Lung function in young adulthood: differences between males and females with asthma

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Current or previous asthma is associated with lower lung function in early adulthood. In females, in contrast to males, the association between asthma and lower lung function is attenuated after adjustment for known risk factors. https://bit.ly/37vDzzu

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Abstract

Background There are phenotypic differences in asthma in males and females. Differences in lung function between the sexes at the peak lung function level in young adulthood are so far not directly addressed. The aim of the present study was to assess lung function in early adulthood in males and females depending on asthma onset and remission.

Methods Participants were included from the population-based birth cohort BAMSE and classified as having: never asthma, childhood asthma in remission, adolescent onset asthma or persistent asthma. Pre- and post-bronchodilator lung function (in Z-score) and lung clearance index (LCI) were measured at age 24 years. Lung function was compared stratified for sex between the never asthma and asthma groups univariately and in multiple linear regression analyses adjusted for maternal and paternal asthma, maternal smoking during pregnancy, secondary smoking, daily smoking, early respiratory syncytial virus infection, traffic pollution, childhood allergic sensitisation, and body mass index at age 24 years.

Results All asthma phenotypes were associated with a lower forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) post-bronchodilation at 24 years. This was most pronounced in males with persistent asthma compared to males with never asthma (regression coefficient: −0.503; 95% CI: −0.708– −0.298). Childhood asthma (in remission or persistent) was associated with a lower FEV_1. After adjustment, the associations remained significant for males. For females, the significant associations with lower FEV_1 and FEV_1/FVC remained only for subjects with asthma in remission. Persistent asthma was associated with higher LCI in females.

Conclusions In females, in contrast to males, the association between asthma and lower lung function was attenuated after adjustment for known risk factors.

Introduction

Asthma and wheeze have different prevalence patterns among boys and girls, with a higher prevalence in boys before puberty [1, 2]. A shift occurs around 16 years of age, both due to a higher rate of remission among boys and a higher incidence among girls [1, 2]. However, the asthmatic disease differs depending on sex also in other aspects [3–5]; female and male asthma has in some studies been found to associate differently with environmental exposures such as farm environment, and traffic or cigarette air pollution [6–8], as well as to adiposity [9, 10]. Allergic asthma, with allergen exposure as an important trigger for airway inflammation, is common in both childhood and adulthood [11]. The prevalence of allergic sensitisation is higher among males than females [12], although the association with asthma seems to be similar [13].

The impact of asthma on lung function has previously been investigated [14, 15]. Asthma and wheeze are strongly associated with an impaired lung function development [16, 17], with a lower maximal lung function reached [16]. Lung function development in an individual tends to follow a trajectory, and a low lung function at an early age often results in a lower peak lung function [18] attained in early adulthood at 25–30 years of age [19].

Despite phenotypic differences in male and female asthma, the association between asthma characteristics and lung function in males and females has, to our knowledge, not been addressed directly in young adults. A better understanding of sex-specific differences affecting the lung function in young adults with asthma could lead to better and more specific treatments at an early stage, and thereby a better prognosis.

The aim of this study was to assess differences in lung function in early adulthood in males and females depending on asthma onset and remission. Lung function was measured with spirometry and multiple-breath nitrogen washout test (MBWO).

Material and methods

Included population

The included population comes from the BAMSE (Children, Allergy, Milieu, Stockholm, Epidemiology) study, a population-based birth cohort initiated in 1994 in Stockholm, Sweden [20]. The participants or participants' parents have responded to questionnaires covering environmental exposures, health status and asthmatic- and allergic symptoms at the ages of 2–3 months and, 1, 2, 4, 8, 12, 16 and 24 years. Clinical examinations have been done at 4, 8, 16 and 24 years of age.

In the follow-up at 24 years of age, all participants were invited to fill out a questionnaire and participate in a clinical examination. The questionnaire was responded to by 3064 participants (75% of the original cohort), and 2270 (56%) participated in the clinical examination, including dynamic spirometry before and after bronchodilation. MBWO was done in a subset of the study population (n=1040 participants).

Participants who had successfully performed a pre- and post-bronchodilator spirometry at the 24 years follow-up [17] and had information on whether the criteria for asthma at 24 years of age was fulfilled were included, resulting in a study population of 1928 participants.

