ORIGINAL ARTICLE

Sex Differences in Baseline Risk Factors for Asthma Between Early Adolescence and Young Adulthood

Kalm-Stephens P[1], Nordvall L[1], Janson C[2], Malinovschi A[3*], Alving K[1*]

[1]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden
[2]Department of Medical Sciences: Lung, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden
[3]Department of Medical Sciences: Clinical Physiology, Uppsala University, Uppsala, Sweden
*These authors contributed equally.

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Abstract

Background: Several studies have shown sex differences in the prevalence of asthma and an association with age. The aim of the present study was to prospectively investigate the development of asthma, wheeze, rhinitis, and allergic symptoms in adolescence and adulthood. We also aimed to determine whether sex modifies the association between baseline risk factors and incidence of asthma in early adulthood.
Methods: In the Screening Project Asthma in Schools (SPAIS) study, adolescents aged 12-15 years completed a standardized respiratory questionnaire (International Study of Asthma and Allergies in Childhood) and underwent measurements of fractional exhaled nitric oxide (FeNO) and lung function (FEV_1) at baseline. Two follow-up assessments with similar questionnaires were performed after 4 and 16 years, with a total of 491 participants in all 3 examinations.
Results: The prevalence of asthma and wheeze were unchanged after 4 years but had increased after 16 years. However, the increase was significant only for females. The prevalence of rhinitis and allergy symptoms increased steadily, albeit with no differences between the sexes. The sex interaction analysis showed that higher FeNO (*P*=.01) and a family history of asthma (*P*=.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; the difference was significant for females but not for 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 of the associated risk factors is important in clinical practice.

Key words: 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 (FEV_1) al inicio del estudio. Se realizaron dos seguimientos con cuestionarios similares después de 4 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 4 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 hombres, 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 hombres. 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

Several studies have shown sex differences in the prevalence of wheeze and asthma, as well as an association with 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 predominance, occurred at 16.3 years [4]. However, no association was found between pubertal stage and prevalence of asthma. 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, study results differ. Triebner et al [6] reported an increased incidence of asthma in postmenopausal women.

Age at diagnosis of asthma was examined in a retrospective analysis of the European Respiratory Health Survey [7], which included individuals from the general population aged 20-44 years. The results showed a sex reversal, with more females than males developing incident asthma after puberty. Similar results were recently confirmed in a large meta-analysis, and the shift seems to be stronger for nonatopic asthma [8]. Thus, several studies have shown a sex shift in the prevalence of asthma during puberty. However, to our knowledge, no studies have yet identified sex differences in objective risk factors including airway inflammation in early adolescence. Moreover, most previous longitudinal prospective studies on the development of respiratory symptoms have focused on either children or adults. Studies following individuals from childhood to adulthood are scarce.

Measurement of fractional exhaled nitric oxide (FeNO) is a noninvasive method for monitoring airway inflammation [9] and has proven cost-effective in the routine management of asthma in persons aged 4-18 years [10]. Using baseline data recording during early adolescence in this cohort of schoolchildren [11] and 4-year follow-up data from late adolescence, we previously reported that elevated FeNO at baseline predicted incident allergic symptoms [12]. Furthermore, we showed 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 aim of this longitudinal study was 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. We also determined whether there were sex differences in the development of respiratory and allergic symptoms and whether sex modified the association between baseline risk factors and incidence of asthma in early adulthood.

