
Risk factors for wheezing in early adolescence: a prospective birth cohort study in Brazil

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Background: Many asthma studies are available in the literature, but few investigated whether risk factors for asthma differ by sex.

Objective: To evaluate risk factors for wheezing in early adolescence, with emphasis on sex differences.

Methods: A prospective birth cohort study was initiated in 1993; 87.5% of the original cohort was traced at 11 years, totaling 4,452 adolescents. Current wheezing was defined as at least 1 crisis in the previous 12 months. The following independent variables were analyzed: maternal smoking during pregnancy, wheezing at 4 years, maternal wheezing, and adolescent body mass index.

Results: Current wheezing affected 13.5% (95% confidence interval [CI], 12.4%–14.5%) of the cohort. The prevalence of current wheezing was 15.3% (95% CI, 13.7%–16.8%) in boys and 11.7% (95% CI, 10.4%–13.1%) in girls ($P < .001$). Maternal smoking was related to an increased risk of wheezing for boys but not for girls. There was a significant tracking of wheezing from 4 to 11 years in both sexes, although the magnitude was stronger for boys. A dose-response association between maternal wheezing and adolescent wheezing was observed in boys but not in girls. Finally, obesity was associated with an increased risk of wheezing in boys but not in girls.

Conclusions: The variables explored in this investigation had a stronger effect on adolescent wheezing in boys than in girls. Public health strategies aimed at minimizing the burden of wheezing should take these sex differences into account.

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INTRODUCTION

Asthma is the most prevalent chronic disease in childhood and also affects a substantial proportion of adolescents,¹ and there is some evidence that its prevalence is rising.^{2–4} The presence of asthma increases the risk of mortality.^{3,4} A combination of environmental and lifestyle factors seems to be responsible for the increase in asthma estimates.^{5,6} Obtaining a precise estimate of the prevalence of asthma is challenging for public health researchers, and studies that focus on wheezing provide a useful alternative.

Previous studies on risk factors for asthma suggested that the variables associated with its prevalence vary throughout the lifespan. For example, the “hygiene hypothesis” proposes that living in a poor environment increases the risk of respiratory diseases in the short-term but provides long-term protection from asthma due to increased immunity.⁷ Previous

research^{8–10} has also suggested that the prevalence of asthma differs across the sexes. However, it has also been suggested that the risk factors for asthma may be different for boys and girls,⁹ but this issue has received less attention. In a prospective birth cohort study in Brazil, risk factors for wheezing in early adolescence (age 10–12 years) were evaluated, with special attention to interactions between sex and other independent variables. The initial hypothesis was that risk factors for wheezing differ between boys and girls.

METHODS

Pelotas is a medium-sized Brazilian city located near to the southern border of the country. In 1993, all hospital births (>99% of all city births) were monitored, and the mothers were invited to join a birth cohort study. Mothers who agreed to take part in the study answered a standardized and pre-tested questionnaire soon after delivery. The questionnaire included questions on maternal smoking during each trimester of pregnancy (yes/no). For this analysis, a variable categorized only as smoker or nonsmoker during pregnancy was used given that analyses using each trimester variable did not produce different results. Mothers were also asked about history of wheezing. Three categories were analyzed: non-wheezers, ever wheezers (those who reported wheezing at least once but not currently), and current wheezers.

Several follow-up visits to subsamples of the whole cohort took place in infancy and childhood.¹¹ At 4 years, all low-birth-weight children and a systematic sample of 20% of the remaining cohort members were selected for a follow-up

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visit; 87.2% of those sampled were traced. At that occasion, the ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire was applied.¹² The following question was used as the outcome in this study: "Have you had wheezing or whistling in the chest in the past 12 months?" Participants who answered "yes" to this question were classified as wheezers.

In 2004–2005, all cohort members were sought. The ISAAC questionnaire was used again. Weight, height, and triceps and subscapular skinfolds were measured twice, and the mean values were used in the analyses. Obesity was defined as a body mass index (BMI) greater than the 85th percentile and triceps and subscapular skinfolds greater than the 90th percentile, in accordance with current World Health Organization recommendations for adolescents.¹³ Interviewers were standardized in the measurements of anthropometry using the margins of error from the National Center for Health Statistics.¹⁴ Measurements were restandardized monthly during the fieldwork, which was performed between July 16, 2004, and March 31, 2005.