Definition of the asthma phenotypes

At each follow-up, asthma was defined as present when at least two of the following was reported: wheeze the previous year, asthma medication the previous year or doctor's asthma diagnosis at any time [20].

Participants were stratified into groups of never asthma, not fulfilling criteria for asthma at any of the attended follow-ups; childhood asthma in remission, fulfilling criteria for asthma at 1, 2, 4 and/or 8 years age, but not 24 years of age (independent of asthma status at 12 and 16 years of age); adolescent/early adulthood onset asthma (hereafter labelled "adolescent onset asthma"), with asthma onset after 8 years age; and persistent asthma, fulfilling criteria for asthma at 1, 2, 4 and/or 8 years of age and 24 years of age (figure 1). This grouping aimed to separate asthma with an onset before and after puberty, and asthma in remission [1, 2].

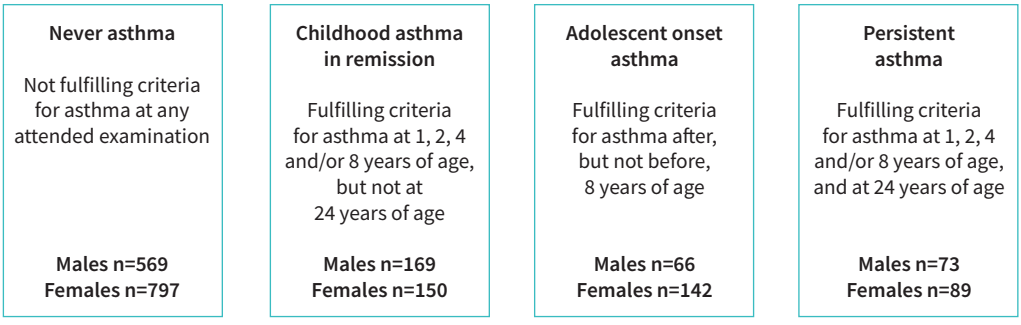

FIGURE 1 Definition of the asthma phenotypes.

Description of self-reported variables

Questionnaire data were collected from the participant's parents at 0 (2–3 months of age), 1, 2, 4, 8, 12 and 16 years age, and from the participant at 12, 16 and 24 years of age.

Family history of asthma and early symptoms

Maternal and paternal asthma was defined as the parent reporting a doctor's diagnosis of asthma at any time at baseline. Early wheeze was defined as three or more episodes of wheeze between the ages of 3 months and 2 years. Infection with respiratory syncytial virus (RSV) was reported by the parents up to the first 19 months of life.

Smoking

Maternal smoking during pregnancy was reported in the baseline questionnaire and defined as present if the mother smoked at least one cigarette per day at any period during the pregnancy or at baseline. Secondary smoke exposure was defined as present if the participant's parents reported daily smoking at any of the follow-ups up to 16 years of age, or if the participant had been exposed to indoor smoking at least weekly at the 24 years follow-up. Smoking at 24 years of age was self-reported, and the participants were stratified into groups of daily smokers and occasional/nonsmokers to distinguish the group with a higher cigarette smoke exposure.

Traffic pollution exposure

At 24 years, the participant reported whether the home had a window over a busy road or not, as a measure of exposure to traffic air pollution.

Anti-inflammatory medication

Use of inhaled corticosteroids (ICS) was self-reported and divided into no, intermittent or continuous use at 4 years (covering the period from the child's second birthday), 8 years and 24 years (covering the previous 12 months). Use of leukotriene receptor antagonists (LTRA) was self-reported at 24 years.

Clinical examinations

Height (precision in millimetres) and weight (precision in hectograms) were measured by research nurses at the clinical examinations. Body mass index (BMI) was grouped as under/normal weight, overweight and obesity at 8 years of age [21] according to the International Obesity Task Force cut-offs [22]. At 24 years, overweight was defined as a BMI $\geqslant$25 kg m^{-2} and obesity $\geqslant$30 kg m^{-2}. BMI was used as a continuous variable in the multiple regressions.

Allergic sensitisation

Allergic sensitisation was assessed at the ages of 4, 8 and 24 years and defined as present with a positive Phadiatop mix ($\geqslant$0.35 kiloUnits L^{-1}) (Phadiatop; Thermo Fischer Scientific, Uppsala, Sweden; Department of Clinical Immunology, Karolinska University Hospital, Stockholm), with IgE against mould, birch, cat, dog, horse, timothy, mugwort and/or house dust mite [12].

