

Sex differences in baseline risk factors for the incidence of asthma between early adolescence and young adulthood

Short title: Asthma from adolescence to adulthood

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Abstract

Background: Several studies have shown sex differences in the prevalence of asthma and a relationship to age. The aim of the present study was to prospectively investigate the development of asthma, wheeze, rhinitis and allergic symptoms, between adolescence and adulthood. Furthermore, to determine if sex modifies the associations between baseline risk factors and incidence of asthma in early adulthood.

Methods: In the study *Screening Project Asthma in Schools*(SPAIS), adolescents aged 12–15 years answered a standardised respiratory questionnaire (ISAAC) and underwent measurements of fractional exhaled nitric oxide (FeNO) and lung function (FEV₁) at baseline. Two follow-ups with similar questionnaires were performed after four and 16 years, with 491 subjects participating in all three examinations.

Results: The prevalence of asthma and wheeze were unchanged after four years, but had increased after 16 years. However, the increase was significant only for females. A more continuous increase in rhinitis and allergic symptoms showed no difference between the sexes. Sex interaction analysis showed that higher FeNO ($p = 0.01$) and family asthma ($p = 0.02$) increased the risk of incident asthma for males but not for females.

Conclusions: An increased prevalence of respiratory symptoms was seen primarily between late adolescence and young adulthood, and was significant for females but not males. Allergic risk factors in early adolescence for incident asthma in early adulthood were confirmed in males but not in females. Awareness of these sex differences in the development of symptoms, and the associated risk factors, are important in clinical practice.

Keywords: Adolescents, Allergic symptoms, Epidemiology, Incidence, Lung function, Nitric oxide, Prevalence, Sex.

Resumen

Antecedentes: Varios estudios han mostrado diferencias por sexo en la prevalencia del asma y una relación de la misma con la edad. El objetivo del presente estudio fue investigar prospectivamente el desarrollo de asma, sibilancias, rinitis y síntomas alérgicos, entre la adolescencia y la edad adulta. Más aún, determinar si el sexo modifica las asociaciones entre los factores de riesgo iniciales y la incidencia de asma en la edad adulta temprana.

Métodos: En el estudio "Screening Project Asthma in Schools" (SPAIS), los adolescentes de 12 a 15 años respondieron un cuestionario respiratorio estandarizado (ISAAC) y se sometieron a mediciones de óxido nítrico exhalado (FeNO) y función pulmonar (FEV1) al inicio del estudio. Se realizaron dos seguimientos con cuestionarios similares después de cuatro y 16 años, con 491 sujetos que participaron en los tres exámenes.

Resultados: La prevalencia de asma y sibilancias se mantuvo sin cambios después de cuatro años, pero aumentó a los 16 años. Sin embargo, el aumento fue significativo sólo para las mujeres. Un aumento más continuo de la rinitis y los síntomas alérgicos no mostró diferencias entre los sexos. El análisis de interacción sexual mostró que un FeNO más alto ($p = 0,01$) y los antecedentes familiares de asma ($p = 0,02$) aumentaron el riesgo de asma incidente para los varones, pero no para las mujeres.

Conclusiones: Se observó una mayor prevalencia de síntomas respiratorios principalmente entre la adolescencia tardía y la edad adulta temprana, que fue significativa para las mujeres pero no para los varones. Los factores de riesgo alérgico en la adolescencia temprana para el asma incidente en la edad adulta temprana se confirmaron en hombres pero no en mujeres. El conocimiento de estas diferencias por género en el desarrollo de los síntomas y los factores de riesgo asociados son importantes en la práctica clínica.

Palabras clave: Adolescentes, Síntomas alérgicos, Epidemiología, Incidencia, Función pulmonar, Óxido nítrico, Prevalencia, Sexo.

