ONLINE REPOSITORY

Gender differences in prevalence, diagnosis and incidence of allergic and non-allergic asthma; a population-based cohort.

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COMPETING INTERESTS
The authors have no competing interests to declare.

METHODS

Study Design – Sample

At baseline (screening survey), large representative samples of the 20-44 year-olds from the general population were screened for asthma to estimate the variation in the prevalence of asthma, asthma-like symptoms and bronchial responsiveness in Europe (E1).

Definition and Analysis

The following questions were used to define asthma status:

1. Have you ever had asthma?

IF 'YES':

1.1. Was this confirmed by a doctor?

1.2. Have you had an attack of asthma in the last 12 months?

1.3. Are you currently taking any medicines including inhalers, aerosols or tablets for asthma?

Doctor-diagnosed asthma was defined as a positive answer to the questions "have you ever had asthma" *and* "was this confirmed by a doctor?".

Asthmatics who reported having had an attack of asthma in the last 12 months, or who were "currently taking any medicines including inhalers, aerosols or tablets for asthma" were considered to have ***current asthma***.

Symptoms of asthma in the last 12 months were considered via an ***asthma score*** that consists of a simple sum of positive answers to the 5 items: i) breathless while wheezing, ii) woken up with a feeling of chest tightness, iii) attack of shortness of breath at rest, iv) attack of shortness of breath after exercise, and v) woken by an attack of shortness of breath. This score

was derived from a previously proposed score including 8 items (E2), but the 3 questions including the term "asthma" were not considered to reduce possible bias related to potential differences in diagnostic practices.

Asthma incident cases were defined as subjects who reported never having had asthma at baseline and who reported a doctor-diagnosis of asthma at the follow-up survey.

Bronchial hyper-responsiveness (BHR) was defined as a decrease in forced expiratory volume in 1 second (FEV_1) of 20% or more, as compared to FEV_1 post-dilutent, at a cumulative methacholine dose ≤1mg.

To examine differences in age-specific prevalence at each survey and assess possible cohort or period effects, participants were divided into age groups of 8 years each, corresponding to the mean duration of follow-up (E3). Thus, 80 to 97% of the subjects included in one age-group at follow-up were in the preceding age group at baseline.

Chi-square tests were used to test for differences in asthma prevalence, remission and persistence. Cox regression models were used to test for gender differences in the risk of new-onset asthma after adjustment for potential confounders and compute hazard ratios (HR).

Participants were considered to have ***allergic rhinitis*** if they answered positively to the questions "Do you have any nasal allergies including hay fever?". ***Maternal asthma,*** or ***severe respiratory infections in childhood*** were defined according to the participant's answers to the corresponding questions. ***Smoking*** was considered using four categories: ***non-smokers, ex-smokers*** (stopped for ≥1 year), ***moderate smokers*** (<20 cigarettes a day), and

heavy smokers (≥20 cigarettes a day). Reported age at leaving ***education*** was used. ***Body mass index (BMI)*** was calculated as weight in kilogram divided by the square of height in meters, and was included in the analysis as a categorical variable. The complete work history over the follow-up was recorded at ECRHS-II. Any job held during the follow-up were linked to an asthma-specific job exposure matrix. The participants' ***occupational exposure*** to agents known to be related to occupational asthma was considered using 3 categories : "no exposure", "low-risk exposure" and "high exposure". Adjustment for FEV_1 was carried out after standardization through Z-scores, in order to control for the physiological differences in FEV_1 between men and women.

Subjects who reported never having had asthma at baseline were considered to be ***at risk*** for incident asthma. ***Incident asthma cases*** were defined as those at risk who reported a doctor-diagnosis of asthma at the follow-up survey. To compute incidence estimates the person-years contributed by each individual was defined as the number of years from the baseline survey to the age at first asthma attack reported at follow-up in incident cases, or to the age at follow-up in those without asthma. Incident cases who reported at follow-up that asthma onset occurred at an age prior to the age at baseline, but less than 5 years before baseline, contributed to 1 day follow-up (E4). We set the limit of 5 years considering that a discrepancy of less than 5 years could be due to inaccurate recall when reporting age of onset (E3). Subjects with onset of asthma more than 5 years before baseline were excluded from the analysis. Cox regression models were used to estimate the adjusted hazard-ratio (HR), the ratio of the instantaneous hazard of developing asthma at time t in women without asthma until time t, compared with that in men, after adjustment for potential confounders, and to test for potential interactions.