Methods

Study Participants

The Screening Project Asthma in Schools (SPAIS) study has been described in detail previously [11]. Baseline screening

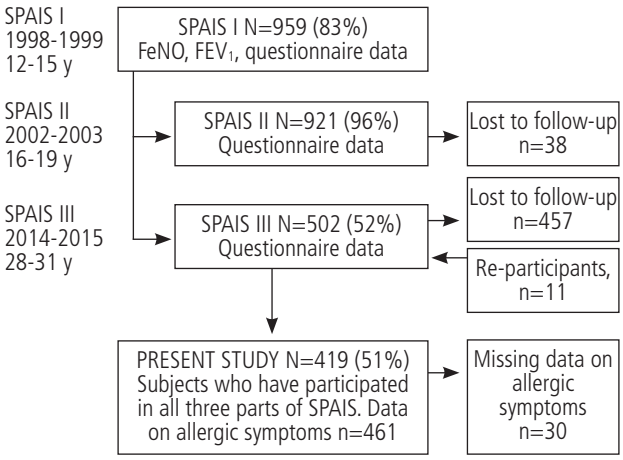

Figure 1. Flow chart of the SPAIS studies.

data were collected during 1998-1999 from 959 individuals aged 12-15 years at 9 randomized 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 participants completed 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 (cat, dog, and/or pollen), asthma diagnosis, asthma medication, atopic disease in childhood, family history of asthma and rhinitis, family history of smoking, and environmental issues. All pupils also underwent measurements of FeNO, dynamic spirometry, and height and weight at their schools.

Two follow-up studies (SPAIS II and SPAIS III) based on slightly abbreviated versions of the original questionnaire were performed 4 and 16 years after the baseline examination (2002-2003 and 2014-2015). A total of 921 individuals (96.0%) participated in SPAIS II, and 502 (52.3%) participated in SPAIS III (Figure 1). At both follow-up assessments, the participants completed the questionnaires themselves. The present study included only those who participated in all 3 parts of SPAIS (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 wheezing or whistling in the chest or a respiratory infection that caused wheezing or whistling in the chest in the preceding year (E-table 1) [12]. In SPAIS III, asthma was defined as above, although 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 rhinorrhea during the preceding year, without having a cold.

At baseline, allergic symptoms were defined as hypersensitivity to cat, dog, or pollen noticed and reported by the parents. Allergic symptoms in SPAIS II were defined as above but reported by the participant. In SPAIS III, allergic

symptoms were defined as ever having had allergic symptoms to cat, dog, and/or pollen (owing to a missing page in the paper questionnaire, data on allergic symptoms were missing for 30 individuals). In a subsample (n=374), a low frequency (3.3%) of sensitization to mite was confirmed with skin prick tests at baseline; this was expected, since such sensitization is uncommon in this part of Sweden [12]. For this reason, there were no questions about allergic symptoms to mites in SPAIS II or III.

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

Family asthma, rhinitis, and smoking habits, including information reported by mothers, fathers, and siblings, were questionnaire-assessed. Current smoking habit at follow-up was defined as smoking at least 1 cigarette a day during the preceding 6 months.

Exhaled NO

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

Pulmonary Function

Pulmonary function testing was performed in accordance with the criteria of the American Thoracic Society using a Spirolab spirometer (Medical International Research). No postbronchodilation examinations were carried out. Lower limit of normal and percentiles for forced expiratory volume in 1 second (FEV_1) were calculated using the Excel macro (Microsoft Corporation) for the Global Lung Function Initiative reference values [17]. The lower limit of normal was defined as FEV_1 <–1.65 SD and is referred to as reduced FEV_1 in the text.

Statistical Analyses

Statistical analyses were performed using STATA IC 14 (StataCorp). Comparisons at the group level were made using the *t* test for normally distributed continuous variables or using the χ^2 test for categorical variables. The McNemar test was used to assess within-person changes in categorical variables across 2 time points. FeNO was log-transformed to achieve a normal distribution, and the *t* test was performed using log-transformed FeNO values. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Multiple logistic regression analyses were performed with incident asthma as the 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 <.05 was considered statistically significant.