Descriptive analyses included calculations of proportions and 95% confidence intervals (CIs). The prevalence of current wheezing among subgroups was compared using χ^2 tests. Analyses stratified by sex are presented in bar graphs. The interactions between sex and other independent variables were tested using logistic regression models. All the analyses were weighted to take into account the oversampling of low-birth-weight children at the 4-year follow-up visit.

Further details of the methods of the 1993 Pelotas (Brazil) birth cohort study are available elsewhere.¹¹ Ethical approval for all phases of the cohort study was provided by the Federal University of Pelotas Medical School Committee for Ethics in Research. Written informed consent was obtained from parents, and confidentiality was ensured.

RESULTS

The 1993 Pelotas (Brazil) birth cohort includes 5,249 individuals born in 1993 in the city of Pelotas. Only 16 children born in 1993 were not included in the cohort study, which represents a response rate of 99.7%. At 4 years, 1,273 children were included in a follow-up visit, representing 87.2% of those sampled for this visit. At 11 years, 87.5% of all cohort members were interviewed.

Of 4,425 participants with complete data on wheezing patterns in the 2004–2005 visit, 1,935 (43.7%) reported wheezing at least once in life. Current wheezing (≥ 1 crisis in the previous 12 months) affected 13.5% (95% CI, 12.4%–14.5%) of the cohort members. The prevalence of current wheezing was 15.3% (95% CI, 13.7%–16.8%) in boys and 11.7% (95% CI, 10.4%–13.1%) in girls ($P < .001$).

Figure 1 presents the prevalence of wheezing at 11 years according to maternal smoking during pregnancy. Boys born to mothers who smoked during pregnancy were 36% more likely to have wheezing ($P = .003$). Among girls, there was no significant difference in the prevalence of wheezing in those born to mothers who smoked during pregnancy or not. The P value for the interaction between sex and maternal smoking during pregnancy was .03. When boys and girls were analyzed together, adolescents born to mothers who smoked during pregnancy had a wheezing prevalence of 14.8%, and those born to mothers who did not smoke had a prevalence of 12.8% ($P = .06$).

The frequency of wheezing at 4 and 11 years is presented in Figure 2. Boys who had wheezing at 4 years were 144% more likely to wheeze at 11 years ($P < .001$). Among girls, the difference was also significant ($P = .02$), but the increased risk for those with wheezing at 4 years was 85%. The P value for the interaction between sex and wheezing at 4 years was .39. Combining boys and girls, the prevalence of

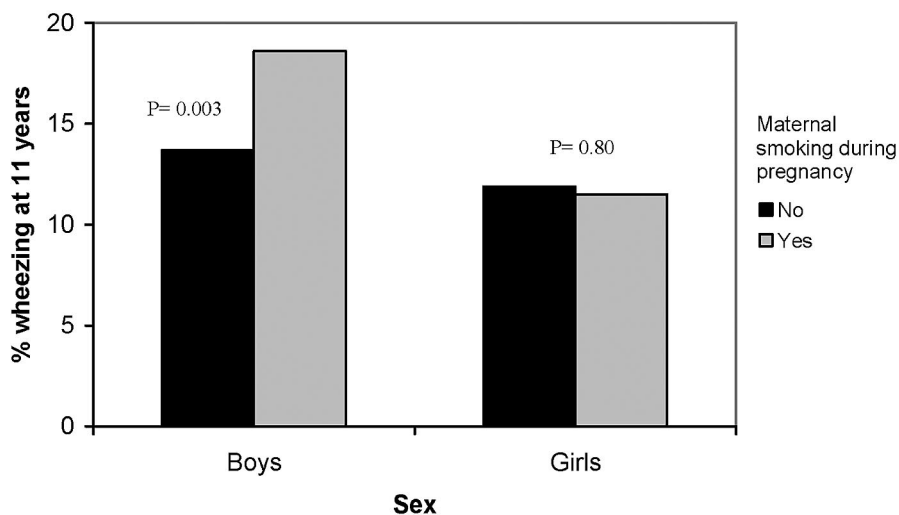


Figure 1. Prevalence of wheezing at 11 years according to maternal smoking during pregnancy and stratified by sex.

