ORIGINAL ARTICLE

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

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ABSTRACT

Background Although women with severe non-allergic asthma may represent a substantial proportion of adults with asthma in clinical practice, gender differences in the incidence of allergic and non-allergic asthma have been little investigated in the general population.

Methods Gender differences in asthma prevalence, reported diagnosis and incidence were investigated in 9091 men and women randomly selected from the general population and followed up after 8—10 years as part of the European Community Respiratory Health Survey. The protocol included assessment of bronchial responsiveness, IgE specific to four common allergens and skin tests to nine allergens.

Results Asthma was 20% more frequent in women than in men over the age of 35 years. Possible under-diagnosis of asthma appeared to be particularly frequent among non-atopic individuals, but was as frequent in women as in men. The follow-up of subjects without asthma at baseline showed a higher incidence of asthma in women than in men (HR 1.94; 95% CI 1.40 to 2.68), which was not explained by differences in smoking, obesity or lung function. More than 60% of women and 30% of men with new-onset asthma were non-atopic. The incidence of non-allergic asthma was higher in women than in men throughout all the reproductive years (HR 3.51; 95% CI 2.21 to 5.58), whereas no gender difference was observed for the incidence of allergic asthma.

Conclusions This study shows that female sex is an independent risk factor for non-allergic asthma, and stresses the need for more careful assessment of possible non-allergic asthma in clinical practice, in men and women.

Key messages

What is the key question?

- Are women really at increased risk of asthma, and what could explain this difference?

What is the bottom line?

- Women were found to be at increased risk of developing non-allergic asthma (no difference was found for allergic asthma), and this increased risk was not explained by differences in diagnosis, lung function (as a surrogate of airway calibre), obesity or smoking.

Why read on?

- Our data provide evidence that non-allergic asthma is still poorly recognised in men and women, and that women are at increased risk of developing non-allergic asthma compared with men. We suggest that sex hormones or other biological markers that significantly differ between men and women (such as adipocytes) may be involved in the development of non-allergic asthma.

INTRODUCTION

The prevalence of asthma shows a sex reversal around puberty from a higher risk in boys early in life to a higher risk in girls after adolescence.[1–6] This pattern has raised several hypotheses about the susceptibility to asthma of men and women, such as an effect of sex hormones, airway calibre, obesity, differences in exposure or diagnosis.[1–6] Further studies are needed to appraise how much these determinants could explain the higher risk of asthma in women. Data are lacking on whether women remain at increased risk of asthma throughout all the reproductive years, and few studies have investigated the possibility of a differential diagnosis.[2–8] Furthermore, most studies are not of a prospective nature that allows separating new-onset asthma from persistent asthma or relapse. In addition, new-onset of non-allergic asthma appears to be relatively frequent in adulthood.[9] Clinical studies suggest that non-allergic (or 'intrinsic') asthma may be more severe and difficult to control than allergic asthma, and that women might be at increased risk of non-allergic asthma.[10–14] However, most of our knowledge on non-allergic asthma comes from clinical studies which often include patients with more severe asthma, and little is known on non-allergic asthma in the general population.[14]

We used data collected as part of the European Community Respiratory Health Survey (ECRHS) to estimate gender differences in the prevalence of asthma according to age; appraise possible differences in asthma diagnosis; prospectively investigate gender differences in the remission/persistence of asthma; and assess gender differences in the risk of new-onset asthma, accounting for potential confounders and considering allergic and non-allergic asthma separately, within the age range 20–55 years.

METHODS

Study design

The analysis is based on data collected in 29 centres from 14 countries as part of the ECRHS. The protocol and participation rates have been described elsewhere.[15–17] Briefly, between 1991 and 1993, each participating centre randomly selected about 1500 men and 1500 women, representative of the age group 20–44 years, to answer a postal questionnaire (European Community Respiratory Health Survey I [ECHRS-I] stage 1; 'screening'). A 20% random sample of respondents was then invited to a clinical investigation (ECHRS-I stage 2). Participants in stage 2 were eligible for the follow-up survey in 1998–2002 (ECRHS-II). At ECHRS-I stage 2 ('baseline') and follow-up, the protocol included assessment of respiratory symptoms via questionnaire and measurements of bronchial responsiveness and IgE specific to four common allergens. In each centre, the protocol was approved from the appropriate ethics committee, and written consent was obtained from each participant.