Ethics

The study was approved by the Ethics Committee of the Medical Faculty of Uppsala University, Sweden (registration numbers 243/1998, 499/2001), and the Regional Ethics 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 in SPAIS I, a completed parental section of the questionnaire was considered written informed consent from the parents. The adolescents gave their informed consent by completing the ISAAC part of the questionnaire and by

Table 1. Baseline Characteristics of the Study Population and Participants Lost to Follow-up (N=959)[a]

	SPAIS III n=491 (51.2%)	Lost to follow-up n=468 (48.8%)	*P* Value
Male sex, No. (%)	218 (44.4)	259 (55.3)	.001
Age, y	13.6 (0.40)	13.7 (0.42)	.002
$FeNO_{0.1}$, ppb	4.68 (4.27-5.12)	4.78 (4.35-5.25)	.76
FEV_1, % predicted	94.86 (10.35)	95.18 (11.19)	.65
FEV_1 (< –1.65 SD), No. (%)	37 (7.5)	42 (9.1)	.40
BMI, kg/m^2	19.78 (2.96)	20.06 (3.21)	.16
Height, cm	162.1 (8.04)	162.8 (8.25)	.20
Wheeze, No. (%)	68 (13.9)	59 (12.6)	.57
Asthma, No. (%)	41 (8.4)	42 (9.0)	.73
Rhinitis, No. (%)	122 (24.9)	121 (25.9)	.72
Family smoking, No. (%)	137 (27.9)	176 (37.6)	.001
Allergic symptoms to cat, No. (%)	49 (10.0)	50 (10.7)	.72
Allergic symptoms to dog, No. (%)	31 (6.3)	20 (4.3)	.16
Allergic symptoms to pollen, No. (%)	91 (18.5)	77 (16.5)	.40

Abbreviations: BMI, body mass index; $FeNO_{0.1}$, fractional exhaled nitric oxide measured at 100 mL/s; FEV_1, forced expiratory volume in 1 second; ppb, parts per billion; SPAIS, Screening Project Asthma in Schools.
[a]All results presented as % or mean (SD or geometric mean and 95% CI).

verbally agreeing to participate in the study. In 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 the Participants

Out of 959 individuals included in the baseline study, 468 (48.8%) were nonresponders who differed from responders only with regard to more commonly being male, and more reported smoking in the family at baseline (Table 1). A sex-stratified analysis revealed that female nonresponders tended to have a 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 nonresponders more frequently 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). Stepwise examination of the incidence of symptoms between SPAIS I, II, and III revealed that the incidence of asthma was very low in 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, the overall prevalence of asthma increased between SPAIS II and III, with a strongly significant change in females and a trend in males (E-table 4). The prevalence of wheeze increased continuously from SPAIS I to III for females, albeit with no significant changes between the 3 time points (Figure 2A, E-tables 3 and 4). For males, the prevalence of wheeze was nonsignificantly higher in SPAIS III than at baseline, but lowest in SPAIS II. The prevalence of rhinitis and allergy to cat, dog, and pollen increased significantly during both time periods (Figure 2).