Spirometry

Spirometry was done according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [23]. At the 8 years follow-up, a spirometry was performed pre-bronchodilation with a 2200 Pulmonary Function Laboratory (Sensormedics, Anaheim, CA, USA) spirometer. Spirometry at the 24 years follow-up was performed using a Vyaire Vyntus system (Vyaire Medical, Chicago, IL, USA). The spirometry was done before and after 15 min after four puffs of 0.1 mg salbutamol. Lung function was converted to Z-score according to the Global Lung Initiative (GLI) reference values [24]. Post-bronchodilator spirometry was chosen as the main outcome to reduce the impact of active/undertreated asthma.

Multiple-breath nitrogen wash out

Lung clearance index (LCI) was measured with MBWO performed at least twice with an Exhalyzer D (Ecomedics Technologies™, San Diego, CA, USA) according to ERS guidelines [25]. The software Spiroware 3.2.0 was used, and results were then migrated to Spiroware 3.3.1 to correct for previously reported calculation errors [26, 27].

Study design and statistical analyses

The participants included in the study population were compared with the original cohort regarding prevalence of early wheeze, RSV infections and asthma at 1 and 2 years of age, maternal smoking during pregnancy, and maternal and paternal asthma with Wald's test, stratified for sex.

The asthma groups were characterised based on background and clinical factors and compared with the never asthma group as reference, stratified by sex. Then the asthma groups were compared with the never asthma group (reference) regarding pre- and post-bronchodilator lung function with t-tests, sex-stratified. Comparison within the asthma groups between the sexes was further done with t-tests.

The never asthma group (reference) and asthma groups were compared regarding LCI and then between the sexes within the asthma groups with Wilcoxon rank sum test, due to non-normal distribution.

Thereafter, the post-bronchodilator spirometry was analysed using simple and multiple linear regression. The multiple regressions were adjusted for maternal and paternal asthma [28], maternal smoking during pregnancy [18], secondary smoke exposure, daily smoking at 24 years of age, living close to a busy road at age 24, RSV infection up to 19 months of age, childhood allergic sensitisation [18, 28, 29], and BMI [30]. The confounders were selected based on their association with asthma and lung function or their association with male or female sex with a possible association with asthma and lung function.

Interaction analyses between sex and asthma phenotype were performed in the linear regression models.

The statistical analyses were performed using STATA, Statistical Software release 16.0 (College Station, TX, USA). A p-value <0.05 was considered statistically significant. Missing information was handled with complete cases.

Ethical permission

The Ethical Review Board at Karolinska Institute (Dnr: 93-189; Dnr: 98:175; Dnr: 02-420; Dnr: 2007/1634-31; Dnr: 2010/1474-31/3; Dnr: 2016/1380-31/2) has approved the BAMSE-study. All parents (up to 16 years) and participants (16, 24 years) provided an informed consent.

Results

Study population

The study population consisted of 1928 individuals, 811 males and 1117 females. Of the females in the original cohort, 55% (n=1117) were included in the study population, in contrast to 39% (n=811) of the males. No differences were found between the study population and the original cohort stratified for sex, except for males in the study population who to a lesser extent were exposed to maternal smoking during pregnancy compared to males in the original cohort (10.7% *versus* 13.7%, p<0.001), (supplementary S-Table 1). In total, 70% of the males (n=569) and 71% of the females (n=797) did not fulfil the criteria for asthma at any attended examination. Childhood asthma in remission was found in 25% (n=169) of the males compared to 17% (n=150) of the females (p<0.001). Adolescent onset asthma was more common in females (16% (n=142) *versus* 12% (n=66) of the males, p=0.015). The prevalence of persistent asthma was similar between the sexes (males 13%, n=73, *versus* females 11%, n=89; p=0.28). Prevalence of early exposures and characteristics in males and females are presented in supplementary S-Table 2 and S-Table 3a and b.

Baseline and clinical characteristics of the asthma phenotypes

All asthma groups had a higher prevalence of allergic sensitisation in childhood than in the never asthma group, in both sexes. Also, maternal asthma was more common in all asthma groups, while paternal asthma tended to be more common in the groups with childhood asthma in remission (for both sexes), and females with persistent asthma. High BMI at 8 years of age was more common in females with adolescent onset asthma (*i.e.*, not yet fulfilling criteria for asthma) or persistent asthma, compared to those in the never asthma group. Living close to a busy road at age 24 was more common among females with childhood asthma in remission and with persistent asthma, than females in the never asthma group (table 1).