Analysis

Doctor-diagnosed asthma was defined as a positive answer to the questions 'Have you ever had asthma?' and 'Was this confirmed by a doctor?' Because only specific IgEs were assessed at follow-up, the main analysis was conducted with atopy defined as specific IgE≥0.35 kU/litre to any of the four common allergens tested. In a sensitivity analysis, atopic status was defined according to specific IgE and skin test reactivity measured at the baseline survey for nine common allergens. Atopic subjects with asthma were considered to have 'allergic asthma'. Further details including cross tables are provided in the online supplement. All the analyses were conducted in Stata V.8 (StataCorp 2001).

RESULTS

Gender differences in asthma prevalence and diagnosis

Participation of men and women at each step of the survey is described in the online supplement.

Prevalence

At ECRHS-I stage 1 (table 1, first column), large representative samples were screened to estimate asthma prevalence.[15] There was no gender difference in the prevalence of asthma from age 20 to 35 years. However, women had a 20% higher risk of asthma than men after age 35 years. This pattern of results was consistent across the participating centres, despite large geographical variations in the prevalence of asthma.

To assess whether the magnitude of the gender difference had changed over time, we considered prevalence at ECRHS-II. Although the prevalence of asthma was higher at ECRHS-II, within each age-group the ORs for the gender difference were remarkably similar at each survey, showing no difference before age 35 and a 20% higher risk of asthma in women in the age group 36–44 years (table 1, third column). The higher risk of asthma in women appears to be further marked after age 45 years (OR 1.68; 95% CI 1.24 to 2.29).

Investigating possible differential diagnosis

We considered data collected at ECRHS-I stage 2 (including bronchial hyperresponsiveness [BHR] assessment) to assess whether the higher prevalence of asthma in women could be explained by differences in diagnosis.

Besides diagnosed asthma, women were also more likely than men to have asthma-like symptoms or asthma-like symptoms and BHR (table 1 and online supplement).

Furthermore, among subjects with respiratory symptoms and BHR (table 2), the likelihood of having received a diagnosis of asthma decreased with increasing smoking and was higher in atopic than in non-atopic subjects. However, in each group, it was similar or even lower in women than in men. As shown in table 2, in non-atopic subjects, only 16% of those with asthma-like symptoms and BHR reported a diagnosis of asthma. However, this low rate of diagnosis was similar in women and in men.

No major gender difference was observed for asthma treatment, apart from a more frequent use of inhaled steroids in women (online supplement, table E2).

Gender differences in the natural history of asthma

Forty-three per cent of men and 63% of women with a current diagnosis of asthma from the doctor at follow-up reported asthma onset in adulthood (online supplement, table E2).

Asthma remission, persistence and relapse in subjects with asthma at baseline

Women with current asthma at baseline were as likely as men to still have asthma at follow-up (asthma persistence: 68.1% in 213 women vs 74.1% in 135 men; p>0.20).

In subjects who had ever had asthma before the baseline survey, but without 'current' asthma at baseline, women were as likely as men to have current asthma at follow-up (asthma relapse after remission: 21.2% in 189 women vs 18.0% in 178 men; p>0.30).

Asthma incidence

The risk of developing asthma over the follow-up was investigated in the 4281 women and 3956 men without asthma at baseline (figure 1). The asthma incidence rate was higher in women than in men (table 3). There was no interaction with age (p for interaction =0.13). At baseline, women more frequently reported rhinitis, respiratory infections in childhood and maternal asthma compared with men. Women less frequently had positive specific IgE to dust mites and grass, had lower total IgE and smoked less than men. Women had lower body mass index (BMI) than men at baseline and at follow-up, but the mean increase in BMI between the two surveys was slightly higher in women than in men. Adjustment for the subject's characteristics at baseline or follow-up had little effect on the gender difference in incidence (online supplement, table E3**)**. The risk of developing asthma remained significantly higher in women than in men after adjustment for centre, maternal asthma, smoking, total IgE, atopic sensitisation, rhinitis, forced expiratory volume in 1 s (FEV_1) and BMI at baseline (HR 1.94; 95% CI 1.40 to 2.68) as well as after additional adjustment for change in smoking status and change in BMI (HR 2.25; 95% CI 1.57 to 3.23). Further adjustment for occupational exposure over the follow-up to agents known to be related to occupational