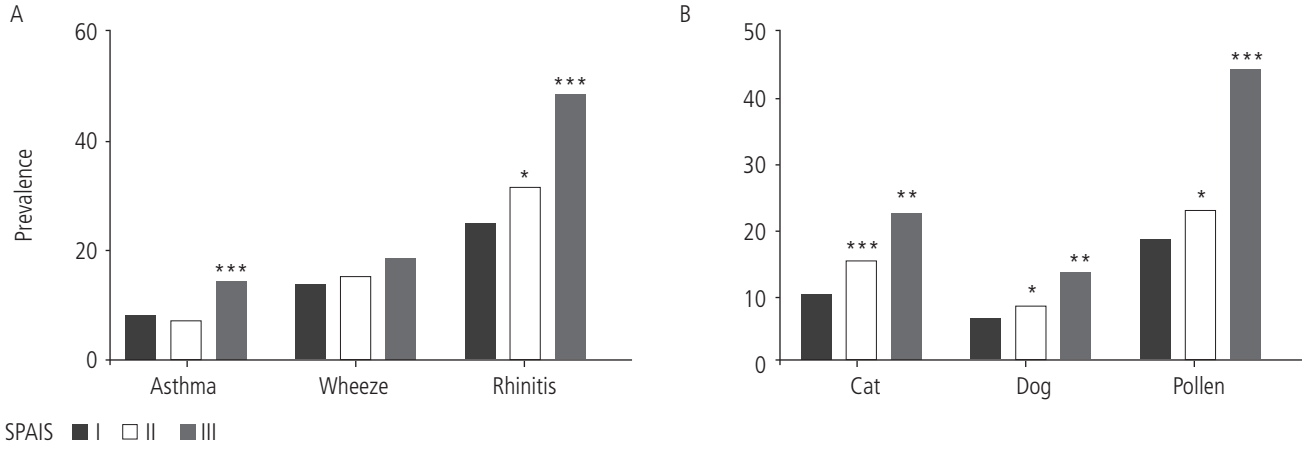

Figure 2. Prevalence, % of respiratory symptoms (A) and allergic symptoms (B) reported in SPAIS I-III. ***P<.001, **P=.01, *P<.05, significant increase in reported symptoms.

Table 2. Progress of Symptoms Between SPAIS I (Age 12-15 y) and SPAIS III (Age 28-31 y)

	Prevalence of symptoms in SPAIS I and III	Remission of symptoms between SPAIS I and III	Persistence of symptoms between SPAIS I and III	Incidence of symptoms between SPAIS I and III	Prevalence of symptoms in SPAIS III	*P* Value[a]
Wheeze, No. (%)						
All participants, N=491	68 (13.8)	39 (7.9)	29 (5.9)	61 (12.4)	90 (18.3)	.03
Females, n=273	40 (14.7)	21 (7.7)	19 (7.0)	40 (14.7)	59 (21.6)	.02
Males, n=218	28 (12.8)	18 (8.3)	10 (4.6)	21 (9.6)	31 (14.2)	.63
Asthma, No. (%)						
All participants, N=491	40 (8.1)	16 (3.3)	24 (4.9)	48 (9.8)	72 (14.7)	<.001
Females, n=273	22 (8.1)	7 (2.6)	15 (5.5)	35 (12.8)	50 (18.3)	<.001
Males, n=218	18 (8.3)	9 (4.1)	9 (4.1)	13 (6.0)	22 (10.1)	.39
Cat symptoms, No. (%)						
All participants, N=461	47 (10.2)	3 (0.7)	44 (9.5)	60 (13.0)	104 (22.6)	<.001
Females, n=258	27 (10.5)	3 (1.2)	24 (9.3)	33 (12.8)	57 (22.1)	<.001
Males, n=203	20 (9.9)	0 (0)	20 (9.9)	27 (13.3)	47 (23.2)	<.001

Abbreviation: SPAIS, Screening Project Asthma in Schools.
[a]*P* values comparing prevalence rates in SPAIS I and III (McNemar test).

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). Almost three-quarters (72.5%) of the females had reached menarche. Current smoking in SPAIS III was reported by 53 participants (11.5% of the females and 10.4% of the males) (*P*=.69). Examination of sex differences in the prevalence of reported respiratory symptoms at all 3 time points revealed no significant differences in SPAIS I and II, although females tended to report more wheeze in SPAIS II