Introduction

A number of studies have shown sex differences in the prevalence of wheeze and asthma, and a relationship to age, with boys being more affected in childhood, and girls more affected in adolescence and adulthood [1-3]. Results from a population-based, longitudinal study of children investigated at age 11.1, 13.6 and 16.3 years concluded that a sex shift in the prevalence of asthma, from male to female dominance, had occurred at 16.3 years [4]. However, no association between pubertal stages and asthma prevalence was found. Other studies have suggested a role of female sexual hormones in the incidence and persistence of asthma symptoms in women, an argument strengthened by the fact that the incidence of asthma tends to decrease after menopause [5]. However, there have been differences in reported results and Triebner et al. [6] reported increased incidence of asthma in postmenopausal women.

Age of diagnosis of asthma was examined in a retrospective analysis of the European Respiratory Health Survey [7], including subjects from the general population aged 20–44 years. Results from the study showed a sex reversal with more females than males with incident asthma after puberty. Similar results have recently been confirmed in a large meta-analysis, and the shift seems to be stronger for non-atopic asthma [8]. Thus, several studies have shown a sex shift in asthma prevalence during puberty but, as far as we know, there is no study yet that has identified sex differences with regard to objective risk factors including airway inflammation in early adolescence. Moreover, the majority of previous longitudinal prospective studies looking at the development of respiratory symptoms have focused on either children or adults. Thus, studies following up individuals from childhood to adulthood are scarce.

Measurements of the fraction of exhaled nitric oxide (FeNO) is a non-invasive method to monitor airway inflammation [9], and is cost-effective in routine management of asthma in ages 4–18 years [10]. Based on baseline data in early adolescence from this cohort of schoolchildren [11] and a four-year follow-up in late adolescence, we have previously reported that elevated fraction of exhaled nitric oxide (FeNO) at baseline predicted incident allergic symptoms [12]. Furthermore, we have shown that obesity at baseline and current smoking were related to an increased risk of developing wheeze in females, while an atopic constitution was associated with incident wheeze in males [13].

The aims of this longitudinal study were to investigate the prevalence of asthma, wheeze and rhinitis as well as allergic symptoms, from early adolescence to young adulthood, with a total follow-up time of 16 years. Secondly, to determine if there are sex differences in the development of respiratory and allergic symptoms, and, thirdly, if sex modifies the associations between baseline risk factors and incidence of asthma in early adulthood.

Methods

Study subjects

The *Screening Project Asthma in Schools* (SPAIS) study has been described in detail previously [11]. Baseline screening data were collected in 1998–1999 from 959 subjects, aged 12–15 years, at nine randomised schools in Uppsala, Sweden. All children in the seventh grade were invited to participate and 83%, together with their parents, agreed to take part in the study. The subjects answered a questionnaire from the International Study of Asthma and Allergies in Childhood (ISAAC) [14, 15], while parents answered additional questions concerning their child's hypersensitivity to cat, dog or pollen, asthma diagnosis, asthma medication, atopic disease in childhood, family history of asthma and rhinitis, family smoking and environmental issues. Furthermore, all pupils underwent measurements of FeNO, dynamic spirometry, and height and weight measurements at their schools.

Two follow-up studies (SPAIS II and SPAIS III), with slightly abbreviated versions of the original questionnaire, were performed four and 16 years after the baseline examination (2002–2003 and 2014–2015). At SPAIS II, 921 subjects (96.0%) participated, and at SPAIS III, 502 subjects (52.3%) participated (Figure 1). At both follow-ups, the subjects completed the questionnaires themselves. In the present study, only subjects who participated in all three parts of SPAIS were included ($n = 491$; 51.2%).

Questionnaires and definitions

Asthma was defined as ever having had parent- or self-reported asthma, in combination with having used inhaled corticosteroid treatment or having wheezing or whistling in the chest or having a respiratory infection that caused wheezing or whistling in the chest in the preceding year (E-table 1) [12]. At SPAIS III, asthma was defined as above, but instead of only inhaled corticosteroid treatment, any asthma medication in the preceding year was included in the

definition. Wheeze was defined as having had wheezing or whistling in the chest at any time in the preceding year. Rhinitis was defined as having had sneezing, nasal congestion or rhinorrhoea during the preceding year, without having a cold.