Table 1 Prevalence of asthma in representative samples of men and women screened for asthma at ECRHS-I, and in men and women participating in ECHRS-I, stage 2 (1991–1993) and ECHRS-II (1998–2002)

	ECRHS-I screening (N = 87 188)		ECRHS-I, stage 2 (N = 15 483)		ECRHS-II (N = 9091)	
Current asthma (number of cases/number of subjects included*) %						
Age 20–27 years						
Men	(731/12 897)	5.67	(103/1998)	5.16		–
Women	(769/13 694)	5.62	(114/2099)	5.43		–
OR†	0.98 (95% CI 0.88 to 1.09)		1.06 (95% CI 0.80 to 1.39)			–
Age 28–35 years						
Men	(622/13743)	4.53	(97/2371)	4.09	(62/940)	6.60
Women	(696/14655)	4.75	(110/2670)	4.12	(64/1016)	6.30
OR	1.03 (95% CI 0.92 to 1.16)		1.01 (95% CI 0.76 to 1.33)		0.95 (95% CI 0.66 to 1.37)	
Age 36–44 years						
Men	(641/14608)	4.39	(95/2803)	3.39	(89/1551)	5.74
Women	(841/15909)	5.29	(141/3004)	4.69	(120/1751)	6.85
OR	1.21 (95% CI 1.09 to 1.34)		1.40 (95% CI 1.08 to 1.83)		1.21 (95% CI 0.91 to 1.60)	
Age 45–52 years						
Men					(70/1491)	4.69
Women					(124/1648)	7.52
OR					1.68 (95% CI 1.24 to 2.29)	
Doctor-diagnosed current asthma (n/N) %						
Men			(269/7411)	3.63	(220/4317)	5.10
Women			(351/8053)	4.36	(304/4753)	6.40
OR			1.21 (95% CI 1.03 to 1.42)		1.27 (95% CI 1.06 to 1.52)	
Subjects reporting ≥3 asthma-like symptoms‡ (n/N) %						
Men			(467/7418)	6.30	(227/4326)	5.25
Women			(628/8065)	7.79	(338/4765)	7.09
OR			1.26 (95% CI 1.11 to 1.42)		1.38 (95% CI 1.16 to 1.64)	
Asthma-like symptoms plus bronchial hyperresponsiveness (n/N§) %						
Men			(308/6809)	4.52	(147/3853)	3.82
Women			(464/7092)	6.54	(230/4072)	5.65
OR			1.48 (95% CI 1.27 to 1.71)		1.51 (95% CI 1.22 to 1.87)	

*1190 subjects with age at screening >44 years and 492 subjects with data on 'current asthma' missing at the screening survey were not included. For ECRHS-I stage 2 the corresponding figures are 519 and 19. For ECRHS-II, 673 subjects with age >52 years and 21 with data on 'current asthma' missing were not included.
†OR >1 indicates a higher prevalence in women compared with men. For ECRHS-I screening the ORs are Mantel-Haenszel OR stratified for centre. Within each age group, Breslow-Day tests for heterogeneity across centres were all not significant (p>0.30). Other ORs are crude estimates.
‡Number of positive answers to any of the five 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.
§Subjects were only included if they did not have missing values for the BHR test.
ECHRS, European Community Respiratory Health Survey.

asthma did not change the estimate (HR 2.25; 95% CI 1.54 to 3.29).

Incidence of allergic and non-allergic asthma

Women were at greater risk of developing non-allergic asthma than allergic asthma: 65% of the women with new-onset asthma had no atopic sensitisation at follow-up. In men, 37% of incident asthma cases were non-atopic. No gender difference was observed for the incidence of allergic asthma (p>0.60; table 3). In contrast, the incidence of non-allergic asthma was significantly higher in women than in men (HR 3.51; 95% CI 2.21 to 5.58; p<0.0001). In men, the incidence rate of non-allergic asthma remained very low until the age of 40 years and then increased to levels similar or slightly higher than that for allergic asthma (figure 2). In women, the incidence rate of non-allergic asthma was already relatively high between the ages of 20 and 30 years, and it remained high and significantly higher than that in men throughout all the reproductive years. A similar pattern of results was obtained in the sensitivity analyses, including the analysis using skin test results for the nine common allergens to define atopy (online supplement, tables E4–E6).