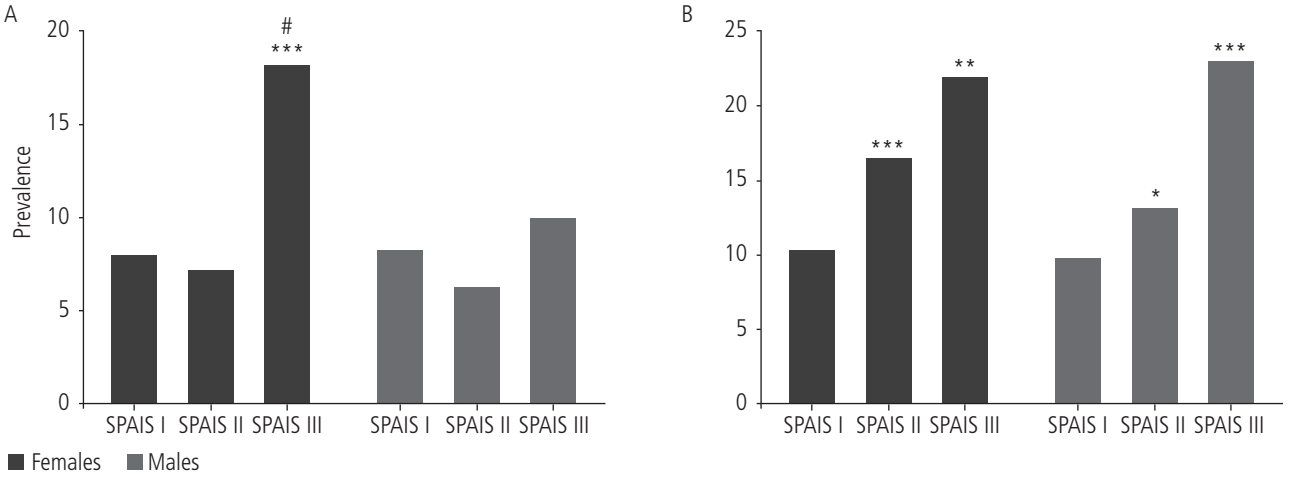

Figure 3. Prevalence, % of asthma (A) and allergic symptoms (B) to cat by sex in SPAIS I-III.
****P*<.001, ***P*=.01, **P*<.05, significant increase in reported symptoms. #*P*=.01, significant sex difference in reported symptoms.

Table 3. Characteristics of Females and Males at Baseline, Except Current Smoking and Pets at Home,[a] in Relation to Incidence of Asthma in SPAIS III (Age 28-31 Years)[b]

	Females			Males		
	No asthma at baseline or at SPAIS III (n=216)	Incident asthma at SPAIS III (n=35)	*P* Value	No asthma at baseline or at SPAIS III (n=186)	Incident asthma at SPAIS III (n=13)	*P* Value
$FeNO_{0.1}$, ppb	4.46 (3.99-4.99)	3.37 (2.12-5.35)	.09	4.39 (3.79-5.10)	9.69 (4.58-20.48)	.009
FEV_1, % predicted	95.02 (8.98)	92.88 (9.60)	.20	95.67 (11.08)	93.36 (12.18)	.47
FEV_1 (<–1.65 SD), %	5.1	14.3	.04	7.0	15.4	.27
BMI, kg/m^2	19.66 (2.94)	20.12 (3.20)	.39	19.80 (2.99)	21.18 (2.73)	.11
Height, cm	160.7 (6.51)	161.0 (5.43)	.83	163.6 (9.52)	164.4 (10.6)	.76
Wheeze, %	7.4	17.1	.06	5.4	30.8	.001
Rhinitis, %	18.5	42.9	.001	17.2	53.9	.001
Allergic symptoms to cat, %	4.2	17.1	.003	4.8	30.8	<.001
Allergic symptoms to dog, %	1.4	5.7	.09	3.2	15.4	.03
Allergic symptoms to pollen, %	12.0	17.1	.40	16.1	23.1	.52
Family asthma, %	29.6	42.9	.12	20.4	69.2	<.001
Family rhinitis, %	51.9	74.3	.01	45.7	69.2	.21
Family smoking, %	31.9	25.7	.46	25.3	30.8	.66
Current smoking, %	11.3	11.8	.93	11.6	8.3	.73
Cat at home, %	17.8	22.9	.47	15.1	8.3	.52
Dog at home, %	12.2	17.1	.42	9.2	7.7	.85

Abbreviations: BMI, body mass index; $FeNO_{0.1}$, fractional exhaled nitric oxide measured at 100 mL/s; FEV_1, forced expiratory volume in 1 second; SPAIS, Screening Project Asthma in Schools.
[a]Self-reported in SPAIS III.
[b]All results presented as % or mean (SD or geometric mean and 95%CI).