The protocol at follow-up included IgE measurements to 4 common allergens. ***Atopic sensitization*** was defined as having specific IgE≥0.35 kU/L to any of the four specific allergens tested at ECRHS-II (*Dermatophagoides pteronyssinus,* timothy grass, cat and *Cladosporium herbarum)*. The asthma incident cases were first divided into "***allergic asthma" and "non-allergic asthma" incident cases***, according to whether they were or were not sensitized to any of the four specific allergens tested at ECRHS-II.

The protocol at baseline included assessment of sensitization via skin tests to nine common allergens in addition to IgE measurements. In order to appraise how much the findings might be influenced by possible misclassification of "allergic" subjects as "non-allergic", we rerun the analysis considering as ***allergic-asthma incident cases*** also those with negative IgE at follow-up but positive skin tests at baseline. Skin-prick tests were done with Phazets (Pharmacia Diagnostics, Uppsala, Sweden), which are lancets coated with standardised lyophilised allergens extracts. The allergens selected in all centres were *Dermatophagoides pteronyssinus* (house dust mite), cat, *Alternaria alternata*, *Cladosporium herbarum*, timothy grass, birch, *Parietaria judaica*, olive, and common ragweed. Results were regarded as positive if the mean weal diameter was over 3 mm. Individuals with at least one positive skin-prick test were considered to be atopic **(see Model 1b in table E4, and cross tables in table E6)**.

RESULTS

Participation

Overall, 87,188 individuals (51.74% female) completed the screening questionnaire, 15,483 were invited to ECRHS-I-stage-2 and answered the asthma questions, of whom 9,091 (52.41% female) completed the asthma questions at follow-up (mean follow-up 8.78 years (standard deviation 1.22)) (**figure E1**). Participation at follow-up was similar in men and women. In addition, when stratified by age-group, no significant interaction between sex and asthma could be detected for the likelihood to participate in follow-up.

Investigating possible differential diagnosis

Besides diagnosed asthma, women were also more likely than men to report asthma-like symptoms (34.3% vs. 30.0% reported at least one asthma-like symptoms; $p<0.001$). Women were also more likely to have respiratory symptoms *and* bronchial hyper-responsiveness (BHR) (**Table 1**), even when the analysis was limited to non-smokers (5.1% vs. 4.1%; OR=1.25 95%CI 1.03-1.52).

Furthermore, when comparing men and women reporting the same asthma-like symptoms and smoking history, the proportion of women in whom asthma had been diagnosed was generally close to, - or even lower than -, the proportion of men in whom asthma had been diagnosed (**Table_E1**). In particular, among individuals with respiratory symptoms *and* BHR (**Table 2**), the likelihood to have received a diagnosis of asthma decreased with increasing smoking and was higher in atopic than in non-atopic subjects, but, in each strata, it was similar or even lower in women than in men.

Sensitivity analysis : gender differences in the incidence of allergic asthma and non-allergic asthma, with allergic asthma defined according to skin tests results.

The protocol at follow-up included assessment of specific IgE to 4 common allergens. The protocol at baseline additionally included assessment of sensitization via skin tests to nine common allergens. In order to appraise how much the findings might be influenced by possible misclassification of "atopic" subjects as "non-atopic", we rerun the analysis considering as allergic-asthma incident cases also those with negative IgE at follow-up but positive skin tests at baseline. Using this definition, the proportion of incident cases found to have non-allergic asthma was still 57% in women (vs. 32% in men), and the incidence of non-allergic asthma remained significantly higher in women than in men (HR=3.54 (95%CI 2.16-5.82)). Again, no significant difference was observed for the incidence of allergic asthma. **(see Model 1b in table E4, and cross tables in table E6)**

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Table E1 Comparison of the likelihood to be diagnosed with asthma in men and women according to the number of asthma like symptoms, and smoking history

