

Wheezing disorders in children: Are girls and boys different?

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Asthma and wheezing disorders in children present a heterogeneous spectrum with varied pathophysiologies, genetic determinants, and effects of environmental exposures. Despite our current knowledge about children with wheezing illnesses, predicting their future clinical course accurately remains a challenge.¹ There is a keen interest in understanding this heterogeneity and identifying risk factors for the development and persistence of symptoms. Epidemiologic studies have shown sex-specific differences in the incidence of wheezing and long-term respiratory health; however, there is limited understanding of the role of sex-specific risk factors in modifying these outcomes.

Male subjects have much higher rates of wheezing in early childhood than female subjects but are twice as likely to remit by early adult life.² A reversal of this early male predominance is seen in adolescence, when female subjects have a higher rate of persistence and relapse that persists through most of adult life.^{2,3} Differences in genetics, lung morphology, maturation, growth rates, and patterns between male and female subjects might explain some of these sex differences.⁴ Male subjects are born with a larger lung size but have a disproportionately lower forced expiratory flow rate. This has been attributed to dysanapsis, which is the discordant growth between airways, air spaces, and lung size.³ A smaller relative airway size with higher specific airway resistance, higher airway tone, and higher airway reactivity likely predisposes younger boys to wheeze more than girls.⁴ Hormonal influences have also been suggested, given the cyclical variations in girls during menstrual cycles, to explain the increased rates of asthma/wheezing and severity after adolescence in female subjects.³

Wheezing incidence, patterns, and outcomes vary with underlying physiologic differences in male and female subjects. There are limited data on whether the effect of risk factors varies by sex. *In utero* maternal smoke exposure in infants at risk for asthma

seems to be more detrimental in male subjects, resulting in larger lung function deficits compared with female subjects.⁴ Rates of hospitalization in prepubertal boys have been reported to be twice as high as those in girls,⁵ including higher rates of status asthmaticus, as well as intensive care unit stays.⁴ In contrast, adult female subjects were hospitalized 3 times more than male subjects,⁵ reflecting differences in severity and varying outcomes by age and sex. In a cohort study of high-risk children, maternal asthma was a risk factor for wheezing in both sexes, whereas paternal asthma and infant bronchiolitis were risk factors in boys only, and breast-feeding was protective in boys only.⁶ Stratified by sex, Mandhane et al² showed that maternal asthma was a risk factor for wheezing in female subjects, whereas paternal asthma was a risk factor for male subjects in childhood-onset wheezing. For adolescent-onset wheezing, maternal asthma and early bronchial hyperreactivity were risk factors in female subjects, and atopy was a risk factor for male subjects only. The effect of obesity on the risk of asthma varies by sex, where female subjects who became overweight between the ages of 6 and 11 years were more likely to wheeze in their early adolescent years compared with female subjects who did not become overweight, and this effect was not seen in male subjects.⁷ A recent study characterizing lung function into long-term trajectories over 3 decades in children with persistent asthma showed that male subjects were more likely to have reduced lung function, as well as reduced lung function with early decrease,⁸ suggesting differences in long-term outcomes between the sexes. The cause of these sex differences is not entirely clear but raises questions about the differential susceptibility to early-life exposures, wheezing patterns, physiologic variations, genetic pathways, and other inherent sex-specific differences.

Several phenotypic classifications have been proposed for wheezing disorders based on age, clinical presentation, severity, atopy, and outcomes.^{9,10} There is also recent interest in defining endophenotypes that are based on underlying molecular pathways to identify correlations between symptom severity, functional impairment, and degree of lung damage.¹ In general, factors such as early childhood lower respiratory tract infections, maternal smoking, and day care are significant for early-onset wheezing, whereas breast-feeding appears to be protective. Atopy and allergic sensitization predict late-onset and persistent wheezing.^{1,11} Factors predicting persistence or relapse of wheezing included allergen sensitization, airway hyperresponsiveness, female sex, early age at onset of wheezing, and smoking exposure.^{1,2} Although it is known that risk factors and outcomes vary by the type of wheezing phenotype and female sex is a significant risk factor for persistence, sex-specific risk factors for wheezing phenotypes have not been studied previously in children.

The article by Tse et al¹² in this issue of the *Journal* is an important contribution to elucidating sex-specific risk factors for childhood wheeze and identifying longitudinal wheeze phenotypes

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with sex-specific risk factors for these phenotypes in children through midchildhood. Using data from a large prospective pre-birth cohort, they demonstrated that maternal and paternal asthma, being black or Hispanic, infant bronchiolitis, and infant atopic dermatitis were predictors of wheeze through age 9 years in both sexes. The effect of paternal asthma was more significant in boys, whereas being black or Hispanic was more significant in girls. Infant smoke exposure was specifically associated with wheezing after age 5 years in boys.

The study by Tse et al¹² used an unselected prebirth cohort to identify 3 wheezing phenotypes in both sexes that included never/infrequent wheeze, early transient wheeze, and persistent wheeze. Risk factors for the early transient wheeze phenotype were infant bronchiolitis (larger effect size in boys compared with girls but did not show a statistically significant difference by sex), maternal asthma in boys, and infant atopic dermatitis in girls. Risk factors for persistent wheeze in both sexes included maternal asthma, infant bronchiolitis, and infant atopic dermatitis. However, paternal asthma was a predictor of persistent wheeze in boys only, and being black was a predictor of persistent wheeze in girls only. The authors conclude that they identified risk factors for childhood wheeze and the wheezing phenotypes that varied by sex and age.

Overall, this is a well-designed study using data from a large prospective prebirth cohort with frequent parental assessments of participant wheeze until age 9 years. The article follows children until age 9 years, which does not allow for identifying sex-specific differences through later years, when there is a reversal of the frequency of wheezing prevalence because girls are more likely to wheeze in later postpubertal adolescent and adult years. The late-onset wheezing phenotype identified in other long-term cohorts has not been identified in this analysis.^{9,10} Wheezing has been studied as the outcome here, but associated lung function information is not presented in this article and might help further characterize sex-specific effects and interaction with risk factors.

In conclusion, it is clear that sex is an important determinant of wheezing incidence, patterns of disease presentation, and persistence. This study demonstrates that sex is an important modifier and that the risk factors for childhood wheeze and wheezing phenotypes differ between sexes in prepubertal children. Risk

factors like maternal asthma are important in both sexes, but others, such as paternal asthma, early-life events, and race/ethnicity, tend to show a differential sex-specific effect in wheezing and wheezing phenotypes. Knowledge of sex-specific risk factors for childhood wheeze and asthma might have significant clinical and prognostic implications to help predict the likelihood of wheezing persistence, disease severity, and long-term lung function. There needs to be further investigation of the mechanisms behind such sex differences to thereby identify endophenotypes that could lead to individualized preventive and therapeutic approaches.

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