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Gender- and age-specific risk factors for wheeze from birth through adolescence

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Abstract

Background and objective—Cross-sectional gender differences in wheeze are well documented, but few studies have examined the gender-specific risk factors for wheeze longitudinally. This study aims to identify gender- and age-specific risk factors for wheeze from birth through adolescence.

Methods—The incidence of wheeze was ascertained every 6 months through age 14 years in a birth cohort consisting of 499 children with a parental history of atopy. Gender- and age-specific risk factors were identified through generalized estimating equations.

Results—A total of 454(91.0%) and 351(70.3%) children were followed past age 7 and 13 years, respectively. Maternal asthma was a risk factor for wheeze in girls (OR=2.05, 95% CI 1.44–2.91, $p<0.0001$) and boys (OR=1.79, 1.29–2.48, $p=0.0004$) and had a similar effect on wheeze throughout the ages. Paternal asthma (OR=1.83, 1.38–2.57, $p=0.0005$) and infant bronchiolitis (OR=2.15, 1.47–3.14, $p<0.0001$) were risk factors for boys only, with similar effects throughout the ages.

Conclusion—Using a prospective cohort, we identified gender- and age-specific risk factors for wheeze. The identification of gender-specific early life risk factors may allow for timely interventions and a more personalized approach to the treatment of asthma.

Keywords

asthma; sex differences; parental asthma; bronchiolitis

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Introduction

Cross-sectional gender differences in the prevalence of wheeze and asthma and their associated morbidities are well documented, and a more limited number of European and Australasian birth cohort studies have also documented a higher male-to-female ratio in childhood and the reverse in adulthood¹⁻⁶. The reversal of this ratio is usually observed during adolescence. Several etiologies have been proposed to explain these gender differences, including dysanapsis⁷, female and male hormonal influences⁸⁻¹⁰, and differences in consultation practices¹¹. Limited evidence also suggests that response to inhaled corticosteroid may be gender-specific. In a study of 3416 patients with uncontrolled asthma randomized to one of two inhaled corticosteroids, being female was associated with decreased odds of having uncontrolled persistent asthma¹². It is unclear whether there may also be pharmacogenetic differences in asthma therapy between males and females as no study examined this issue specifically.

While several studies, including large birth cohorts, have identified risk factors for wheeze and asthma in childhood, most simply adjust for gender in their analytic model and few have examined gender-specific risk factors. Most of the studies in this field are also limited by their cross-sectional nature, leaving the temporal relationship of exposure to outcome unknown. This study attempts to address the above knowledge gaps by examining gender- and age-specific risk factors for wheeze.

Materials and Methods

Subjects

The Home Allergens cohort is a birth cohort of children with a parental history of allergy or asthma. Details of the study design have been published previously¹³. Briefly, 505 infants were recruited within 48h of birth in a large Boston hospital between September 1994 and June 1996, 499 of whom had outcomes assessed in the first year of life and were included in this study. All subjects lived within the metropolitan Boston area (within Route 128, which encircles the Boston area with a roughly 24-kilometer or 15-mile radius). A screening questionnaire was administered to the eligible mothers. Telephone questionnaires about the child's health and interim events were administered at 1 month of age, every 2 months for the first 2 years of life, and then every 6 months. The research protocol was approved by the Institutional Review Board and the children's parents or guardians provided written informed consent.

Ascertainment of wheeze

Wheeze was assessed through parental questionnaires (modified from the American Thoracic Society (ATS)- Division of Lung Diseases questionnaire¹⁴) from age 2 to 14 years, at 6-month intervals. Wheeze was considered present at any time point if an affirmative response was given to the question: "Has your child had wheezing or whistling in the chest with colds, exertion, or exposure to cold air since we last spoke?" Prior to age 2 years, the definition differed, as it did not include wheeze with exertion. Thus, for the purpose of this analysis, only data from age 2 to 14 years were included.

