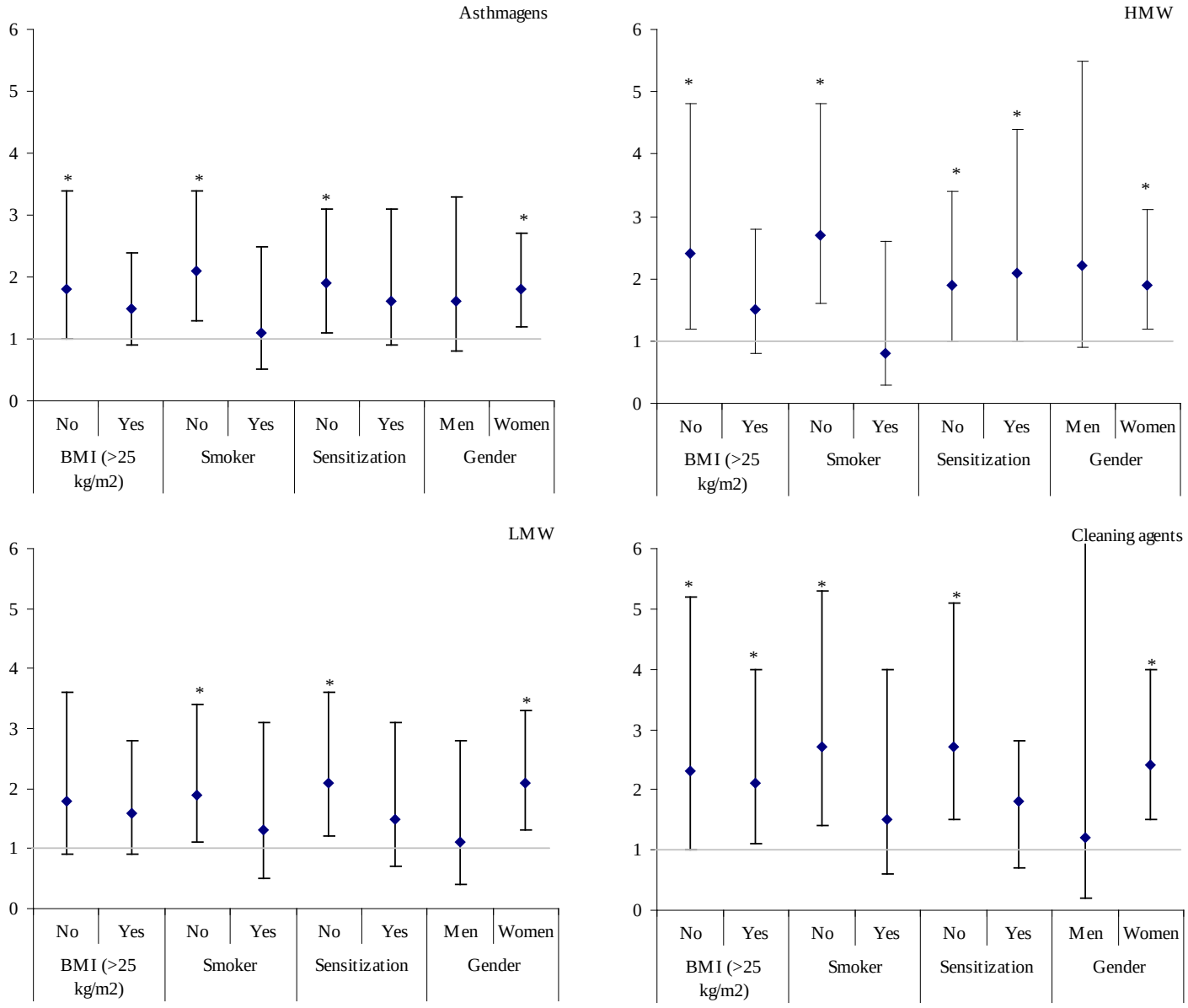
Adjusted for age, sex, smoking habits, country (random effect)

Reference: participants with 'never asthma'

* Participants exposed to asthmagens were compared to non exposed participants (participants exposed to non-asthmagens excluded). A: asthmagens; HMW: high molecular weight agents; LMW: low molecular weight agents; C: Cleaning agents

To study associations between occupational exposures and current asthma according to age at asthma onset, nominal logistic regressions were performed

Figure E1 – Relationship between 10-year occupational exposure to asthmagens and uncontrolled adult-onset asthma (*vs.* never asthma) stratified by BMI, Smoking, Sensitization, Gender



Adjusted for age, sex, smoking habits, country (random effect); Reference: participants with 'never asthma'
Participants exposed to non-asthmagenic agents or exposed to asthmagens were compared to non-exposed participants
BMI: body mass index
Atopic sensitization: participants classified 'with sensitization' have specific serum Immunoglobuline E antibodies to at least one out of four common inhalant allergen (house dust mite, cat, timothy grass or *Cladosporium herbarum*) at concentrations of 0·35 U/mL or more.

Annex 1 - Questions used to evaluate the three domains of asthma control

1- Lung function (FEV1 ≥ 80% predicted, yes/no), at the exam

2- Symptoms, in past 3 months

Q14.5 Have you had an attack of asthma in the last 12 months?
Q14.6 How many attacks of asthma have you had in the last 12 months?
Q14.7 How many attacks of asthma have you had in the last **3 months**?

Q14.8 How many times have you woken up because of your asthma in the last **3 months?**

every night or almost every night	1
more than once a week, but not most nights	2
at least twice a month, but not more than once a week	3
less than twice a month	4
not at all	5

Q14.9 How often have you had trouble with your breathing because of your asthma in the last **3 months?**

continuously	1
about once a day	2
at least once a week, but less than once a day	3
less than once a week	4
not at all	6

3- Exacerbations, in past 12 months

Q77.3 **oral steroids**
Q77.3.3 In the last 12 months, how have you used them:

a) when needed	1
b) ***in short courses***	2
c) ***continuously***	3

Q84. Since the last survey have you visited a hospital casualty department or emergency room because of breathing problems?

Q84.1 Have you visited a hospital casualty department or emergency room because of breathing problems in the last 12 months?

Q85. Since the last survey have you spent a night in hospital because of breathing problems?

Q85.1 Have you spent a night in hospital because of breathing problems in the last 12 months?

4- Limitation of activity, in past 12 months

Q90. Are you currently working?

Q90.1. How many days of work have you lost because of asthma, shortness of breath or wheezing in the last 12 months**?**

Q91. Have there been any days when you have had to **give up activities other than work** e.g. looking after children, the house, studying) because of your asthma, wheezing or shortness of breath in the last 12 months?

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