
Sex differences in asthma, atopy, and airway hyperresponsiveness in a university population

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Background: A male predominance in atopy, a preadolescent male predominance in asthma, and a female predominance in airway hyperresponsiveness (AHR) have been previously documented, mostly in separate populations.

Objective: We examined gender differences in a single population of 500 randomly selected university students from a previous publication which addressed sensitivity and specificity of histamine bronchoprovocation (Cockcroft et al. *J Allergy Clin Immunol.* 1992;89:23–30).

Methods: In these 500 subjects (age 21.8 ± 1.5 years) we assessed gender differences in asthma, atopy, and AHR. We compared our findings with those in the literature from a PUBMED search using the keywords *gender, asthma, atopy, AHR, and bronchial reactivity*.

Results: A diagnosis of asthma made by another physician was seen in 31, a male-to-female ratio of 2.9:1 ($P = 0.004$). Our definition of asthma increased the total to 52 and reduced the male-to-female ratio to 1.2:1. Atopy was seen in 190, male-to-female ratio of 1.5:1 ($P = 0.001$). Borderline to mild AHR had a female predominance with a male-to-female ratio of 1:1.5 ($P = 0.02$), whereas moderate AHR had a marked predominance with a male-to-female ratio of 7:1 ($P = 0.03$).

Conclusions: In our population, the associations among gender and asthma, atopy, and AHR were similar to those seen in the literature with the exception of males having more severe AHR. This may be the one factor contributing to the higher prevalence of asthma (including previous doctor-diagnosed asthma in our population) in boys and young men.

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INTRODUCTION

The association among sex and asthma, atopy, and airway hyperresponsiveness (AHR) has been well documented in several publications.^{1–15} Our definition of asthma is a clinical diagnosis that includes various symptoms such as wheezing most days or nights, shortness of breath, or wheezing on exposure to various allergens. AHR is an objective measure of airway abnormality (frequently evaluated with histamine or methacholine challenge testing) that is strongly associated with a clinical diagnosis of asthma.

Young males are more likely to have atopy and asthma with male-to-female ratios of 1.5:1 for both.^{1,3,4,6,7,14} There is a reversal for AHR with a male to female ratio of 1:1.5 to 2.4.^{5,9–13} It is unclear why there is such a well documented difference in the prevalence of asthma between boys and girls. Various theories include the difference in prevalence of atopy and AHR and even a possible diagnostic bias favoring males.¹

We revisited these three issues in a single population of 500 university students that was the subject of an earlier publication to determine the sensitivity and specificity of histamine PC₂₀ (provocation concentration causing a 20% fall in forced expiratory volume in 1 second).² Using this population, an arbitrary cut point of 8 mg/mL had 100% sensitivity, 93% specificity, and 100% negative predictive value if

the patient had symptoms of current asthma. By lowering the cut point to 1 mg/mL, the specificity and positive predictive value approached 100%, and the sensitivity fell to less than 50%. These data indicate that a PC₂₀ greater than 8 mg/mL rules out current asthma in most cases, whereas a PC₂₀ less than 1 mg/mL is almost diagnostic of current asthma.

The associations among sex and asthma, atopy, and AHR have all been identified from different studies with different populations. To the best of our knowledge, this is the first look at all three issues in the same population.

METHODS

Subjects

In 1989, 500 students at the University of Saskatchewan were randomly selected to participate in a study (published in 1992) evaluating the sensitivity and specificity of histamine PC₂₀ determination. Initially, the American Thoracic Society Questionnaire on Respiratory Disease¹⁶ was administered to each subject. Modifications were made to include questions regarding allergy. The added questions addressed rhinitis, conjunctivitis, and allergies (drugs, foods, inhaled substances, manifestations such as asthma, rhinitis, conjunctivitis, rash, other).

The subject was considered to have asthma if there was a positive response to Q20C (asthma previously diagnosed by a physician) and, in those without a previous diagnosis of asthma, if there was a positive response to Q10A3 (wheezing most days or nights), Q11C (two or more episodes of wheezing resulting in shortness of breath), or Q10A2 (wheezing that occurred on response to an allergen to which the subject had a positive skin test result).

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Methods

Allergy prick skin tests were performed with a standard battery of a control and seven allergens, including *Derмато-phagoides farinae*, mixed tree pollen, mixed grain dust, mixed grass, mixed weed, mixed animal danders, and mixed molds. Wheal size was scored as 1+ (1 to 2 mm), 2+ (3 to 5 mm), 3+ (6 to 8 mm), or 4+ (>8 mm) at 10 minutes. Subjects were considered significantly atopic if they had two 1+ or one 2+ response to any of the allergens.

