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Sex Differences in Lung Function in Asthma Across the Ages

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To the Editor:

Human lung maturation, including alveolarization and microvascular maturation, continues until young adulthood.[1] This process may be adversely affected by childhood asthma. Indeed, a longitudinal cohort study that followed patients with asthma from childhood to adulthood found that adult patients with asthma with reduced lung function reported asthma beginning when they were 9 years of age.[2] This was attributed to airway remodeling and chronic inflammation that progressed throughout the course of the disease.[3] Furthermore, asthma varies throughout life, with a clear sex difference, where asthma is more prevalent in males than females during childhood, but females take the lead in prevalence compared with males in adulthood.[4] Here, we hypothesized that adult males with asthma have lower lung function than females due to younger age at asthma onset.

Study Design and Methods

This is a cross-sectional analysis of data from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2015. Patients were included if they had spirometry measurements available. We identified NHANES participants as having asthma if

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they reported that they still have asthma at the time of interview, and as a control participant if they did not report either asthma or COPD. Participants with resolved asthma, COPD, or asthma-COPD overlap syndrome were excluded. The main outcome was to compare differences in prebronchodilator FEV_1 % predicted between the two groups (asthma and control).

Data are presented as median and interquartile range for continuous variables and count (%) for categorical variables. Student *t* test was used in two group comparisons of continuous normally distributed variables, and the Wilcoxon rank sum test was used when the normality assumption was not demonstrated. Categorical variables were compared using a χ^2 test. Analysis of covariance test was used to compare FEV_1 % predicted between participants with asthma and control participants in males and females while statistically controlling for age. We ran the analysis of covariance model including an interaction term between age and sex to assess whether the slope of the association between age and outcome (FEV_1) varies by sex. Differences between peak FEV_1 (liters) in male and female participants with asthma compared with control participants were assessed using the Wald test. The rspiro package in R (R Project for Statistical Computing) was used to calculate spirometry predictive values using a race neutral approach according to the 2022 Global Lung Initiative equations method described by Bowerman et al.[5] All statistical analyses were conducted with R version 4.0.5.

Results

Of the 19,960 NHANES participants with spirometry data, 18,048 (90.4%) met inclusion criteria and 1,476 (7.4%) had asthma (Table 1). Asthma was more common in younger male participants (15.9%) than female participants (12.4%). However, after 20 years of age, asthma prevalence became higher in female participants (13.7%) than male participants (10.9%) (interaction $P < .001$) (Fig 1A). Similarly, male participants had significantly lower age at asthma diagnosis than female participants ($P < .001$) (Fig 1B, Table 1). Peak FEV1 (liters) was lower in males with asthma ($P < .001$) but not in females with asthma compared with control participants for each sex, respectively (Fig 1C). After 20 years of age, the slope of the curve of FEV1 by age was similar in male participants with asthma and control male participants ($\beta = -0.0345$ vs -0.0347 L/year of age, respectively; interaction $P = .896$), but steeper in female participants ($\beta = -0.031$ vs -0.027 L/year of age, respectively; interaction $P < .001$) (Fig 1C). FEV_1 % predicted was lower in male participants with asthma than female participants with asthma (Fig 1D). Decreases in FEV_1 % predicted for each year increase in age were more noticeable among female participants with asthma than control female participants ($\beta = -0.24$ vs -0.1, respectively; interaction $P < .001$). Similarly, decreases in FEV_1 % predicted for each year increase in age were more noticeable in male participants with asthma between 20 and 30 years of age than control male participants ($\beta = -1.43$ vs -0.28, respectively; interaction $P < .024$). After 30 years of age, decreases in FEV_1 % predicted for each year increase in age did not significantly differ between male participants with asthma and control male participants ($\beta = -0.15$ vs -0.13, respectively; interaction $P < .42$) (Fig 1 D).

Discussion

To date, little is known regarding sex and age differences in respiratory function patterns in patients with asthma. Hence, the aim of this research is to characterize lung function variations in female and male patients with asthma across the ages.