Statistical analysis

A descriptive analysis of baseline characteristics was performed. Based on the non-linear pattern of wheeze prevalence in this cohort (Figure 1a) and for ease of interpretation, the longitudinal data were divided into three ages stages: 1) 2 to 5 years; 2) 5 to 8 years; and 3) 8 years or greater. Generalized estimating equations were used to examine risk factors associated with wheeze, stratified by gender. Based on the results from previous studies^{15–19}, the following predictors were included in the final model: age stage, race/ethnicity, maternal and paternal asthma, in utero smoke exposure, birth weight for gestational age, ever breastfed, bronchiolitis before age 1 year, and body mass index (BMI) percentile. Other covariates considered but not included in the final model are: maternal hay fever, paternal hay fever, season of birth, gestational age at birth, household endotoxin, household income, daycare attendance in the first year of life, and second-hand smoke exposure. P-values are 2-sided. All analyses were performed using R, version 2.12.1 (www.r-project.org). Generalized estimating equations was performed using the packages "geepack"²⁰.

Results

Baseline characteristics of the 499 subjects in the Home Allergens cohort are presented in Table 1. This is a predominantly white cohort (75.2%) with a higher prevalence of parental atopy (maternal or paternal history of asthma, eczema or hay fever) given the inclusion criteria. The prevalence of bronchiolitis before age 1 year was 13.2% and was similar between boys (13.5%) and girls (12.8%). A total of 351 children were followed past age 13 years, representing 70.3% of the original cohort. There were 10,222 observations over the study period (2,892, 2,669, and 4,661 observations in age stage 1, 2, and 3, respectively), with a maximum cluster size of 25 observations per subject.

The prevalence of wheeze differed longitudinally by gender and age (Figure 1a and 1b). Girls had a similar prevalence of wheeze than boys early on, but this prevalence decreased to a nadir around age 8 years and increased thereafter, surpassing the prevalence in boys at around 12 years.

Gender-specific risk factors for wheeze

When looking across all three age stages, maternal asthma (OR=2.05, 95% CI 1.44–2.91, $p<0.0001$) and ever breastfed (OR=1.56, 95% CI 1.02–2.39, $p=0.04$) were significantly associated with wheeze in girls (Table 2). In boys, maternal asthma (OR=1.79, 95% CI 1.29–2.48, $p=0.0004$), paternal asthma (OR=1.83, 95% CI 1.38–2.57, $p=0.0005$), and bronchiolitis before age 1 year (OR=2.15, 95% CI 1.47–3.14, $p<0.0001$) were predictors of wheeze, while ever breastfed and race/ethnicity other than white, black and Hispanic were protective of wheeze in boys.

Gender- and age-specific risk factors for wheeze

Figure 2 demonstrates the adjusted odds ratio for predictors of wheeze whose effects vary by age stage or by gender. Maternal asthma was associated with increased odds of wheeze throughout the three age stages and had similar effect sizes for both genders. Interestingly,

paternal asthma and a history of bronchiolitis before age 1 year were risk factors for wheeze throughout the age stages in boys only, with the effect sizes similar for all three age stages. These relationships were not observed in girls (p-value for gender x paternal asthma interaction=0.0001, gender x bronchiolitis interaction=0.04). Although not statistically significant, a higher birth weight was associated with increased odds of wheeze in the early age stage, but the estimated effects, similar in both genders, decrease across age stages. On the other hand, the effect of BMI seems to be more important in later age stages, with similar effects in both genders (p-value for BMI percentile x age interaction=0.14 for boys, 0.28 for girls).

Discussion

In this birth cohort study we identified gender- and age-specific risk factors for wheeze. There are three key findings. First, while girls have a similar prevalence of wheeze than boys early on, this prevalence decreased to a nadir around 8 years of age and increased thereafter, surpassing the prevalence in boys at around 12 years. This is consistent with prior observations on the natural history of asthma. Second, while maternal asthma was a predictor for wheeze for both genders, paternal asthma and bronchiolitis before age 1 year were risk factors for boys only. Finally, our findings also suggest that the associations of birthweight and BMI percentile with wheeze may vary depending on the age stage of the child.