AHR to inhaled histamine was performed with a shortened technique starting with diluent inhaled for a 2-minute period of quiet tidal breathing.¹⁷ Doubling concentrations of histamine starting from 1.0 mg/mL (occasionally lower if suspicion of asthma) to a maximum of 8.0 mg/mL were inhaled for 2 minutes at 5-minute intervals. The forced expiratory volume in 1 second (FEV₁) was measured 3 times at baseline and once at 30 seconds and 90 seconds in each interval. The test was continued until the FEV₁ had fallen 20% or more or until the highest concentration had been administered. The PC₂₀ was then interpolated by a linear interpolation formula of the last two data points. When the FEV₁ fall at 8 mg/mL was between 10 and 20%, the PC₂₀ was extrapolated as high as 16 mg/mL.¹⁸

Analysis

Prevalence of asthma, atopy, and AHR in males and females was compared using the χ^2 test on 2×2 contingency tables¹⁹ with STATISTIX4.1 (Analytical Software, Tallahassee, FL). Significance was considered at $P < 0.05$. Detailed protocols are described in the initial publication.²

RESULTS

Five hundred Caucasian students aged 20 to 29 years (mean age, 21.8 ± 1.5 years) participated in the study. There were no inclusion criteria apart from being a randomly selected university student, and there were no exclusion criteria. No severe asthmatic patients were encountered in the 500 random students, and nobody was excluded from this study. There were 253 female and 247 male subjects. Subjects with

current asthma had symptoms within the last week, whereas those with *past asthma* had not had symptoms within the previous year, and those who had symptoms within the past year but not within the past week proved to be subjects with *seasonal asthma*.

Asthma had been previously diagnosed by a physician in 31 of the subjects with a male-to-female ratio of 2.9:1 ($P = 0.004$). Thirteen of 31 had current asthma, 13 of 31 had past asthma, and 5 of 31 had seasonal asthma. The study's extrapolation of the definition of asthma to include additional questions from the American Thoracic Society questionnaire improved sensitivity and increased the total number of students with the diagnosis of asthma to 52, resulting in a male-to-female ratio of 1.2:1, with 17 having current, 19 with past, and 16 with seasonal asthma. Fifty-eight subjects had a family history positive for asthma.

AHR, when defined by a histamine PC₂₀ less than 8 mg/mL, was present in 58 of the 500 subjects and included 25 of the 52 with the diagnosis of asthma. At the various ends of the spectrum for histamine responsiveness, sex differences were noted. At a histamine PC₂₀ of 1 to 16 mg/mL ($n = 138$), which is mild to borderline AHR,²⁰ the male-to-female ratio was 1:1.5 ($P = 0.015$). At a histamine PC₂₀ less than 1 mg/mL ($n = 8$), which is moderate to marked AHR,²⁰ the male-to-female ratio was 7:1 ($P = 0.03$).

Atopy (defined as one 1+ wheal) was observed in 190 of 499 subjects (one refused skin tests). Significant atopy (defined as two or more 1+ wheals) was seen in 147 subjects with a male-to-female ratio of 1.5:1 ($P = 0.001$). Forty-two of the 52 asthmatic subjects were atopic (at least one 1+ wheal). Results of the male-to-female prevalence ratio for asthma, atopy, and AHR are shown in Figure 1.

DISCUSSION

Upon reviewing the sex differences for asthma, atopy, and AHR in a local university population, many similarities are found with published literature. Our study is the first to analyze all three of these factors in the same population. By

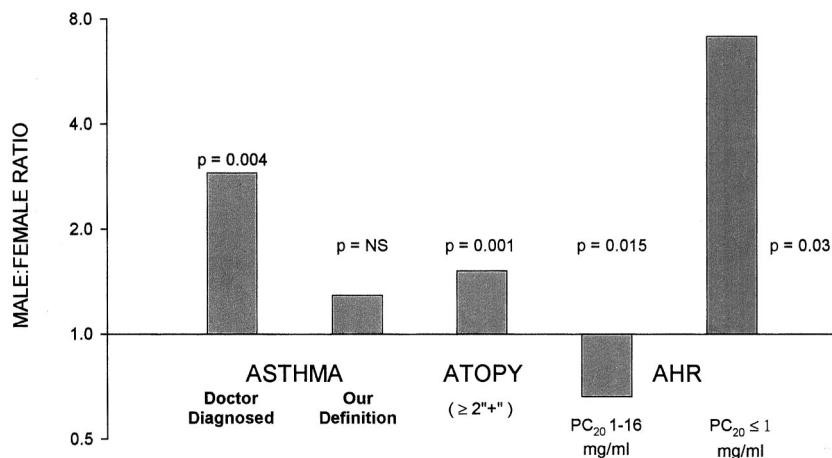


Figure 1. Bar graph demonstrating the male-to-female prevalence ratio for asthma, atopy, and airway hyperresponsiveness (AHR).

liberalizing the diagnostic criteria for asthma, we lessened the well published sex difference for asthma.