DISCUSSION

In this large population-based cohort, the gender difference in the prevalence of asthma increased with increasing age and showed an increased risk of more than 20% in women than in men after age 35 years. The findings were consistent across the centres and during the two survey periods. Possible under-diagnosis of asthma appeared to be particularly frequent in non-atopic subjects, but was not more frequent in men than in women. In subjects without asthma at baseline, the risk of new-onset asthma over the follow-up was twofold higher in women than in men, and this was not explained by differences in smoking, lung function or obesity. More than 60% of the women with new-onset asthma were not sensitised to any of the allergens tested. The incidence of non-allergic asthma was significantly higher in women than in men throughout all the reproductive years, whereas no gender difference was observed for the incidence of allergic asthma.

Gender differences in non-allergic asthma

To our knowledge, this is the first study to demonstrate that the incidence of non-allergic asthma is higher in women than in men

Table 2 Asthma diagnosis in men and women with asthma-like symptoms and bronchial hyperresponsiveness

	Subjects diagnosed with asthma* in men and women with asthma-like symptoms and BHR (n/N) %					
	All subjects		**Non-smokers§**		**Current smokers**	
Men	(105/306)	34.3	(73/169)	43.2	(31/130)	23.9
Women	(131/463)	28.3	(97/256)	37.9	(31/199)	15.6
p Value†		p=0.08		p=0.27		p=0.06
Atopic subjects						
Men	(80/191)	41.9	(56/120)	46.7	(23/64)	35.9
Women	(88/223)	39.5	(67/148)	45.3	(19/71)	26.8
p Value†		p=0.62		p=0.82		p=0.25
Non-atopic subjects‡						
Men	(12/77)	15.6	(9/27)	33.3	(3/50)	6.0
Women	(29/182)	15.9	(20/83)	24.1	(9/98)	9.2
p Value†		p=0.94		p=0.34		p=0.75

*Data from ECRHS-I, stage 2. Proportion of subjects reporting current doctor-diagnosed asthma among subjects with BHR and asthma-like symptom (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) in the last 12 months.
†p Values are for gender differences in the proportion of subjects reporting a diagnosis of asthma (χ^2 test or Fisher exact test when number of subjects is low).
‡Overall, there were 6032 men and 6050 women with IgE to the four allergens tested of whom 77 (1.28%) men and 182 (3.01%) women had asthma-like symptoms and BHR but no atopic sensitisation.
§Non-smokers include never smokers and smokers who had quit smoking for more than 1 year.

throughout all the reproductive years. In the Tucson cohort, Dodge and Burrows reported that new diagnoses of asthma in subjects older than 40 years occurred almost entirely in women, and these subjects had no more allergic sensitisation than the remainder of the population.[6] Following a group of children from age 10 to 20 years, Nicolai *et al* observed that most of the incident cases were female, and atopy at age 10 was not associated with subsequent asthma onset.[18] More recently, Mandhane *et al* reported that in the Dunedin birth cohort, atopy was a risk factor for adolescent wheeze in boys but not in girls.[19] However, none of these studies have assessed the magnitude and significance of the gender difference in the incidence of allergic and non-allergic asthma. To our knowledge, our study is also the first to report a lack of gender difference in the incidence rates of allergic asthma. The incidence of allergic asthma appears to decrease with age. This decrease has to be interpreted with caution because subjects from younger cohorts contributed to a greater extent to the incidence estimate at a younger age, and there might be a cohort effect.[17] However, the magnitude of the gender difference in the incidence of allergic asthma is unlikely to be biased by a cohort effect because the same increase in atopic sensitisation with younger age is observed in men and women (online supplement, table E5).