At baseline, allergic symptoms were defined as the subject's hypersensitivity to cat, dog or pollen, noticed and reported by the parents. Allergic symptoms at SPAIS II were defined as above, but reported by the participant. At SPAIS III, allergic symptoms were defined as the subject's experience of ever having had allergic symptoms to cat, dog or pollen (due to a missing page in the paper questionnaire, data on allergic symptoms were missing for 30 subjects). In a sub-sample (n=374), a low frequency (3.3%) of sensitization to mite was confirmed with skin-prick tests at baseline, which was expected since such sensitization is uncommon in this part of Sweden [12]. For this reason, there were no questions about allergic symptoms to mite at SPAIS II or III.

Incidence of symptoms refers to no reported symptoms at baseline but reported at SPAIS III. Persistent symptoms were those reported at both SPAIS I and III and remission was defined as symptoms reported at baseline but not at follow-up.

Asthma, rhinitis and smoking habits in the family, including information reported by mothers, fathers and siblings, were questionnaire-assessed. The subject's current smoking habit at follow-up was defined as smoking at least one cigarette a day during the preceding six months.

Exhaled NO

Measurements of FeNO were performed with the Aerocrine NO system (Aerocrine AB, Sweden), including the CLD 77 AM chemiluminescence analyser (Eco Physics AG, Dürnten, Switzerland), as previously described [11], and in accordance with the prevailing recommendations from the European Respiratory Society [16]. Before measurement, each subject's mouth was washed with 25 ml of 10% sodium bicarbonate for 20 seconds. Three exhalations were performed during 10 seconds each and an average value was calculated. FeNO was measured at 0.1 L/s.

Pulmonary function

Pulmonary function measurements were performed in accordance with the criteria from the American Thoracic Society, using a Spirolab spirometer (Medical International Research,

Rome, Italy). No post-bronchodilation examinations were carried out. Lower limit of normal and percentiles for forced expiratory volume in 1 second (FEV₁) were calculated using the Excel (Microsoft Corporation, Redmond, WA, USA) macro for the Global Lung Function Initiative reference values [17]. The lower limit of normal was defined as FEV₁ < -1.65 standard deviations (SDs) and is referred to as reduced FEV₁ in the text.

Statistical analyses

Statistical analyses were performed using STATA IC 14 (StataCorp, College Station, Texas, USA). Comparisons at the group level were made using t-tests for normally distributed continuous variables or using chi-squared tests for categorical variables. McNemar's test was used to assess within-subject changes of categorical variables across two time points. FeNO was log-transformed to achieve normal distribution and t-tests were performed on log-transformed FeNO. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared.

Multiple logistic regressions were performed with incident asthma as outcome and all variables identified as significant in the univariate analyses, for either females or males, used as predictors. A stepwise multiple regression model was used, and variables were excluded if no significant association with the outcome was found. Interaction analyses were performed to study significant sex differences concerning risk factors. A p value < 0.05 was considered statistically significant.

Ethics

The study was approved by the Ethical Committee of the Medical Faculty of Uppsala University, Sweden (registration numbers 243/1998, 499/2001), and the Regional Ethical Review Board in Uppsala, Sweden (registration number 440/2013). The study procedures were in accordance with the Declaration of Helsinki [18]. As described in an information letter appended to the questionnaire at SPAIS I, a completed parental part of the questionnaire was seen as written informed consent from the parents. The adolescents gave their informed consent by completing the ISAAC part of the questionnaire and by verbally agreeing to participate in the study. At SPAIS II and III, a completed and returned questionnaire was seen as written informed consent from the participants, in accordance with an information letter appended to the questionnaire.

Results

Characteristics of participants

Out of 959 individuals included in the baseline study, there were 468 (48.8%) non-responders who differed from responders only with regard to more commonly being males, and more reported smoking in the family at baseline (Table 1). Sex-stratified analysis revealed that female non-responders had a tendency to have higher BMI and more reported family smoking at baseline than females who were included in the study (E-table 2). Corresponding data for males showed that the non-responders had more reported family smoking.