Compared with control participants, the slope of the curve of FEV_1 % predicted for each year increase in age was steeper in male participants with asthma before 30 years of age but not after that age. On the other hand, decreases in FEV_1 % predicted were more pronounced in female participants with asthma than control participants across all ages. This suggests that although males with asthma lose their lung function early during life, females with asthma continuously lose their lung function throughout adulthood. This mirrors the sexual dimorphism in asthma prevalence and severity across the lifespan which we and others have described.[6] It also reflects the important role sex hormones play during pubertal transition and their impact on asthma pathophysiology.[6,7] Our findings also reflect the study conducted by Ricciardolo et al[8] on 499 patients with asthma in Italy, which showed that adult females with asthma had higher FEV_1 than males (86.98 vs 79.32, respectively; $P <$ .0022). Similarly, in another cross-sectional study in Brazil, Forte et al[9] described a trend toward lower lung function parameters in adult males with asthma (FEV_1 % predicted: 83.1 vs 76.3; $P <$ .078). Another population-based birth cohort demonstrated similar differences in FEV_1 between males and females with asthma.[10] Sex differences in FEV_1 % predicted are likely due to earlier disease onset in males and increased severity in adult females. Other causes include differences in environmental exposure (eg, smoking) or interactions between sex and obesity.[11] Although corticosteroid therapy may influence lung function, we speculate that loss of lung function may reflect asthma severity especially during lung development at younger age. We acknowledge that our study and others are limited by the cross-sectional nature of the analysis. However, it informs us about differences in lung function between males and females with asthma across the life span. In addition, this study is limited by the exclusion of children aged < 6 years due to the difficulty in diagnosing asthma and the limited accuracy of spirometry in this age group.

Interpretation

This study identifies sex-specific periods of vulnerability that may benefit from targeted interventions to minimize long-term lung function loss due to asthma. These groups include male patients < 20 years of age or young adult female patients.

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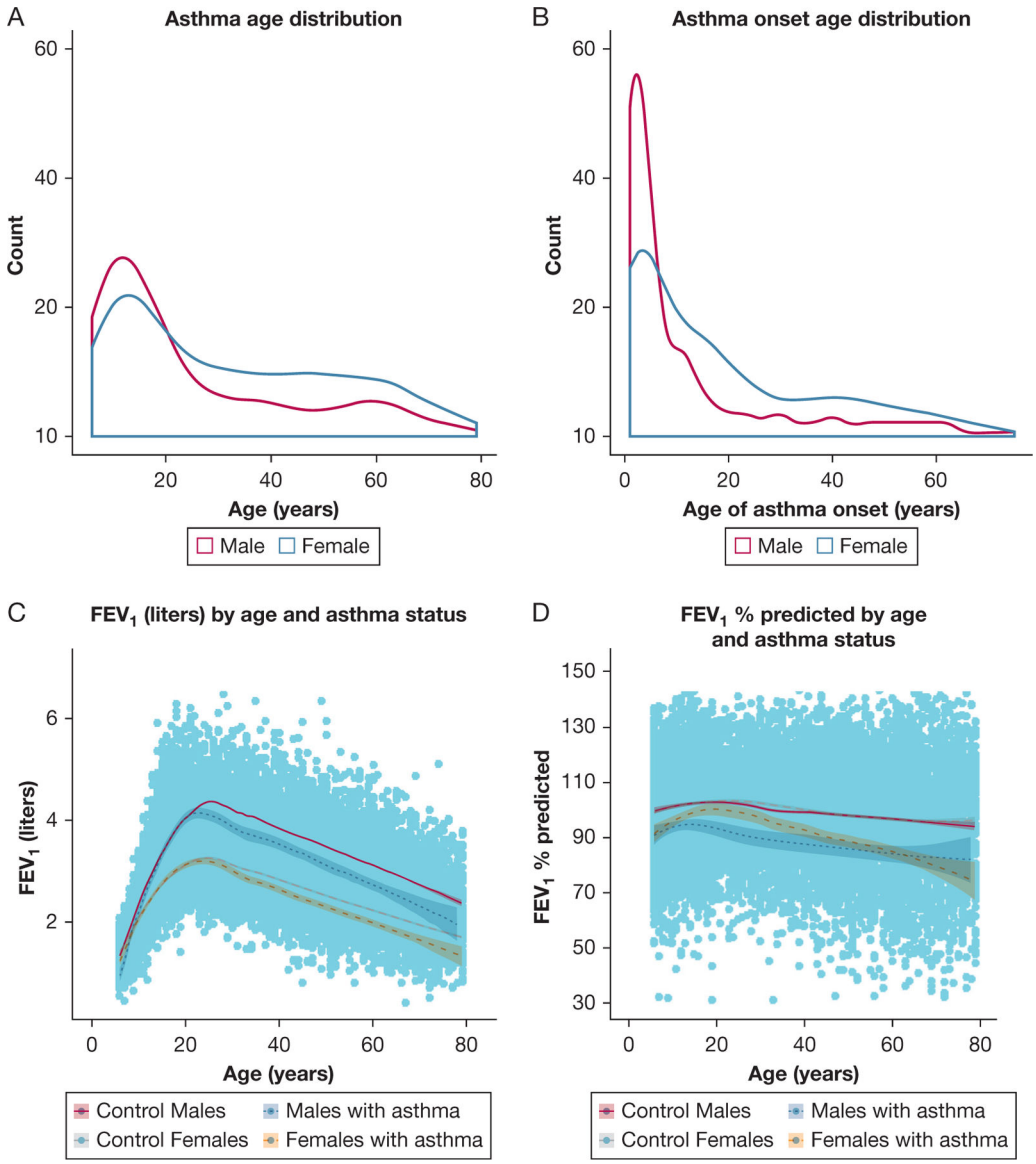