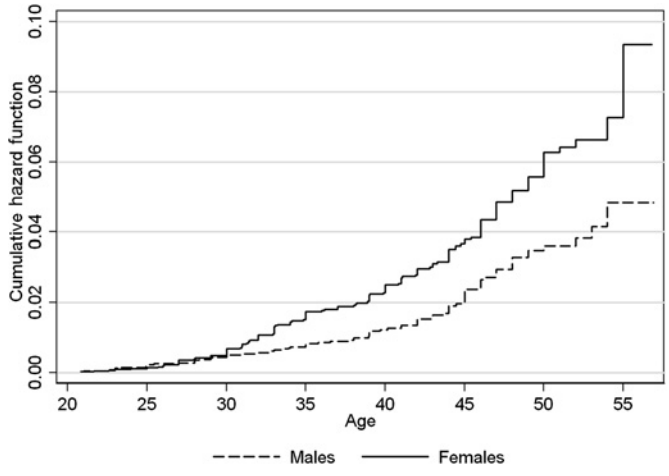

Figure 1 Cumulative hazard function for new-onset asthma in men and women. The figures show the cumulative expected number of men and women developing asthma over follow-up, based on the Nelson–Aalen estimator using age as the time scale.

Possible explanations for gender differences in asthma incidence

Although most prospective studies in adults show a higher incidence of asthma in women than in men, few studies have simultaneously tested the possible effects of other relevant factors.[2–6 20] Gender differences in asthma diagnosis have been demonstrated in children, but there are few data in adults.[7 8] We did not find any suggestion of a more frequent diagnosis in women. Gender differences in environmental exposure have been put forward.[4] In our study, women were at increased risk of non-allergic asthma, suggesting that exposure to allergens is unlikely to account for the higher incidence of asthma in women. Higher exposure of women to other bronchial irritants at home[21] or at work[22] cannot be excluded. Another possibility might be a greater susceptibility of women at the same level of exposure,[23] which might, in turn, be related to their lower airway calibre. However, the incidence of asthma remained significantly higher in women than in men after adjustment for smoking, occupational exposure and lung function. In addition, the higher risk of asthma in women is supported by their increased risk of BHR, which cannot be explained by gender differences in airway calibre.[24 25] Other factors are likely to be involved in the gender difference in asthma risk. The fact that the gender differences in asthma prevalence were consistent during the two survey periods and across countries with different levels of exposure to environmental factors suggests an effect of genetic and biological factors rather than socio-cultural and environmental factors.

Obesity appears to be a potential major risk factor for asthma development in women.[5] In some studies, but not all, obesity was found to be a risk factor for incident asthma in women but not in men.[5] Furthermore, obesity has been found to be more strongly associated with non-allergic asthma than with allergic asthma.[26] A detailed analysis of the ECRHS suggested a potential differential diagnosis linked to the presence of obesity in

Table 3 Incidence of asthma in women and men who reported they never had asthma at baseline

Outcome at follow-up	Number of incident cases		Person-years		Incidence per 1000 person-years (95% CI)		HR* (95% CI) Women/men
	Women	Men	Women	Men	Women	Men	
Asthma	152	82	36 733	34 351	4.14 (3.48 to 4.80)	2.39 (1.87 to 2.90)	1.74 (1.33 to 2.27)
Asthma by age at baseline:							
20–27 years	34	20	9118	8538	3.73 (2.48 to 4.98)	2.34 (1.32 to 3.37)	1.58 (0.91 to 2.75)
28–35 years	52	17	11 761	10 709	4.42 (3.22 to 5.62)	1.59 (0.83 to 2.34)	2.76 (1.60 to 4.77)
≥36 years	66	45	15 854	15 104	4.16 (3.16 to 5.17)	2.98 (2.11 to 3.85)	1.40 (0.96 to 2.04)
Allergic asthma	44	39	27 403	27 189	1.61 (1.13 to 2.08)	1.43 (0.98 to 1.88)	1.12 (0.73 to 1.72)
Non-allergic asthma	81	23	27 403	27 189	2.96 (2.31 to 3.60)	0.85 (0.50 to 1.19)	3.51 (2.21 to 5.58)