Prevalence of allergic and respiratory symptoms

The prevalence of asthma, wheeze, rhinitis, and allergic symptoms to cat, dog and pollen had all increased significantly between baseline and follow-up at SPAIS III (Figure 2, Table 2). When examining the incidence of symptoms stepwise between SPAIS I, II and III, we found that the incidence of asthma was very low at SPAIS II, and that the overall prevalence of asthma tended to be reduced between SPAIS I and SPAIS II (Figure 2a, E-table 3). In contrast, overall asthma prevalence increased between SPAIS II and III, with a strongly significant change in females and a trend in males (E-table 4). Concerning the prevalence of wheeze, there was a continuous increase from SPAIS I to III for females, but with no significant changes between the three study time points (Figure 2a, E-tables 3 and 4). For males, the prevalence of wheeze was non-significantly higher at SPAIS III than at baseline, but lowest at SPAIS II. The prevalence of rhinitis as well as allergic symptoms to cat, dog and pollen increased significantly during both time periods (Figure 2).

Sex differences in baseline characteristics, and respiratory and allergic symptoms

At baseline (SPAIS I), the only significant sex differences were that males were taller and females tended to report more family asthma (E-table 5). A proportion of 72.5% of the females had reached menarche. Current smoking at SPAIS III was reported by 53 subjects, or 11.5% of the females and 10.4% of the males ($p = 0.69$). When examining sex differences in the prevalence of reported respiratory symptoms at all three time points, there were no significant differences at SPAIS I and II, but females tended to report more wheeze at SPAIS II (E-table 6). At SPAIS III, females reported more asthma than males (Figure 3a) as well as

more wheeze (E-table 6), whereas the prevalence rates of rhinitis and allergic symptoms to cat, dog and pollen did not show any sex differences at any time point (Figure 3b, E-table 6).

Risk factors in early adolescence for incident asthma in early adulthood

As the development of respiratory symptoms showed clear sex differences, sex-specific analysis of baseline risk factors for incident asthma was undertaken. Females with incident asthma more commonly had reduced FEV₁, and reported more rhinitis, allergic symptoms to cat and family rhinitis at baseline, relative to females with no reported asthma at SPAIS I or SPAIS III (Table 3). Males who developed asthma had higher FeNO and more reported wheeze, rhinitis, and allergic symptoms to both cat and dog at baseline, relative to males who did not report asthma symptoms at any time point. Furthermore, males with incident asthma reported more allergic symptoms at baseline than females. At SPAIS III, allergic symptoms to cat were reported by 66.7% of subjects with persistent asthma between SPAIS I and III, compared with 31.3% of those with asthma remission during the same period. The corresponding proportions for allergic symptoms to pollen were 91.7% and 50.0%, respectively. There were more female than male cat and/or dog owners among the subjects who had developed asthma at SPAIS III, but pet ownership did not differ from that of subjects without asthma symptoms for either sex.

In multiple logistic regression analyses, stratified for sex and after adjustments for confounders (see Statistical analyses), reduced FEV₁, reported rhinitis and family rhinitis at baseline were related to incident asthma in females. In contrast, higher FeNO, reported rhinitis and family asthma at baseline were related to incident asthma in males (Table 4). There were no effects on the results when data on current smoking at SPAIS III, a non-significant variable for both sexes (Table 3), were added into the female model. However, in the male model, reduced FEV₁ ($p = 0.04$), wheeze ($p = 0.02$) and allergic symptoms to cat ($p = 0.02$) at baseline became related exposures, and rhinitis at baseline ($p = 0.11$) ceased being a related exposure. Sex interaction analysis revealed that higher FeNO ($p = 0.01$) and family asthma ($p = 0.02$) at baseline were the only risk factors that differed between the sexes (Table 4).

Discussion

The main finding of this population-based cohort study, on subjects followed from early adolescence to early adulthood, was that the prevalence of respiratory and allergic symptoms had increased significantly between these life stages. When stratifying for sex, the prevalence of both asthma and wheeze had increased significantly in females, but not in males, while the prevalence of rhinitis and allergic symptoms had increased significantly in both sexes. Objective measurements at baseline revealed that reduced FEV₁ in females and higher FeNO in males were independent risk factors for the development of asthma sixteen years later. However, a higher FeNO and reported family asthma were the baseline risk factors for incident asthma that showed significant sex differences, with males having a higher risk than females.