		(n/N) % of subjects diagnosed with asthma			
		in never-smokers	*in ex-smokers*	*in moderate smokers*	*in heavy smokers*
symptoms score*					
score=1	Men	(22/346) **6.4**	(9/228) **4.0**	(6/296) **2.0**	(5/400) **1.3**
	Women	(16/556) **2.9**	(11/242) **4.6**	(8/383) **2.1**	(3/273) **1.1**
	p‡	**0.02**	**0.75**	**0.96**	**0.86**
score=2	Men	(28/119) **23.5**	(10/90) **11.1**	(6/90) **6.7**	(5/161) **3.1**
	Women	(41/237) **17.3**	(11/109) **10.1**	(14/184) **7.6**	(3/116) **2.6**
	p‡	**0.17**	**0.82**	**0.78**	**0.80**
score=3	Men	(60/125) **48.0**	(37/90) **41.1**	(30/107) **28.0**	(27/138) **19.6**
	Women	(113/262) **43.1**	(39/106) **36.8**	(40/130) **30.8**	(20/114) **17.5**
	p‡	**0.36**	**0.54**	**0.65**	**0.68**
score≥1+BHR†	Men	(47/105) **44.8**	(26/64) **40.6**	(18/50) **36.0**	(13/80) **16.3**
	Women	(69/177) **39.0**	(28/79) **35.4**	(23/106) **21.7**	(8/93) **8.6**
	p‡	**0.34**	**0.52**	**0.06**	**0.13**

* Number of positive answers to any of the 5 following items: breathless while wheezing, woken up with a feeling of chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise, and woken by an attack of shortness of breath. Data from ECHRS I – stage2.

† in subjects with at least one asthma-like symptoms and BHR (as presented in table 2 of the manuscript)

‡ p values are for gender differences in the proportion of subjects reporting a diagnosis of asthma (Chi-square test or Fisher exact test when number of subjects are low).

Table E2. – Gender differences in age at first asthma attack and asthma treatment, in men and women with current doctor-diagnosed asthma

	ECRHS I – stage 2 Asthmatic		ECRHS II Asthmatic	
	Men (n=269)	Women (n=351)	Men (n=220)	Women (n=304)
Age at first asthma attack, %				
<10 years	42.7	26.2	32.7	19.6
10-19 years	28.3	23.3	24.3	17.9
≥ 20 years	29.0	50.4	43.0	63.0
p for gender difference		*p<0.0001*		*p<0.0001*
Treatment				
used in last 12 months				
inhaled short-acting β-2 agonist, %	70.3	73.2	65.9	64.5
p for gender difference		*0.42*		*0.73*
inhaled long-acting β-2 agonist*, %			14.6	17.8
p for gender difference				*0.33*
% inhaled steroids, %	25.3	35.3	42.7	46.7
p for gender difference		*0.007*		*0.36*
oral steroids, %	5.2	11.4	5.0	7.9
p for gender difference		*0.007*		*0.19*
used every year since last survey*				
Inhaled steroids, %			19.6	27.6
p for gender difference				*0.04*

* information not available at ECRSH I ;

Table E3. – Comparison between men and women characteristics at baseline, and effect of adjustment for intermediate and confounding variables on the Hazard Ratio for the gender difference in asthma incidence