Several studies have identified the male gender as a risk factor for wheeze in early life^{1,21,22}. It has been hypothesized that dysynapsis and the relative collapsibility or size of airways may account for the predominance of wheeze in infant boys, compared to girls, while the effect of many other risk factors (e.g., parental asthma) have been assumed to be similar in boys and girls. Consistent with our findings, Arshad et al found that paternal asthma was associated with asthma in boys only. However, the authors showed that maternal asthma was associated with asthma in girls only, while our findings suggest that it was a predictor of wheeze for both genders²³. This may reflect the differences in the study cohorts, with the Home Allergens being a high-risk cohort for asthma and allergies. Another study documented a positive interaction between the male gender and parental allergic diseases on childhood persistent wheeze, although it was focused on wheeze up to age 4 years only²⁴. The differential effect of parental asthma with respect to the child's gender may be due to differential environmental, genetic and epigenetic influences²⁵ and mechanisms are being elucidated. For example, a recent study documented an association between alleles in the 17q12-21 regions and asthma in males²⁶. Interestingly, sex- and age-specific DNA methylation patterns in the promoter region of zona pellucida binding protein 2 (ZPBP2), a gene in this region, attenuated the effect of the alleles on asthma development. This suggests that epigenetic factors may play an important role in gender-specific asthma development.

In this study, bronchiolitis before age 1 year was associated with wheeze in boys only and this effect persisted through adolescence. Most studies examining bronchiolitis as a predictor of future asthma or wheeze did not examine gender-specific effects²⁷. In one study, male gender was associated with recurrent wheeze over the 12 months following respiratory syncytial virus (RSV)-negative bronchiolitis before age 2 years²⁸. A large

population-based study reported that boys with a history of bronchiolitis have a higher risk for asthma than girls during a 3-year follow-up²⁹ and another study documented higher bronchial hyperresponsiveness in boys 11 years after hospitalization for severe bronchiolitis in the first year of life³⁰. Except for the latter study examining bronchial hyperresponsiveness, the follow-up period after the bronchiolitis episode was relatively short and during a period in which boys tend to wheeze more independent of a history of bronchiolitis. Our findings suggest that the effect of infant bronchiolitis on future wheeze is specific to boys and persists until adolescence. This may have important clinical implications, as preventing a modifiable risk factor such as bronchiolitis early in life may modify the risk of subsequent persistent wheeze. Interestingly, the incidence of bronchiolitis was similar between boys and girls in our cohort, while most studies document a higher incidence in boys. This may be explained by the higher prevalence of parental asthma and daycare attendance before age 1 year among girls in our cohort (Table 1), which are known risk factors for infant bronchiolitis. In addition, this observation may relate to the fact that our cohort consisted of high-risk subjects, in that the mother or father had to have a history of asthma or allergic disease for their newborn to be included in the study.

Interestingly, we found that a history of breastfeeding was associated with increased odds of wheeze in girls while this was protective in boys, both with a history of parental atopy. While most studies have documented a protective role of breastfeeding for wheeze and asthma^{18,31,32} or that breastfeeding attenuates the effect of other risk factors for asthma³³, others suggest that breastfeeding has no effect or is a risk factor for future asthma, especially in children with a parental history of asthma^{34–36}. Other than methodological differences, these conflicting findings may reflect the variability in breast milk composition depending on maternal factors such as atopy, diet, metabolism, and environmental exposures. Furthermore, the complex interaction between genes and breast milk exposure in the child may contribute to these differences.

Our findings suggest that BMI percentile and birthweight may have age-specific effects on wheeze, although this was not statistically significant. Obesity has been associated with a higher prevalence of asthma and wheeze, more severe asthma, and poor asthma control³⁷. Consistent with our findings, other studies have documented a relationship association between obesity and asthma in women starting in adolescence, possibly due to gender differences in body composition or the effect of sex hormones³⁸. Most studies have identified a positive association between low birthweight and the development of asthma and wheeze later, although others have found the opposite^{39–41}. In addition to methodological differences such as adjusting for different confounders, these conflicting findings may reflect the complex interaction between in utero exposures and genetic susceptibility of the child.