Previous studies

The prevalence of asthma, wheeze and rhinitis in young adulthood in our study was in line with results of a Swedish cross-sectional study for subjects with an age of 22–40 years [19]. The latter showed that 35.1% of the subjects were IgE-sensitized to pollen, 23.4% to cat and 22.7% to dog. In our study, with self-reported allergic symptoms, the prevalence rates were similar, except for fewer subjects reporting allergic symptoms to dog, 13.4%. A Finnish, population-based, cross-sectional respiratory questionnaire study of more than 4,000 subjects showed that the incidence of asthma peaked in young boys (0–9 years) and in middle-aged women (40–49 years) [20]. These results were confirmed by a recent study, encompassing six population-based birth cohorts, where a male predominance in prevalence was seen before puberty, as was a sex shift towards females after puberty, which was strongest in subjects who had asthma and rhinitis concurrently [21]. In a large population-based cohort study of subjects aged 20–44 years at baseline, 65% of the females with incident asthma at follow-up after 8–10 years were non-sensitized, compared with 37% of the males. During the same period, there was no sex difference concerning incidence of allergic asthma [22]. Studies have reported that female sex, allergic sensitisation, asthma severity and family history of asthma were inversely related to asthma remission [23, 24]. In accordance, two thirds of the subjects with asthma at SPAIS III reported allergic symptoms to cat, compared with less than a third of the subjects with asthma remission at this timepoint.

Overweight and obesity have been reported to associate with increased asthma prevalence in females but not in males, both during adolescence and adulthood [25, 26]. In a previous study based on the SPAIS cohort, incident wheeze in females at SPAIS II was related to higher baseline BMI (obesity), reported rhinitis and current smoking [13]. At the same time point, baseline risk factors for the development of wheeze in males were allergic symptoms to pollen, a family history of asthma and reduced FEV₁. Thus, it seems that factors associated with non-type 2 inflammation and lifestyle were more strongly associated with development of wheeze in females, whereas factors associated with an atopic constitution were related to this development in males. These lifestyle risk factors may have been more important in females during adolescence. The decreased study population (approximately 50%) in the present study, where the females that were lost in follow-up showed a tendency to have a higher BMI and significantly more reported family smoking than the females who were included in the study, may be an important explanation. Nevertheless, rhinitis, family rhinitis and reduced FEV₁ at baseline were the risk factors for incident asthma in females. In males with incident asthma at SPAIS III, risk factors related to an atopic constitution, including type-2 airway inflammation (higher FeNO) remained, and this pattern gained support after adjusting also for current smoking. Thus, incident asthma in young adults seems to be related more closely to atopy in males, whereas females show a more heterogeneous development of asthma, mainly non-allergic. The latter was further supported by the fact that females with incident asthma showed a trend towards lower FeNO at baseline compared to individuals that never reported asthma.

Recently, a subgroup of young subjects with non-atopic asthma, characterized by lack of type-2 inflammation but with airway hyperresponsiveness and non-IgE-mediated cow's milk hypersensitivity, were studied; females predominated in this group [27]. The greater susceptibility of females to develop non-allergic respiratory symptoms could also be explained by their generally narrower airway calibre [7]. A further explanation may be irreversible airflow obstruction, developed in early childhood during periods of bronchial obstruction and with symptom recurrence in adult life, even after long periods of clinical remission [28]. Accordingly, a period of remission in early adolescence in females, characterised by reduced FEV₁ but no reported symptoms of asthma, may be an explanation for the finding that reduced lung function at baseline was a confirmed independent risk factor for the development of symptomatic asthma sixteen years later. Furthermore, looking at

females with incident wheeze in the four-year follow-up of SPAIS, a higher proportion had started to menstruate at baseline, compared with females who never reported wheeze [13]. These results are in line with the view that female sexual hormones might contribute to the development of respiratory disease.