	Females*	Males*	RR* (95% C.I)		% missing	HR‡ (95% C.I.)	
						1.67	(1.22 - 2.28)
Baseline							
Mean Age (SD)	34.1 (7.1)	34.3 (7.1)	0.998	(0.994 - 1.002)	0.0	1.67	(1.22 - 2.28)
BMI					0.0	1.72	(1.25 - 2.37)
≤ 25	76.67	59.57	1				
25 – 35	21.24	40.02	0.60	(0.56 - 0.65)			
>35	2.09	0.41	1.42	(1.27 - 1.58)			
Maternal asthma	6.92	4.76	1.21	(1.11 - 1.33)	0.0	1.63	(1.19 - 2.23)
Respiratory Infections < 5 years	9.54	8.37	1.08	(0.99 - 1.18)	4.2	1.90	(1.36 - 2.65)
IgE to dust mites	11.04	18.11	0.72	(0.66 - 0.79)	0.0	1.83	(1.33 - 2.50)
IgE to cat	6.89	6.98	0.99	(0.89 - 1.09)	0.0	1.66	(1.22 - 2.27)
IgE to grass	13.47	18.97	0.79	(0.73 - 0.86)	0.0	1.74	(1.27 - 2.38)
Atopy	23.02	31.77	0.79	(0.74 - 0.84)	0.0	1.80	(1.31 - 2.46)
Rhinitis	23.73	22.42	1.04	(0.98 - 1.10)	0.0	1.65	(1.21 - 2.25)
Total IgE > 100	17.22	24.31	0.80	(0.74 - 0.85)	0.0	1.80	(1.31 - 2.46)
Smoking					0.0	1.66	(1.21 - 2.28)
Never	47.70	40.77	1				
Ex smoking	21.34	22.70	1.13	(1.05 - 1.21)			
Current	30.96	36.53	1.19	(1.11 - 1.28)			
Mean packyears, (SD)	5.5 (8.7)	9.4 (13.3)	0.98	(0.97 - 0.98)			
Passive Smoking	52.04	22.42	0.89	(0.84 - 0.93)	0.4	1.65	(1.20 - 2.25)
Education					12.5	1.86	(1.33 - 2.61)
Primary	22.40	21.22	1				
Secondary	39.94	39.12	1.00	(0.93 - 1.08)			
High	37.66	39.66	0.96	(0.89 - 1.04)			
Mean family size (SD)	2.3 (1.8)	2.3 (1.8)	1.004	(0.989 - 1.018)	0.1	1.66	(1.22 - 2.27)
Mean zFEV1†, (SD)	0.07 (0.8)	0.07 (1.1)	1.001	(0.974 - 1.029)		1.77	(1.29 - 2.43)
Follow-up							
Mean Age (SD)	42.9 (7.1)	43.1 (7.1)	0.998	(0.995 - 1.002)	0.0	1.67	(1.22 - 2.28)
BMI					16.0	1.99	(1.40 - 2.83)
≤ 25	60.36	41.80	1				
25 - 35	35.44	56.07	0.64	(0.60 - 0.68)			
>35	4.20	2.13	1.09	(0.97 - 1.23)			
Mean change in BMI (SD)	1.7 (2.7)	1.5 (1.9)	1.14	(1.05 - 1.22)	16.0	2.07	(1.46 - 2.95)
Smoking					4.2	1.65	(1.20 - 2.27)
Never	45.92	38.71	1				
Ex smoking	27.77	31.44	1.07	(1.00 - 1.15)			
Current	26.31	29.85	1.26	(1.16 - 1.36)			
Mean packyears, (SD)	7.5 (12.2)	13.1 (20)	0.98	(0.98 - 0.99)			
Mean change in packyears (SD)	2.2 (6.4)	3.9 (12.8)	0.99	(0.99 - 0.99)	3.6	1.67	(1.21 - 2.30)
Occupational Exposure					0.0	1.63	(1.17 - 2.26)
No exposure	65.33	51.45	1				
Low exposure	6.58	27.80	0.34	(0.30 - 0.38)			
High exposure	22.11	15.51	1.03	(0.98 - 1.09)			
Missing information	5.98	5.24	0.94	(0.82 - 1.07)			

* Figures are percentage, except for age, pack-years, family size, zFEV1, change in BMI, and change in pack years, where means are provided with standard deviation in brackets. RR is relative risk for women to have the characteristic listed in 1 column, as compared to men

† Internally standardised difference between FEV1 and value predicted for sex, age and height, divided by residual standard deviation

‡ HR for the association between gender and incident asthma after adjustment for the variables in column 1 using Cox regression among subjects with no missing values for underlined variables

Table E4 - Incidence of allergic and non-allergic asthma in women and men who reported they never had asthma at baseline.