Lung function

Pre-bronchodilator lung function at 8 years of age

Lung function at 8 years showed forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) to be lower in the childhood onset (in remission at age 24, or persistent) asthma groups than in the never asthma group (reference). Among males with adolescent onset asthma (*i.e.* not yet fulfilling the criteria for asthma), both FEV_1 and FEV_1/FVC were lower than in the never asthma group; and FEV_1/FVC was lower than in females with adolescent onset asthma (table 2).

Pre-bronchodilator lung function at 24 years of age

Both males and females with asthma or with a history of asthma had a lower FEV_1 and FEV_1/FVC pre-bronchodilation than the participants never having had asthma (reference), except for females with

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TABLE 1 Prevalence of characteristics compared between the male never asthma group (reference, in bold) and asthma groups respectively with chi-squared tests

Exposure	Male never asthma	Male childhood asthma in remission	p-value	Male adolescent onset asthma	p-value	Male persistent asthma	p-value	Female never asthma	Female childhood asthma in remission	p-value	Female adolescent onset asthma	p-value	Female persistent asthma	p-value
Subjects n	**569**	169		66		73		**797**	150		142		89	
Mother asthma	**42 (8.4)**	**37 (22)**	**<0.001**	**13 (20)**	**0.003**	**13 (18)**	**0.010**	**52 (7.1)**	**20 (13)**	**0.011**	**24 (17)**	**<0.001**	**24 (27)**	**<0.001**
Father asthma	**38 (7.6)**	21 (23)	0.053	7 (11)	0.40	7 (9.6)	0.56	**52 (7.1)**	**21 (14)**	**0.004**	13 (9.5)	0.33	**20 (23)**	**<0.001**
Early wheeze	**20 (4.2)**	**86 (52)**	**<0.001**	5 (8.1)	0.17	**32 (45)**	**<0.001**	**17 (2.4)**	**68 (17)**	**<0.001**	4 (3.0)	0.72	**34 (40)**	**<0.001**
RSV <19 months	**9 (1.8)**	**17 (10)**	**<0.001**	2 (3.1)	0.49	**6 (8.3)**	**0.001**	**21 (3.0)**	**18 (12)**	**<0.001**	6 (4.4)	0.38	**8 (9.1)**	**0.004**
Maternal smoking during pregnancy	**48 (9.7)**	23 (14)	0.16	5 (7.6)	0.57	10 (14)	0.30	**84 (11)**	24 (16)	0.31	13 (9.2)	0.21	14 (16)	0.43
Secondary smoke exposure	**246 (49)**	86 (51)	0.66	33 (50)	0.87	42 (58)	0.17	**394 (54)**	93 (62)	0.057	76 (54)	1.0	**60 (67)**	**0.013**
Daily smoking at 24 years	**29 (5.8)**	8 (4.8)	0.61	4 (6.1)	0.93	5 (6.9)	0.72	**58 (7.9)**	15 (10)	0.39	15 (11)	0.29	8 (9.0)	0.72
Living on a busy road at age 24 years	**121 (24)**	38 (23)	0.71	17 (26)	0.76	21 (29)	0.43	**148 (20)**	**45 (30)**	**0.009**	31 (22)	0.65	**26 (30)**	**0.049**
Allergic sensitisation at 4 and/or 8 years	**97 (23)**	**50 (32)**	**0.036**	**25 (45)**	**<0.001**	**47 (67)**	**<0.001**	**92 (15)**	**30 (23)**	**0.028**	**45 (41)**	**<0.001**	**40 (51)**	**<0.001**
High BMI at 8 years of age	**74 (20)**	25 (17)	0.57	10 (20)	0.94	15 (24)	0.40	**94 (18)**	22 (19)	0.63	**27 (26)**	**0.035**	**23 (33)**	**0.002**
High BMI at 24 years	**128 (25)**	44 (26)	0.88	17 (26)	0.96	**27 (37)**	**0.038**	**131 (18)**	31 (21)	0.41	**37 (26)**	**0.022**	**26 (29)**	**0.010**

Data presented as n (%) unless indicated otherwise. Significant results in bold. High BMI: body mass index defined as overweight/obese for the age group; RSV: respiratory syncytial virus infection up to 19 months of age.