A review study looking at the impact of sex on asthma during childhood and adolescence concluded that asthma after childhood was more severe in females than in males, and was underdiagnosed and undertreated in female adolescents [1]. Furthermore, results from another study showed that adolescent females with asthma had lower asthma control test scores than males with asthma [29]. In a Norwegian study among adolescents with current wheeze, the likelihood of having a doctor's diagnosis of asthma was lower in females compared with males, although more females than males had confirmed airway hyperresponsiveness[30]. Furthermore, a doctor's diagnosis of asthma was strongly related to increased FeNO. This is in line with our results showing that the prevalence of wheeze was higher in females than males at all three study time points, indicating that some of the wheeze reported by females could be due to undiagnosed and untreated asthma, presumably of the non-type-2 phenotype.

Methodological considerations

A major strength of the current population-based, longitudinal prospective study of schoolchildren was the long follow-up period of sixteen years, from adolescence to adulthood. Another strength was the availability of objective functional and inflammatory measurements at baseline, as well as the use of the well-validated ISAAC questionnaire and similar additional questions at all three time points. A limitation may be that the questionnaire was adapted for adolescents aged 13–14 years, which was exactly the appropriate age for the baseline study but not as suitable for the follow-ups. Furthermore, wheeze, which is more commonly used for adolescents than for young adults, was included in our definition of asthma. However, wheeze was only one alternative criterium out of three that had to be fulfilled, in combination with “ever having parent- or self-reported asthma”, to classify an individual as asthmatic. In order to have a consistent definition of asthma from early adolescence to early adulthood, reported wheeze remained in the definition at all parts of the SPAIS study.

A selection bias might be argued due to the response rate of 51.2% in the present study. However, this is similar to response rates in other cross-sectional epidemiological studies [20,

31] and longitudinal studies with similar follow-up times [32]. Moreover, non-responders did not differ significantly in any baseline characteristics when compared to responders, with the exception of a slightly higher representation of males and subjects with a family history of smoking, in agreement with findings of other studies [33].

A limitation of the study may be that no objective data on allergic sensitisation was available. Another limitation may be the use of 100 mL/s as exhalation flow rate for FeNO measurement, the standard flow rate at the time of SPAIS I. However, although the FeNO values cannot be fully extrapolated to current clinical practice, we believe that the validity of the findings of an association between FeNO and incident asthma in males is not impaired.

Conclusions

The results from this longitudinal study, from early adolescence to young adulthood, confirmed previous findings concerning higher prevalence of respiratory symptoms, both asthma and wheeze, in females than males. There was also a significant increase of rhinitis and allergic symptoms to cat, dog and pollen over time, but without sex differences. Allergic risk factors in early adolescence for incident asthma in early adulthood were confirmed in males but not in females. Awareness, in clinical practice, of these sex differences in the development and treatment of respiratory symptoms are important to optimise health and well-being in young individuals.

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Conflicts of interests

LN has received research support from AstraZeneca and LN and KA from Aerocrine AB for the baseline study. No other author reported conflicts of interest in relation to any parts of the study.

Data availability statement

Data cannot be made freely available as they are subject to secrecy in accordance with the Swedish Public Access to Information and Secrecy Act, but can be made available to researchers upon request (subject to a review of secrecy). Requests for data can be sent to the corresponding author.

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FIGURES AND TABLE

Figure 1. Flow chart of the SPAIS studies.