Our study has several strengths. First, this is a large birth cohort with frequent assessment of respiratory symptoms. The longitudinal cohort is the preferred design for studies examining origins of chronic diseases like asthma because of their prospective nature, thus minimizing recall bias. In addition, we assessed wheezing every 6 months and shorter recall periods are associated with decreased reporting or recall bias. The majority (70%) of children were also followed at least until age 13 years, minimizing bias incurred from loss to follow-up.

Furthermore, an analysis of the subjects lost to follow-up at age 13 showed that the lost to follow-up was not dependent on the observed outcome of wheeze at earlier ages, thus making selection bias less likely. Secondly, the comprehensive nature of the Home Allergens cohort allowed the assessment of several risk factors for wheeze, in particular the effect early life risk factors. Early life factors are important because they may represent a window of opportunity where we can act to decrease future wheeze and asthma in susceptible individuals. Third, in addition to examining the gender-specific risk factors for wheeze, we also studied the effect of each risk factor on different age stages. While most factors had a constant effect throughout life, including infant bronchiolitis, BMI percentile seemed to have an increasing effect with increasing age. By looking at age-specific effects, we can gain more information about the therapeutic time window.

Some limitations are noteworthy in this study. The Home Allergens cohort is a predominantly white population with higher risk for atopic diseases. Thus, the nature of this cohort may limit the generalizability of the findings to other populations. Although this was a large cohort, only a minority of the subjects wheezed at any one time, which may lead to reduced power to detect significant risk factors. In this study, we excluded data from ages 2 years and below of each subject because of the differences in the assessment of wheeze. Prior to age 2, "wheeze upon exertion" was not included in the definition of wheeze; therefore we could not create equivalent wheeze outcomes before and after that age.

Although we are unable to conclude about predictors of wheeze in this early preschool age group, this was explored by other publications from the Home Allergens cohort^{13,42,43}. Another limitation of this study is the parental report of wheeze, which may be subject to misclassification. However, this is a standard outcome measure in the International Study of Asthma and Allergies in Childhood (ISAAC) and ATS questionnaires and has been shown to be predictive of physician-diagnosed asthma⁴⁴ and reduced lung function and growth⁴⁵. Although all subjects resided in the metropolitan Boston area, it is probable that they were exposed to different levels of air pollution, a risk factor for wheeze. In addition to our subjects being widely dispersed through this area without clusters by neighborhood, we lacked the power to do adequate spatial clustering analysis, especially with stratification by gender. Instead, we considered household income and race/ethnicity in our models, which are linked to area of residence in Boston.

In conclusion, we identified gender-specific and age-specific risk factors for wheeze using a large birth cohort. Given the gender differences in the natural history of asthma and the evidence for gender-specific risk factors, future asthma studies should consider stratification by gender in their design and analyses. The identification of gender-specific risk factors for wheeze and asthma may allow for better prediction of asthma risk, as well as early life interventions and ultimately a more personalized treatment.

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Figure 1.

a) Prevalence of wheeze by age and gender; b) Difference in prevalence of wheeze between girls and boys by age (Girls – Boys). The shaded area represents the 95% confidence interval for the difference in prevalence. The curves are calculated using local regression (LOESS).

Figure 2.

a) The effect of (a) maternal asthma, (b) paternal asthma, (c) bronchiolitis before age 1 year, (d) birthweight, and (e) BMI percentile (per 25 percentile) on wheeze by age and gender. Odds ratio are adjusted for age stage, race/ethnicity, maternal and paternal asthma, in utero smoke exposure, birth weight z-score for gestational age, ever breastfed, BMI percentile, and bronchiolitis before 1 year.

Table 1

Baseline characteristics of the Home Allergens cohort (n=499).