*Cox regression analysis (based on age at asthma onset) for incidence of doctor-diagnosed asthma in subjects who reported they never had asthma at baseline. Excludes incident cases with age at asthma onset missing or age at onset ≥5 years before baseline (see methods).

women.[16] However, in the present analysis, the higher incidence of asthma in women could not be explained by differences in BMI or change in BMI. Although obesity, as such, seems unlikely to explain the higher risk of asthma in women, regulatory molecules secreted by the adipose tissues (such as leptin) might be involved in the gender differences in asthma.[5]

A role for sex hormones is frequently suggested, but no study has been able to relate the switch in asthma prevalence occurring around puberty to changes in hormonal levels. In particular, a recent cohort of adolescents does not show any relationship between the pubertal stages and the incidence of asthma.[3] However, in a cohort of children with asthma, a marked decrease in bronchial responsiveness was observed after age 11 years in boys, but not in girls.[27] A possible relaxing effect of testosterone on airway smooth muscle, and an anti-inflammatory and immune-modulatory activity of the major adrenal androgen dehydroepiandrosterone have been put forward.[5 27–29] However further studies are needed to assess whether male sex hormones might have a protective effect in asthma. If the higher incidence of asthma in girls after adolescence is related to the rise in female sex hormones, one would expect a decrease in asthma incidence after the menopause. Such a decrease was reported in the Nurse's Health Study, but other studies found contrasting results.[30 31] However, these studies have not considered allergic and non-allergic asthma separately, and most of the animal models that have been used to assess the effect of sex hormones in asthma were based on allergen-induced airway responsiveness. Interestingly, recent studies suggest a possible dual effect of female sex hormones.[30 32 33] Data from a murine model suggested that oestrogen may have a pro-inflammatory effect in the process of antigen sensitisation per se, and an anti-inflammatory effect during the effector phase of the response to inhaled antigens.[32] However, there are insufficient data to speculate on whether such an anti-inflammatory effect of oestrogen in women already sensitised to allergens might decrease their likelihood of developing symptoms.

Study strengths and limitations

One of the strengths of this study lies in the quality of the ECRHS data. Standardised data for lung function, BHR and specific IgE were available at baseline and follow-up, and for a relatively large population-based sample of subjects with different levels of exposure to environmental factors. As regards the study limitations, loss to follow-up is a problem in any longitudinal study. However, there was no suggestion of any gender differential selection bias among subjects. The definition of asthma was based on the subject's report of doctor-diagnosed asthma. This definition has been validated and found to be highly specific, but of rather low sensitivity.[20] We cannot totally rule out a possible less frequent diagnosis of new-onset asthma in men than in women. Overlap of chronic obstructive pulmonary disease (COPD) and asthma is a concern in this type of analysis, particularly in non-atopic subjects. It has been suggested that COPD is more likely to be diagnosed as asthma in women than in men.[34] However, only 12% of women with incident non-allergic asthma were heavy smokers, only 8% had a FEV_1/forced vital capacity ratio lower than 0.70, 75% were younger than 50 years old, and a higher incidence of non-allergic asthma was found in women after excluding smokers at baseline (online supplement, table E4). Furthermore, our data suggest