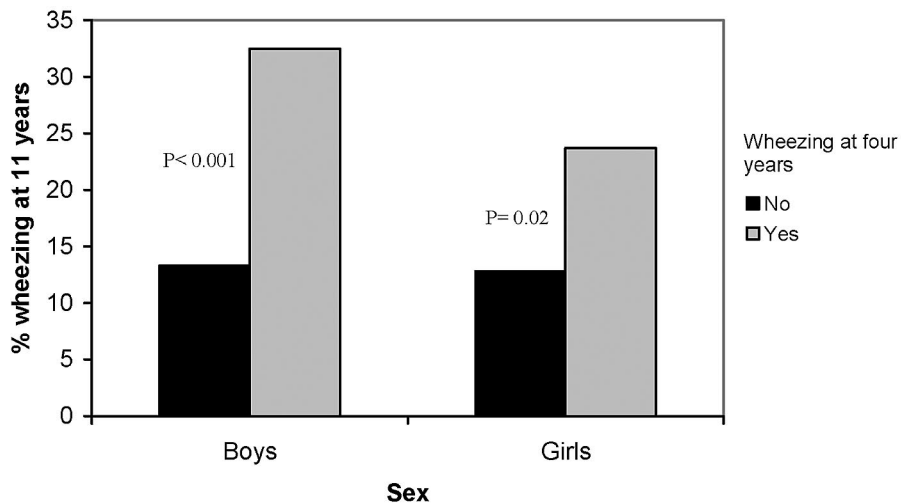


Figure 2. Prevalence of wheezing at 11 years according to wheezing at 4 years and stratified by sex.

wheezing at 11 years was 28.2% and 13.0% for those who wheezed at 4 years or not, respectively.

In Figure 3, the prevalence of wheezing at 11 years is presented according to sex and maternal wheezing. Among boys, there was a dose-response effect; those born to mothers who reported current wheezing were 135% more likely to wheeze than those born to mothers who had never had wheezing. Among girls, the dose-response effect was not clear, but the *P* value for heterogeneity was significant (*P* = .02). Among girls, those born to mothers who had ever had wheezing had the highest prevalence of wheezing at 11 years. The *P* value for the interaction between sex and maternal wheezing was .11. Analyses not stratified by sex resulted in a prevalence of wheezing at 11 years of 12.0% among those

born to mothers who had never wheezed, 20.2% among those born to mothers who had ever had wheezing, and 23.7% among those born to mothers who are current wheezers (*P* < .001).

Figure 4 presents the association between obesity and wheezing at 11 years. Obese boys were 38% more likely to wheeze than nonobese boys at 11 years (*P* = .01). Among girls, there was a 26% increased risk of wheezing among the obese compared with the nonobese, but the difference was not significant (*P* = .21). There was no significant interaction between sex and obesity at 11 years (*P* = .66). When boys and girls were analyzed together, the prevalence of wheezing was 17.9% in obese participants and 12.9% in nonobese ones (*P* = .002).

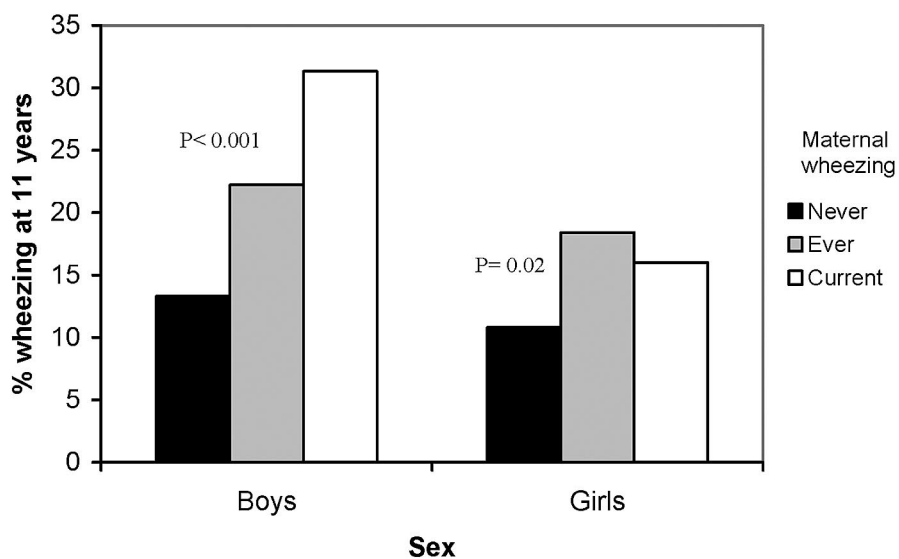


Figure 3. Prevalence of wheezing at 11 years according to maternal wheezing and stratified by sex.