TABLE 2 Lung function at 8 years in the asthma groups[#] compared to the group with never asthma (reference) measured as Z-score in a linear regression stratified for sex

	Never asthma (reference)	Childhood asthma in remission	p-value	Adolescent onset asthma	p-value	Persistent asthma	p-value
Male n	267	109		33		51	
Female n	388	80		75		57	
FEV_1 β (95% CI) male		−0.124 (−0.327–0.078)	0.23	**−0.352 (−0.681– −0.023)**	**0.036**	−0.124 (−0.396–0.149)	0.37
FEV_1 β (95% CI) female		−0.101 (−0.323–0.121)	0.37	−0.017 (−0.245–0.211)	0.88	−0.158 (−0.414–0.098)	0.23
p-interaction male–female			0.87		0.10		0.86
FVC β (95% CI) male		0.048 (−0.154–0.250)	0.64	0.017 (−0.310–0.344)	0.92	0.218 (−0.053–0.489)	0.12
FVC β (95% CI) female		0.079 (−0.132–0.289)	0.46	−0.029 (−0.245–0.187)	0.79	0.120 (−0.123–0.363)	0.33
p-interaction male–female			0.84		0.82		0.60
FEV_1/FVC β (95% CI) male		**−0.254 (−0.457– −0.051)**	**0.014**	**−0.563 (−0.893– −0.234)**	**0.001**	**−0.489 (−0.762– −0.216)**	**<0.001**
FEV_1/FVC β (95% CI) female		**−0.235 (−0.447– −0.023)**	**0.029**	0.067 (−0.150–0.284)	0.54	**−0.401 (−0.645– −0.156)**	**0.001**
p-interaction male–female			0.90		**0.002**		0.63

Significant differences in bold. β: regression coefficient; CI: confidence interval; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: never asthma: not fulfilling criteria for asthma at any attended examination; childhood asthma in remission: asthma onset up to 8 years of age, not at 24 years; adolescent asthma: asthma onset after 8 years of age; persistent asthma: asthma onset before 8 years of age persisting to 24 years of age.

adolescent onset asthma. This group did not have a lower FEV_1 but had a higher FVC than the never asthma group (supplementary S-Table 4).

The males had in general lower results in relation to the reference (GLI) than the females, also seen in the never asthma group (supplementary S-Table 4).

Lung function and asthma phenotype

When comparing the asthma groups with the never asthma group (reference) regarding post-bronchodilator lung function at 24 years, FEV_1 was lower in both males and females with childhood asthma in remission and males with persistent asthma, with borderline significance for females (table 3). Females with adolescent onset asthma had a higher FVC than females with never asthma, a difference not seen among the males. In all asthma groups, FEV_1/FVC were lower compared to the never asthma groups for both sexes (table 3).

Similar to the results pre-bronchodilation, males had in general lower lung function compared to females, although the differences were less pronounced (table 3).

After adjustment, the significant associations between asthma and lower lung function in males remained significant. In females, adjustments generally resulted in attenuated associations, except for childhood asthma in remission (figure 2a–c, for all values supplementary S-Table 5). There was a significant interaction between sex and persistent asthma (p=0.015) and a borderline interaction for sex and adolescent onset asthma (p=0.051) for the outcome FEV_1/FVC, with a lower FEV_1/FVC in males compared to in females (figure 2c).

Lung clearance index at 24 years

In males, there were no significant differences between the never asthma group and the asthma groups in LCI (figure 3a). Females with persistent asthma had higher LCI than females never having had

TABLE 3 Lung function at 24 years

	Never asthma	Childhood asthma in remission	p-value	Adolescent asthma	p-value	Persistent asthma	p-value
Male							
Subjects n	569	169		66		73	
FEV_1	−0.024±0.827[#]	**−0.172±0.85**	**0.046**	−0.147±0.93[¶]	0.26	**−0.324±0.848**	**0.004**
FVC	−0.191±0.860[+]	−0.196±0.866	0.95	−0.061±1.01	0.26	−0.147±0.941	0.68
FEV_1/FVC	0.201±0.825	**−0.017±0.873**	**0.004**	**−0.197±0.825**	**<0.001**	**−0.302±0.847**	**<0.001**
Female							
Subjects n	739	150		142		89	
FEV_1	0.100±0.841[#]	**−0.096±0.82**	**0.009**	0.195±0.78[¶]	0.21	−0.085±0.851	0.051
FVC	−0.061±0.835[+]	−0.101±0.860	0.59	**0.135±0.790**	**0.010**	−0.058±893	0.98
FEV_1/FVC	0.221±0.783	**−0.004±0.900**	**0.002**	**0.033±0.791**	**0.009**	**−0.059±0.909**	**0.002**