(E-table 6). In SPAIS III, females reported more asthma than males (Figure 3A), as well as more wheeze (E-table 6), whereas no sex differences were observed at any time point for prevalence of rhinitis and allergy to cat, dog, and pollen (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, a sex-specific analysis of baseline risk factors for incident asthma was undertaken. Females with incident asthma more commonly had reduced FEV_1 and reported more rhinitis, allergy 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 allergy to both cat and dog at baseline than males who did not report asthma symptoms at any time point. Furthermore, males with incident asthma reported more allergic symptoms at baseline than females. In SPAIS III, allergy to cat was reported by 66.7% of individuals with persistent asthma between SPAIS I and III, compared with 31.3% of those with remission of asthma during the same period. The corresponding proportions for allergy to pollen were 91.7% and 50.0%, respectively. There were more female than male cat and/or dog owners among the participants who had developed asthma in SPAIS III, although pet ownership did not differ from that of participants without asthma symptoms for either sex.

In the multiple logistic regression analyses stratified for sex and after adjustment for confounders (see Statistical Analyses), reduced FEV_1, 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 in SPAIS III, a nonsignificant variable for both sexes (Table 3), were entered into the female model. However, in the male model, reduced FEV_1 (P=.04), wheeze (P=.02), and allergy to cat (P=0.02) at baseline became related exposures, and rhinitis at baseline (P=.11) ceased being a related exposure. The sex interaction analysis showed higher FeNO (P=.01) and family asthma (P=.02) at baseline to be the only risk factors that differed between the sexes (Table 4).

Discussion

The main finding of this population-based cohort study of participants followed up from early adolescence to early adulthood was that the prevalence of respiratory and allergic symptoms had increased significantly between these life stages. Stratification by sex shows that 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 FEV_1 in females and higher FeNO in males were independent risk factors for the development of asthma 16 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 the results of a Swedish cross-sectional study of individuals aged 22-40 years [19], which showed that 35.1% of participants were IgE-sensitized to pollen, 23.4% to cat, and 22.7% to dog. In our study, which was based on self-reported allergic symptoms, the prevalence rates were similar, except that fewer participants reported allergic symptoms to dog (13.4%). A Finnish population-based cross-sectional respiratory questionnaire–based study of more than 4000 individuals 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 6 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 individuals with asthma and

Table 4. Independent Baseline Risk Factors for Incident Asthma in SPAIS III (Age 28-31 y)

Risk factors	Incident asthma Females (aOR[a] [95% CI])	Incident asthma Males (aOR[a] [95% CI])	Interaction with sex P values
FEV_1 < –1.65 SD	4.11 (1.27-13.24)	4.51 (0.59-34.69)	.65
FeNO0.1[b]	0.98 (0.92-1.05)	1.13 (1.06-1.20)	.01
Rhinitis	3.34 (1.54-7.25)	7.39 (1.78-30.78)	.68
Family asthma	1.47 (0.66-3.25)	12.74 (2.88-56.31)	.02
Family rhinitis	2.89 (1.25-6.68)	0.73 (0.14-3.72)	.43

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; FeNO0.1, fraction of exhaled nitric oxide measured at 100 mL/s; FEV_1, forced expiratory volume in 1 second; SPAIS, Screening Project Asthma in Schools.
[a]aOR: Variables adjusted for in incident asthma models: FeNO0.1, FEV_1 < –1.65 SD, rhinitis, wheeze, allergic symptoms to cat and dog, family asthma, and rhinitis at baseline.
[b]Per 1-ppb increase in FeNO.

rhinitis concurrently [21]. In a large population-based cohort study of persons aged 20-44 years at baseline, 65% of the females with incident asthma at follow-up after 8-10 years were nonsensitized, compared with 37% of the males. During the same period, no sex differences were observed for incidence of allergic asthma [22]. Studies have reported that female sex, allergic sensitization, asthma severity, and family history of asthma were inversely related to remission of asthma [23,24]. Similarly, two-thirds of the patients with asthma in SPAIS III reported allergic symptoms to cat, compared with less than a third of those whose asthma had remitted at this time point.