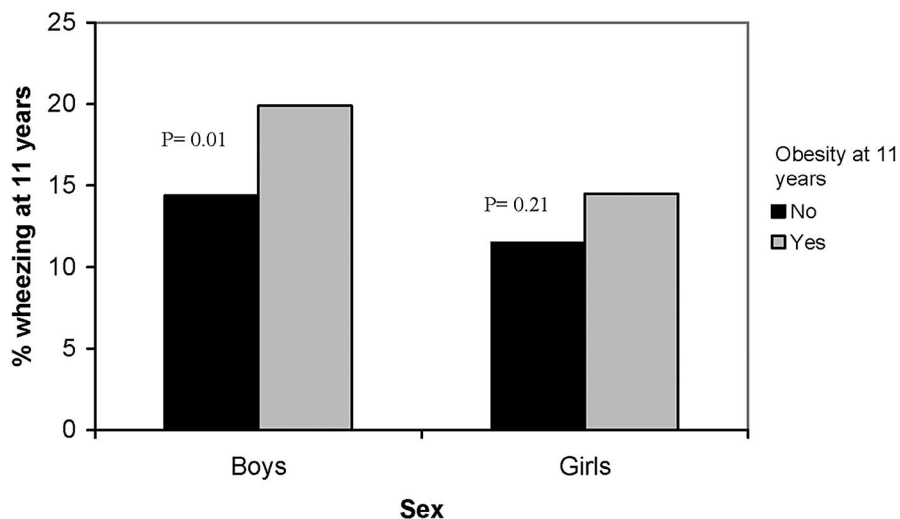


Figure 4. Prevalence of wheezing at 11 years according to body mass index at 11 years and stratified by sex.

The associations between wheezing and the following independent variables were also tested: skin color, family income, maternal schooling, crowding, type of delivery, birth weight, multiple births, gestational age, and breastfeeding. All of these associations were nonsignificant for boys and girls; therefore, they are not presented herein.

DISCUSSION

In accordance with the original hypothesis of this investigation, we found that risk factors for wheezing in early adolescence were different for boys and girls. In summary, the independent variables studied had a greater effect on wheezing in boys than in girls. Other researchers have investigated the role of sex differences in the development of asthma. In a New Zealand birth cohort study, Mandhane and coworkers⁹ showed that boys were more likely to develop asthma in childhood and that girls were more likely to have adolescent onset. In the present cohort, because the participants were in early adolescence, boys were still more likely than girls to have wheezing; it is possible to argue that in the near future girls in this cohort will have a greater likelihood of developing asthma than boys.

In the New Zealand study,⁹ maternal atopy was a risk factor for childhood wheezing in both sexes, and the effect was stronger in girls. For adolescent asthma, the effect was only significant in girls. In the present cohort, the effect of maternal wheezing on adolescent asthma was strong and significant in both sexes, but the magnitude of the effect was greater in boys. In the publication by Mandhane and colleagues,⁹ some possible genetic and hormonal explanations for the sex differences in asthma prevalence and risk factors are proposed, but further research is needed to help understand the biology of such differences.

It was previously shown that maternal smoking during pregnancy is a risk factor for wheezing in adolescence.^{8,15}

Other researchers¹⁵ have investigated the role of household smoking habits on the prevalence of wheezing. In the present cohort, boys born to mothers who smoked during pregnancy were at increased risk for asthma, but this association was not observed for girls.

Studies of persistent asthma¹⁶ may help explain the finding that wheezing tracks from 4 to 11 years. In the present study, this was true for boys and girls, although again the magnitude of the effect was greater for boys. Previous research¹⁰ has proposed that 14-year-old boys with high BMI are more likely to develop asthma than those with lower BMI. In the present study, this finding was confirmed in boys aged 11 years. Furthermore, the present birth cohort study and that followed up by Mannino and colleagues¹⁰ did not find a statistically significant association between BMI and wheezing in girls. In New Zealand, BMI was not associated with asthma development.⁹

Some methodological issues should be considered when interpreting these data. The follow-up rate is high, minimizing the likelihood of selection bias. The fact that this cohort is population based should also be highlighted. Caution should be used when interpreting the association between BMI and wheezing because such a relationship is based on cross-sectional data and, therefore, is subject to reverse causality. Because the aim of this study was to detect specifically interactions between sex and other independent variables, these analyses did not explore interactions between the other exposures or the relationships between them. The lack of measurements of IgE or other atopy markers should also be pointed out as limitations of the present study.

Similar to the conclusions of other researchers,⁹ these data show that asthma may be developed by different mechanisms, which may vary between males and females. Further research is needed to clarify the role of genetics and hormones on the development of asthma. In clinical settings,

practitioners should take into account the sex and age differences on asthma prevalence and risk factors in children and adolescents.

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