Mean±SD post-bronchodilation spirometric lung function expressed as Z-score in the asthma groups[§] compared with the never asthma group (reference). Analyses stratified for sex. Comparisons with t-test. Significant differences in bold. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. Crude comparisons between males and females within the phenotype groups: [#]: p=0.011; [¶]: p=0.006; [+]: p=0.008. [§]: never asthma: not fulfilling criteria for asthma at any attended examination; childhood asthma in remission: asthma onset up to 8 years of age, not at 24 years; adolescent asthma: asthma onset after 8 years of age; persistent asthma: asthma onset before 8 years of age persisting to 24 years of age.

asthma (figure 3b). Comparisons between the sexes within the asthma groups did not show any significant differences, all p>0.1.

Discussion

In this study with data from a population-based birth cohort, our aim was to assess differences in lung function in early adulthood in males and females with asthma depending on age of onset and remission. Our main finding was a lower FEV_1/FVC among participants in all asthma groups, and lower FEV_1 in participants with childhood asthma in remission and persistent asthma, the latter with borderline significance for females. However, after adjustment for known risk factors, the associations remained

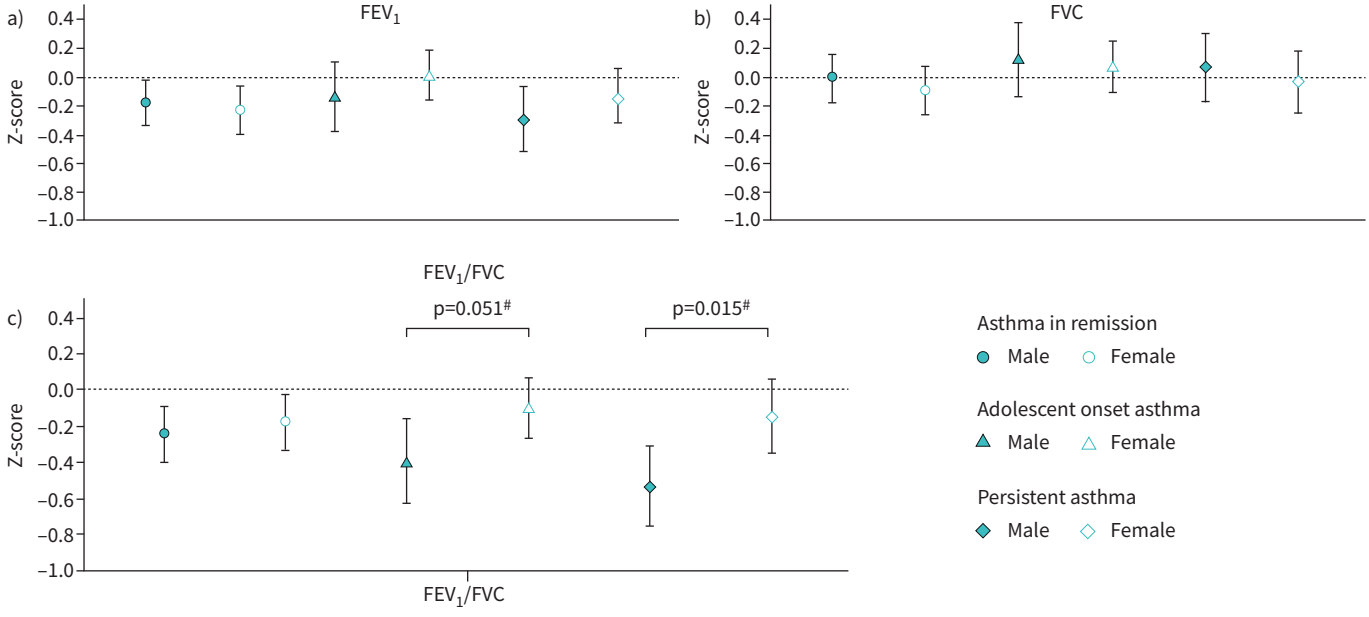

FIGURE 2 Spirometric lung function post-bronchodilation at 24 years in the asthma groups compared with the never asthma group (reference) expressed as Z-score with multiple linear regression adjusted for: maternal and paternal asthma, maternal smoking during pregnancy, respiratory syncytial virus infection up to 19 months of age, secondary smoke exposure, daily smoking at 24 years of age, living on a busy road at age 24, childhood allergic sensitisation and body mass index at 24 years of age. a) Forced expiratory volume in 1 s (FEV_1). b) Forced vital capacity (FVC). c) FEV_1/FVC. [#]: p-interaction.