		Number of incident cases		Person-Years		Incidence per 1000 PY (95%CI)		Hazard Ratio* (95%CI)
		Women	Men	Women	Men	Women	Men	Women/Men
Model 1 – In all subjects without asthma at baseline	***Allergic asthma***	44	39	27403	27189	1.61 (1.13-2.08)	1.43 (0.98-1.88)	**1.12 (0.73-1.72)**
	Non-allergic asthma	81	23	27403	27189	2.96 (2.31-3.60)	0.85 (0.50-1.19)	**3.51 (2.21-5.58)**
Model 2 – Model 1 after excluding subjects who were current smokers at baseline	***Allergic asthma***	30	26	17771	15817	1.69 (1.08-2.29)	1.64 (1.08-2.29)	**1.01 (0.59-1.71)**
	Non-allergic asthma	55	14	17771	15817	3.09 (2.28-3.91)	0.89 (0.42-1.35)	**3.46 (1.92-6.22)**
Model 3 – Model 1 but further excluding incident cases with an age at onset in the 5 years before baseline	***Allergic asthma***	30	26	27403	27189	1.09 (0.70-1.49)	0.96 (0.59-1.32)	**1.15 (0.68-1.94)**
	Non-allergic asthma	68	19	27403	27189	2.48 (1.89-3.07)	0.70 (0.38-1.01)	**3.58 (2.15-5.95)**
Model 4 – Model 1 but further excluding subjects with asthma like symptoms (score>0) *and* BHR at baseline	***Allergic asthma***	37	35	26718	26870	1.38 (0.94-1.83)	1.30 (0.87-1.73)	**1.06 (0.67-1.69)**
	Non-allergic asthma	72	22	26718	26870	2.69 (2.07-3.32)	0.82 (0.48-1.16)	**3.31 (2.05-5.34)**
Model 5 – Model 1 but further excluding any subjects with asthma like symptoms at baseline	***Allergic asthma***	26	21	20006	20540	1.30 (0.80-1.80)	1.02 (0.59-1.46)	**1.27 (0.71-2.25)**
	Non-allergic asthma	45	12	20006	20540	2.25 (1.59-2.91)	0.58 (0.25-0.91)	**3.90 (2.06-7.38)**
Model 1b – using skin test results at baseline in addition to specific IgE at follow-up to define allergic asthma incident cases (†)	***Allergic asthma***	54	42	27403	27189	1.97 (1.44-2.50)	1.54 (1.08-2.01)	**1.27 (0.85-1.91)**
	Non-allergic asthma	71	20	27403	27189	2.59 (1.99-3.19)	0.74 (0.41-1.06)	**3.54 (2.16-5.82)**

* Hazard-Ratios obtained from Cox analysis (based on age at asthma onset) for incidence of doctor-diagnosed asthma, in subjects who reported they never had asthma at baseline. Excluding incident cases with age at asthma onset missing *or* age at onset ≥ 5 years before baseline (see Methods)
(†) as Model 1, but considering as allergic-asthma incident cases also those with negative IgE at follow-up but positive skin tests at baseline

Table E5. Increase in the percentage of subjects with atopic sensitisation in younger age groups as compared to older subjects, in men and women (data at baseline).

	Men					Women				
Age at baseline*	N	% with IgE sensitisation	Odds-Ratio	95% Confidence Interval		N	% with IgE sensitisation	Odds-Ratio	95% Confidence Interval	
20-27 years	915	41.3%	1.58	1.33	1.87	931	32.1%	1.52	1.27	1.82
28-35 years	1144	36.4%	1.28	1.09	1.50	1242	28.3%	1.27	1.07	1.51
36-44 years	1529	30.9%	1.00	(Ref)		1564	23.7%	1.00	(Ref)	

*** subjects with age greater than 45 years were excluded from the table**

Table E6. Association between specific IgE sensitization at follow-up and skin tests reactivity at baseline and specific IgE sensitisation at baseline, in men and women participating to follow-up

	Subjects WITH specific IgE sensitization at Follow-up			Subjects WITHOUT positive IgE sensitization at Follow-up*					
	N*	% WITH IgE sensitization at baseline		N*	% WITHOUT IgE sensitization at baseline		Kappa	95% CI	
Men	1002	83.3%		2053	89.4%		0.72	0.70	0.75
Women	773	81.5%		2289	91.9%		0.72	0.69	0.75
	N*	% WITH positive skin-test at baseline		N*	% WITHOUT positive skin test at baseline		Kappa	95% CI	
Men	893	78.2%		1825	89.8%		0.68	0.65	0.71
Women	702	75.8%		2073	88.6%		0.62	0.59	0.66
	ASTHMATICS incident cases WITH specific IgE sensitization at Follow-up ("allergic incident cases")			ASTHMATICS incident cases WITHOUT positive IgE sensitization at Follow-up ("non-allergic incident cases")					
	N	% WITH positive skin-test at baseline		N	% WITHOUT positive skin test at baseline				
Men	32	78.1%		17	82.4%				
Women	31	67.7%		66	84.9%				

*** Among subjects with IgE-sensitization at follow-up, 237 men and 371 women had missing value for specific IgE at baseline, and 465 men and 587 women had no skin test measures at baseline. Among subjects witouth positive IgE at follow-up, there were 138 men and 150 women with no measure of specific IgE at baseline, and 247 men and 221 women with no skin test measures at baseline.**

Figure E1 - Flow diagram for participation at each step of the analysis on gender differences in asthma