Over the last 20 years, there has been a dramatic increase in the prevalence of atopy in several countries. Numerous studies^{1,3,4,6,7} have found a male predominance of atopy. Our male-to-female ratio of 1.5:1 is similar to the literature. Males have a higher prevalence of atopy, especially to house-dust mite (HDM), grass, and cat dander.^{1,4,6,7} Sears et al¹ demonstrated that the prevalence of four or more positive skin test results from a panel of 11 allergens was more than twofold greater in boys than girls. Sears et al¹ also found that sensitivity to cat or HDM significantly increased the likelihood of asthma, whereas Kuehr et al⁷ agreed with the causal relationship between HDM sensitization and perennial allergic asthma. In addition, a clear correlation was seen between the size of wheal to cat and HDM (individually and combined) and the likelihood of asthma¹ or AHR.⁸ When combining cat and HDM wheal sizes, a diameter totaling 8 mm or more was seen in more than 50% of the subjects with current asthma¹ and in 43% of subjects with a PC₂₀ less than 8 mg/mL.⁸ Atopy has been clearly associated with AHR in a number of studies.^{1,5,9}

AHR is usually more common in females than males.^{5,9-13} However, a trend toward predominance of AHR in male children and adult males⁹ has been reported. AHR is usually evaluated with a methacholine or histamine challenge. The sensitivity and negative predictive value are high and have been reported to be as high as 100%.² In our previously published study using this population, sensitivity and negative predictive values were 100% and specificity 93% if a PC₂₀ less than 8 mg/mL was used for diagnosis.² Female predominance was consistent with the literature when observing a PC₂₀ of 1 to 16 mg/mL (mild to borderline AHR), but when a PC₂₀ of less than 1 mg/mL (moderate AHR), which is more specific for asthma, was used, there was a marked reversal in sex predominance.

Studies have shown that the female predominance in AHR is eliminated when baseline FEV₁ is accounted for.^{10,12,13} It is theorized that because of the smaller airways in females, this may predispose them to react more to a challenge agent as compared with a male.¹⁰ This theory has been disputed by other studies¹¹ that have taken baseline lung function into account and still claim that females have increased AHR compared with males. It is possible that our male predominance with the highly specific histamine cutoff is partly responsible for the higher rate of asthma in our male population as previously diagnosed.

There is a male predominance of asthma in childhood.^{1,14} Various theories of higher rates of viral respiratory tract infections in males, an "intrinsic state" of the airways in males, hormonal changes (attributing to the reversal of prevalence after puberty), and diagnostic biases favoring males have all been postulated to explain this sex difference.¹ Recent studies demonstrating the increased prevalence of atopy in males, especially to HDM and cat dander, appear to play a more prominent role in the greater prevalence of asthma in young males. At adolescence, a reversal in this trend oc-

curs.^{1,14,15} It is unclear if this is attributable in part to hormonal changes, exogenous hormone use, or growth spurts.

The male-to-female ratio for asthma is frequently quoted as 1.5:1 for subjects younger than 15 years.^{14,15} Our university male population had a higher cumulative prevalence of asthma previously diagnosed by a physician of approximately 3:1. When our population was asked further questions to fulfill our definition of asthma, another 21 subjects were included, which made the sex difference nonsignificant. We have seen that our male population did have increased atopy and AHR compared with the females; this almost certainly plays a large role in their incidence of asthma. Although females had an overall increased prevalence of airway responsiveness, the males had markedly more airway hyperresponsiveness. The male subjects were all identified at a young age and our clinical diagnosis of asthma during the study was in subjects that were past adolescence. Our questions increased the incidence of asthma in the females but did not reverse the sex difference, which is seen after adolescence in the literature.

CONCLUSION

Our population of young university students did have similar sex differences for atopy, AHR, and asthma as previously reported in the literature. The associations that these conditions have with one another is undeniable, and all should be considered when one diagnosis is established.

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