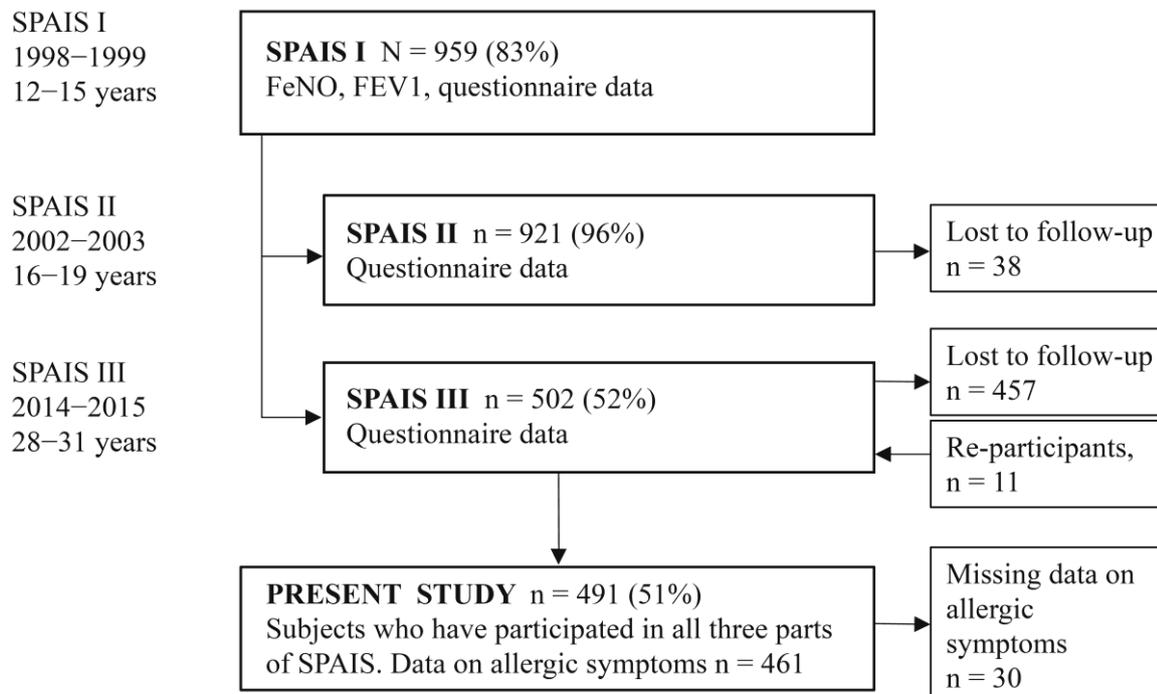
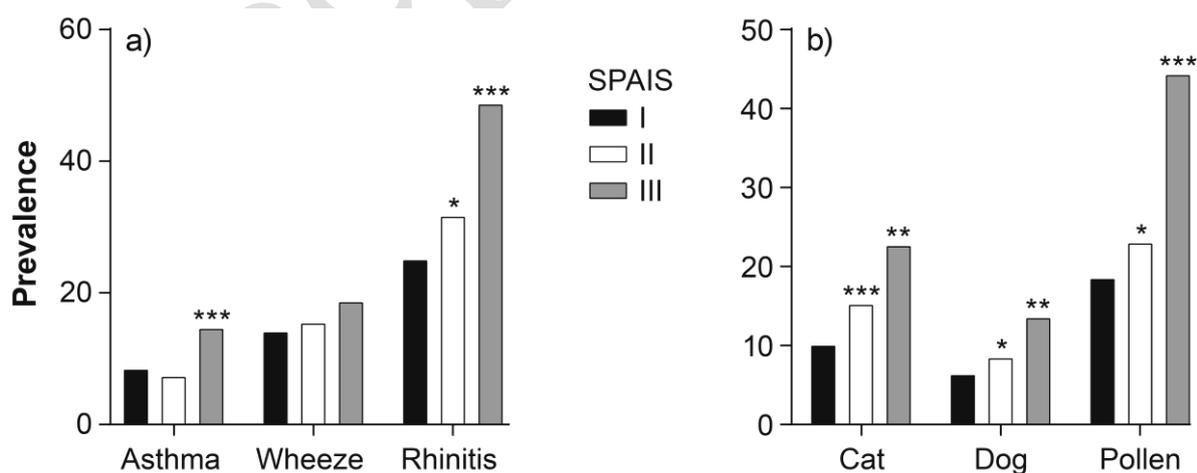
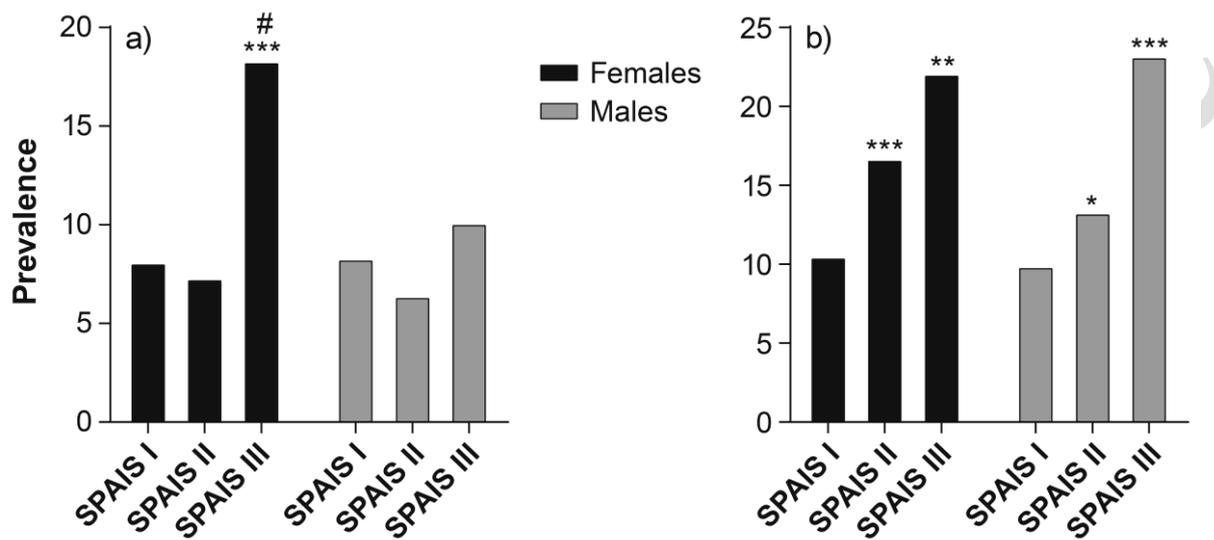