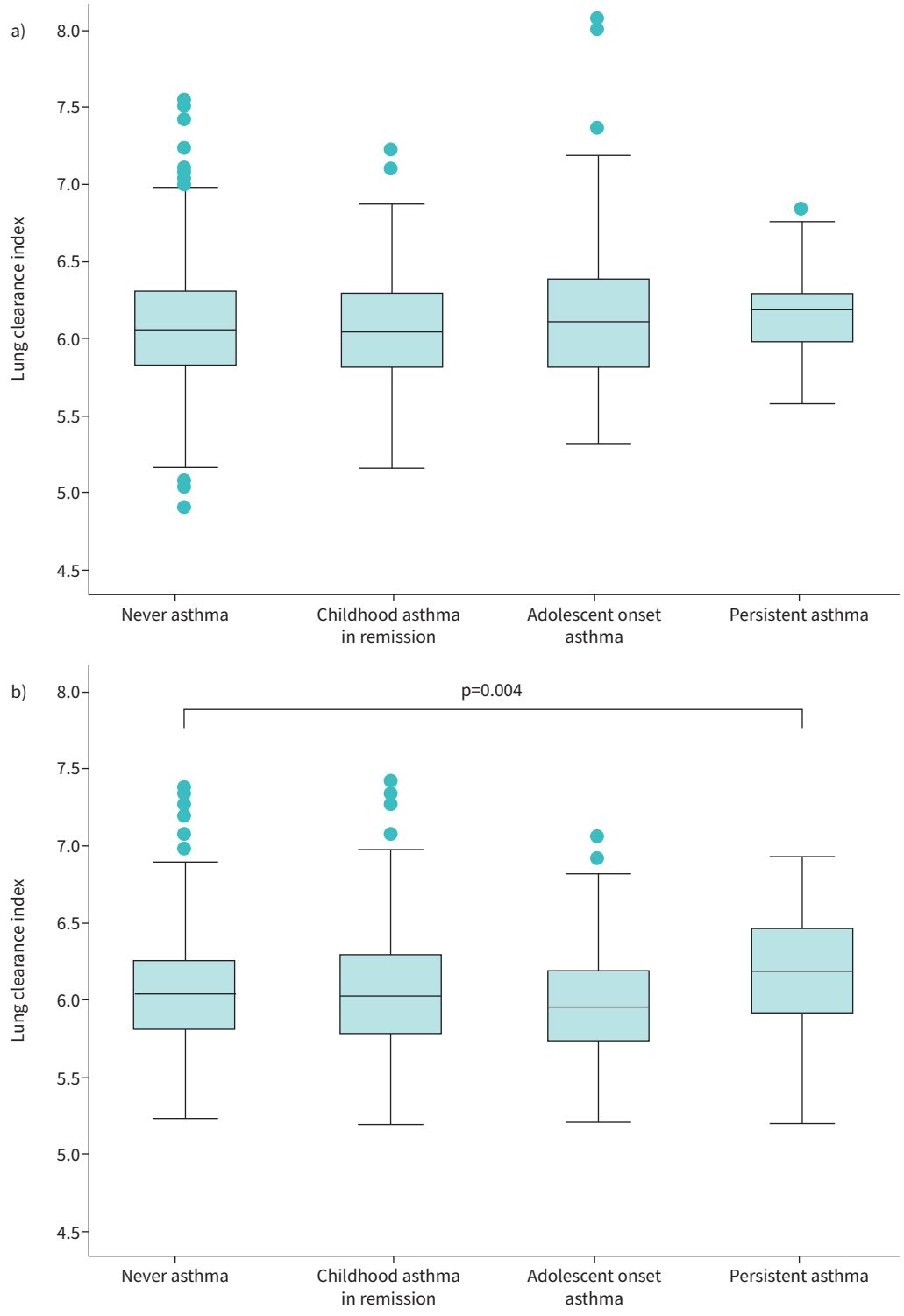

FIGURE 3 a) Median lung clearance index, in the asthma groups respectively, among males. The box represents upper and lower quartile, line in box the median and the whiskers max and min. Outliers are represented as dots. b) Median lung clearance index, in the asthma groups respectively, among females. Significant difference indicated in figure. The box represents upper and lower quartile, line in box the median and the whiskers max and min. Outliers are represented as dots.

significant in all male asthma groups, but only for females with childhood asthma in remission. Participants with persistent asthma had the highest LCI, significant for females.

Lung function has previously been described to follow a trajectory during growth [16–18], and the lower FEV_1 and FEV_1/FVC ratio in adolescents with asthma and a history of asthma, emphasises asthma in early life to be important for adult lung function. In our participants at 8 years of age, the groups with childhood asthma had a lower FEV_1/FVC than the never asthma group. However, rather unexpectedly, male participants in the group with adolescent onset asthma (who had not yet fulfilled the criteria for asthma) had a significantly lower FEV_1/FVC at 8 years of age than both males with never asthma, as well as females with adolescent onset asthma. Further, we found no difference in prevalence of early wheeze or RSV infections among the males with adolescent onset asthma compared to neither males with never asthma nor females with adolescent onset asthma. A possible interpretation could be low lung function playing a larger part in male asthma morbidity than in females.

Indeed, previous research has identified female asthma after puberty as being more symptomatic and severe, more often leading to emergency room visits [31] and hospitalisations [32, 33] despite better lung function than in males. A recent study from our group found lung function in females to have poorer growth from 8 to 24 years of age in uncontrolled *versus* controlled asthma, an association less pronounced among males [20]. An interpretation of this could be characteristics such as heredity for asthma, allergic sensitisation or tobacco smoke exposure to be closer related to lung function development in female than male asthma, or for the likelihood of an asthma diagnosis; or reversed as previously suggested, male asthma to be more closely associated with low lung function.