Overweight and obesity have been associated with increased prevalence of asthma 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 in 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 FEV_1. 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-related risk factors may have been more important in females during adolescence. A key explanation for this observation may be the decreased population (approximately 50%) in the present study, where the females who were lost to follow-up tended to have a higher BMI and significantly more family smoking than the females who were included in the study. Nevertheless, rhinitis, family history of rhinitis, and reduced FEV_1 at baseline were the risk factors for incident asthma in females. In males with incident asthma in SPAIS III, risk factors related to an atopic constitution, including type-2 airway inflammation (higher FeNO) remained, and this pattern gained support also after adjusting for current smoking. Thus, incident asthma in young adults seems to be related more closely to atopy in males, whereas in females, asthma, mainly the nonallergic phenotype, seems to develop more heterogeneously. The latter observation was further supported by the fact that females with incident asthma tended to have lower FeNO values at baseline than individuals who never reported asthma.

A female predominance was observed in a recent study of a subgroup of young persons with nonatopic asthma characterized by lack of type-2 inflammation but with airway hyperresponsiveness and non–IgE-mediated cow's milk hypersensitivity [27]. The greater susceptibility of females to nonallergic respiratory symptoms could also be explained by their generally narrower airway caliber [7]. A further explanation may be irreversible airflow obstruction, which develops in early childhood during periods of bronchial obstruction, with recurrence of symptoms in adulthood, even after long periods of clinical remission [28]. Accordingly, a period of remission in early adolescence in females, which is characterized by reduced FEV_1 but no reported symptoms of asthma, may account for the finding that reduced lung function at baseline was an independent risk factor for the development of symptomatic asthma 16 years later. Furthermore, in the case of females with incident wheeze in the 4-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 sex 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 that it 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 of adolescents with current wheeze, the likelihood of physician-diagnosed asthma was lower in females than in males, although more females than males had confirmed airway hyperresponsiveness [30]. Furthermore, physician-diagnosed asthma was strongly related to increased FeNO. This finding is in line with our results, which show that the prevalence of wheeze was higher in females than in males at all 3 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 16 years, which ran 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 3 time points. A limitation may be that the questionnaire was adapted for adolescents aged 13-14 years, which was the appropriate age for the baseline study but not as suitable for the follow-up assessments. Furthermore, wheeze, which is more commonly used for adolescents than for young adults, was included in our definition of asthma. However, wheeze was only 1 alternative criterion out of 3 that had to be fulfilled, in combination with "ever having parent- or self-reported asthma", to classify an individual as asthmatic. In order to ensure a consistent definition of asthma from early adolescence to early adulthood, reported wheeze remained in the definition in all parts of the SPAIS study.

The study may have been subject to selection bias owing to the response rate of 51.2% in the present SPAIS 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, nonresponders did not differ significantly in any baseline characteristics when compared to responders, with the exception of a slightly higher representation of males and individuals with a family history of smoking, in agreement with findings reported elsewhere [33].

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

Conclusions

The results of this longitudinal study, which covers adolescence to young adulthood, confirmed previous findings indicating a higher prevalence of respiratory symptoms (both asthma and wheeze) in females than in males. There was also a significant increase in the prevalence of rhinitis and allergy to cat, dog, and pollen over time, albeit without sex differences. Allergic risk factors in early adolescence for incident asthma in early adulthood were confirmed in males but not in females. Awareness by clinicians of these sex differences in the development and treatment of respiratory symptoms is important if we are to optimize health and well-being in young individuals.

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Conflicts of Interest

LN has received research support from AstraZeneca and LN and KA from Aerocrine AB for the baseline study. The remaining authors declare that they have no conflicts of interest.

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P Kalm-Stephens

Department of Women's and Children's Health,
Uppsala University, 75185 Uppsala, Sweden
E-mail: pia.kalm-stephens@kbh.uu.se