Figure 2. Prevalence (%) of a) respiratory symptoms and b) allergic symptoms reported at SPAIS I–III.



*** $p < 0.001$, ** $p = 0.01$, * $p < 0.05$, significant increase in reported symptoms compared to previous examination.

Figure 3. Prevalence (%) of a) asthma and b) allergic symptoms to cat in female and male subjects reported at SPAIS I–III.



*** $p < 0.001$, ** $p = 0.01$, * $p < 0.05$, significant increase in reported symptoms compared to previous examination.

$p = 0.01$, significant sex difference in reported symptoms.

Table 1. Baseline characteristics in the study population and those lost to follow up, N = 959.

	SPAIS III n = 491 (51.2%)	Lost to follow-up n = 468 (48.8%)	p value
Sex (male), n (%)	218 (44.4)	259 (55.3)	0.001
Age (years)	13.6 ± 0.40	13.7 ± 0.42	0.002
FeNO _{0.1} (ppb)	4.68 (4.27, 5.12)	4.78 (4.35, 5.25)	0.76
FEV ₁ (% predicted)	94.86 ± 10.35	95.18 ± 11.19	0.65
FEV ₁ (< -1.65 SD), n (%)	37 (7.5)	42 (9.1)	0.40
BMI (kg/m ²)	19.78 ± 2.96	20.06 ± 3.21	0.16
Height (cm)	162.1 ± 8.04	162.8 ± 8.25	0.20
Wheeze, n (%)	68 (13.9)	59 (12.6)	0.57
Asthma, n (%)	41 (8.4)	42 (9.0)	0.73
Rhinitis, n (%)	122 (24.9)	121 (25.9)	0.72
Family smoking, n (%)	137 (27.9)	176 (37.6)	0.001
Allergic symptoms to cat, n (%)	49 (10.0)	50 (10.7)	0.72
Allergic symptoms to dog, n (%)	31 (6.3)	20 (4.3)	0.16
Allergic symptoms to pollen, n (%)	91 (18.5)	77 (16.5)	0.40

Abbreviations: BMI, body mass index; FeNO_{0.1}, fractional exhaled nitric oxide measured at 100 mL/s; FEV₁, forced expiratory volume in one second; ppb, parts per billion; SD, standard deviation.

All results presented as % or mean ± standard deviation or geometric mean and 95% confidence interval.