We could not identify any significant differences between males and females in the self-reported use of anti-inflammatory medication, although the males with adolescent onset asthma tended to report less use of both ICS and LTRA than the females with adolescent onset asthma (supplementary S-Table 2b). ICS use has been suggested to improve lung function development in childhood asthma, possibly through the prevention of exacerbations [34, 35]. Some studies have identified sex-related differences in the response to anti-inflammatory medication of lung function [36, 37], although data are so far sparse and to some extent conflicting [38].

We found a significant association between female persistent asthma and a higher LCI, compared to those with never asthma. Among males with persistent asthma, a similar LCI was found, however not reaching significance. LCI is a measure of ventilatory heterogeneity in the lung [39] and would possibly detect early pathological changes [40]. However, the groups in this subpopulation were small, and the results should be interpreted with caution.

A strength of this study is the longitudinal data collection in a large group of individuals with spirometry measurements. Information on early exposures was collected continuously during the study period, reducing the risk of differential misclassification.

The fit of the reference values used for spirometry was not perfect for the studied population, and in the never asthma group, males had lower FEV_1 and FVC than females. However, the sex-stratified comparisons between the asthma groups and the never asthma group should make both the comparisons and interaction analyses still valid.

A potential weakness of the study is the risk of misclassification of onset and remission of asthma. Still, males in all the asthma groups had poorer lung function development than never asthmatic males, in contrast to females. The lower response rate among males than females could lead to selection bias differing between the sexes. Early life air pollution other than tobacco smoke could potentially affect male and female lung function differently. Although all participants lived in the Stockholm area (*i.e.* not in the countryside/farm environment), this exposure could vary depending on local conditions and is not included in the analysis, which is a limitation.

In conclusion, childhood and adult asthma has important negative effects on adult lung function in both males and females, and this is more pronounced in males than in females. Males with persistent asthma was the most affected group, with significantly lower FEV_1/FVC ratio than seen for females with persistent asthma. Further, the results suggested lung function in females with asthma to be more affected by associated factors compared to lung function in male asthma, although this is a finding in need of more research to be fully understood.

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