Baseline characteristics	Boys (n=266)	Girls (n=233)	All (n=499)
Race/ethnicity, n(%)			
White	204 (76.7)	171 (73.4)	375 (75.2)
Black	27 (10.2)	32 (13.7)	59 (11.8)
Hispanic	15 (5.6)	15 (6.4)	30 (6.0)
Other	20 (7.5)	15 (6.4)	35 (7.0)
History of maternal asthma, n(%)	76 (28.6)	78 (33.5)	154 (30.9)
History of paternal asthma, n(%)	55 (20.7)	60 (25.8)	115 (23.4)
History of maternal hay fever, n(%)	145 (54.5)	126 (54.1)	271 (54.9)
History of paternal hay fever, n(%)	141 (53.0)	121 (51.9)	262 (54.2)
Maternal smoking during pregnancy, n(%)	19 (7.1)	13 (5.6)	32 (6.4)
Gestational age at birth, weeks, median(IQR)	39.7 (38.7,40.4)	39.7 (38.6,40.6)	39.7 (38.7,40.4)
Birthweight z-score for sex and gestational age, median(IQR)	0.19 (−0.48,0.76)	0.19 (−0.48,0.76)	0.19 (−0.48,0.76)
Season of birth, n(%)			
Spring	81 (30.4)	63 (27.0)	144(28.9)
Summer	56 (21.0)	55 (23.6)	111(22.2)
Fall	64 (24.1)	57 (24.5)	121(24.3)
Winter	65 (24.4)	58 (24.9)	123(24.6)
Pneumonia before age 1 year, n(%)	9 (3.4)	5 (2.1)	14 (2.8)
Bronchiolitis before age 1 year, n(%)	36 (13.5)	30 (12.8)	66 (13.2)
Ever breastfed, n(%)	179 (67.3)	157 (67.4)	336 (67.3)
Endotoxin levels in the home at age 2–3 months, EU/mg, median(IQR)	1.9 (1.3,2.1)	1.8 (1.4,2.0)	1.8 (1.5,2.0)
Quartile 1, n(%)	56 (21.0)	44 (18.9)	100 (24.7)
Quartile 2, n(%)	51 (19.2)	50 (21.5)	101 (25.1)
Quartile 3, n(%)	53 (19.9)	48 (20.6)	101 (25.1)
Quartile 4, n(%)	64 (24.0)	37 (15.9)	101 (25.1)
Annual household income <60,000\$, n(%)	18 (10.5)	25 (10.7)	43 (8.9)
Daycare attendance before 1 year, n(%)	122 (45.9)	118 (50.6)	240 (48.1)

Table 2

Risk factors for wheeze from early childhood to adolescence, stratified by gender.

	Girls		Boys	
	n=215		n=250	
	OR (95% CI)	p *	OR (95% CI)	p *
Age stage				
2 to 5 years	Reference		Reference	
5 to 8 years	0.71(0.46,1.10)	0.13	1.06(0.75, 1.50)	0.75
8 years or more	0.96(0.64,1.44)	0.85	1.02(0.72,1.44)	0.94
Race/ethnicity				
White	Reference		Reference	
Black	0.71(0.39,1.29)	0.26	0.86(0.51,1.46)	0.58
Hispanic	0.54(0.22,1.31)	0.17	1.27(0.70,2.28)	0.43
Other	0.58(0.30,1.13)	0.11	0.51(0.27,0.94)	0.03
Maternal asthma	2.05(1.44,2.91)	<0.0001	1.79(1.29,2.48)	0.0004
Paternal asthma	0.76(0.52,1.12)	0.17	1.83(1.30,2.57)	0.0005
In utero smoke exposure	1.48(0.77,2.86)	0.24	0.72(0.35,1.51)	0.39
Birth weight for gestational age, per 1 z-score	1.01(0.84,1.22)	0.92	1.01(0.87,1.19)	0.86
Ever breastfed	1.56(1.02,2.39)	0.04	0.68(0.49,0.94)	0.02
Bronchiolitis before age 1 year	1.08(0.67,1.76)	0.74	2.15(1.47,3.14)	<0.0001
BMI percentile for age and gender, per 25 percentile	1.01(0.92,1.10)	0.86	1.02(0.95,1.10)	0.57

* adjusted for other variables in the table. Other covariates considered but not included in the final model are: maternal hay fever, paternal hay fever, season of birth, gestational age at birth, household endotoxin, household income, daycare attendance in the first year of life, and second-hand smoke exposure.