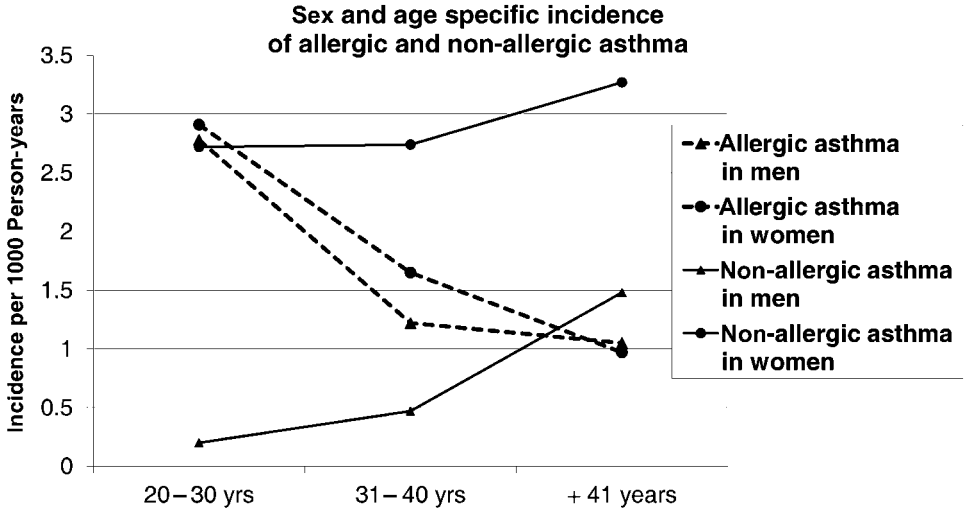

Figure 2 Sex and age-specific incidence rates for allergic and non-allergic asthma. The number of person-years at risk, within each age group, were respectively 5043, 10 696 and 11 451 in men, and 5152, 10 935 and 11 317 in women.

that asthma underdiagnosis is as frequent in women as in men. Because subjects were aged 20 years or more at inclusion, we cannot exclude the fact that a few subjects may have suffered from mild respiratory symptoms as early as childhood, and that these symptoms became severe enough in adulthood to be diagnosed as asthma. However, the results from a longitudinal birth cohort show that female sex is an independent predictor of adult-onset asthma after adjustment for wheeze in childhood.[35] Furthermore, the higher incidence of asthma in women was still significant after excluding subjects with respiratory symptoms at baseline. As regards sensitisation, we cannot exclude that a few subjects with new-onset asthma classified as 'non-atopic' had ever been atopic and developed tolerance. Another possibility is that some subjects sensitised to other less common allergens may have been classified as 'non-atopic'. However, similar findings were observed when baseline skin test sensitisation to any of nine common allergens was additionally used to classify incident cases as allergic and non-allergic asthma.

Implications and conclusion

Although women with severe non-allergic asthma may represent a substantial proportion of the adults with asthma in clinical practice, gender differences in the incidence of non-allergic asthma have been little investigated in the general population. In this large population-based cohort of adults, more than half the women with new-onset asthma and a third of the men with new-onset asthma were found to be non-atopic. This relatively high frequency emphasises the burden of non-allergic asthma in the adult population. However, our results also suggest that this form of asthma is still poorly recognised in men and women, and stress the need for more careful assessment of potential non-allergic asthma in clinical practice. Women were found to be at higher risk of developing non-allergic asthma throughout all the reproductive years, whereas no gender difference was observed for allergic asthma. Overall, our findings suggest that biological factors that significantly differ between men and women are likely to be involved in the development of non-allergic asthma. Further research in this direction is needed.

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Data sharing statement Researchers who wish to run analysis using the ECRHS data are invited to contact the coordinating centre in London. See the ECRHS website http://www.ecrhs.org.

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Journal club

Tyrosine kinase inhibitor use in idiopathic pulmonary fibrosis

This randomised, multicentre, double-blind, placebo-controlled trial evaluated the efficacy and safety of four different doses of BIBF 1120, a tyrosine kinase inhibitor, in order to investigate its effect on progression of idiopathic pulmonary fibrosis (IPF).

The annual rate of decline in forced vital capacity (FVC), the primary end-point of this study, in the highest dose subgroup compared with the placebo subgroup failed to show statistical significance. However, the authors were able to demonstrate that the changes in FVC from baseline, total lung capacity, oxygen saturations, acute exacerbations and quality of life were statistically significantly better in the group receiving the highest dose of BIBF 1120. Serious adverse events were similar between groups, but lower in the highest dosing regimen compared with placebo. The most common reason for discontinuation of the medication was gastrointestinal upset.

Of note, only 33% of the patients recruited fulfilled the criteria for definite IPF with the remainder being diagnosed as probable, possible or no IPF (one patient). Discontinuation of BIBF 1120 was more evident among the group receiving the highest treatment dose relative to other groups (37.6%).

Although BIBF 1120 failed to demonstrate a decline in annual FVC rates, it was associated with numerous clinically significant benefits including reduced numbers of exacerbations and improved quality of life at the highest dose while proving to be safe. With limited options for treatment and the encouraging beneficial effects of BIBF 1120, further research is warranted on a carefully selected cohort of patients with a formal diagnosis of IPF.

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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