Figure 1 –.

A-D, Age, asthma onset, and FEV_1 over the lifespan. A, B, Distribution of age at the National Health and Nutrition Examination Survey interview and age at asthma onset in participants with asthma (n = 1,476). C, FEV_1 (liters) by age across the lifespan stratified by asthma status and sex. Lowest curves drawn on scatterplot show significantly lower FEV_1 % predicted in patients with asthma compared with control patients (n = 16,572; $P < .05$). Peak FEV_1 is significantly lower in male patients with asthma than control patients, but not in females. D, FEV_1 % predicted by age across the life span stratified by asthma status and sex. FEV_1 % predicted was significantly lower in males than females with asthma (n = 1,476; $P < .002$) but not in control patients (n = 16,572). Shaded areas indicate SE.

TABLE 1]

Baseline Characteristics of Participants by Sex and Asthma Status

Characteristic	Control Group			Asthma Group		
	Male (n = 8,453)	Female (n = 8,119)	*P* Value	Male (n = 687)	Female (n = 789)	*P* Value
Age at interview, y	34 (16–53)	33 (15–53)	.114	16 (11–34)	24 (13–46)	< .001
Age at first asthma diagnosis, y	…	…	…	4 (1–12)	11 (3–25)	< .001
Race			.167			.023
Black	1,825 (21.6)	1,865 (23.0)		248 (36.1)	233 (29.5)	
White	3,186 (37.7)	2,967 (36.5)		239 (34.8)	291 (36.9)	
Hispanic	2,650 (31.3)	2,531 (31.2)		141 (20.5)	202 (25.6)	
Other races	792 (9.4)	756 (9.3)		59 (8.6)	63 (8.0)	
BMI, kg/m^2	26 (22–30)	25.5 (21–31)	.825	24 (20–30)	27 (21–33)	< .001
FEV_1 % predicted	100.2 (89.8–110.1)	100.6 (90.2–110.2)	.250	91.2 (79.8–103.4)	95.1 (83.0– 105.5)	.003
FVC % predicted	96.7 (87.1–106.2)	97.3 (87.4– 106.6)	.078	93.4 (82.6– 103.8)	94.9 (84.6– 104.8)	.194
FEV_1/FVC ratio	0.81 (0.75–0.86)	0.83 (0.78– 0.88)	< .001	0.79 (0.73– 0.85)	0.81 (0.75– 0.87)	< .001

Data are presented as median (interquartile range) for continuous variables, No. (%) for categorical variables, or as otherwise indicated. Control group = all patients surveyed by the National Health and Nutrition Examination Survey who do not report obstructive airway diseases.