

Occurrence of new-onset wheeze in a 3-year follow-up study of schoolchildren

Joshua A. Lawson, MSc*†; Donna C. Rennie, PhD*‡; Ambikaipakan Senthilselvan, PhD§; Helen H. McDuffie, PhD*; and Donald W. Cockcroft, MD||

Background: Different wheeze phenotypes have been identified, primarily in preschool children.

Objective: To explore the characteristics of children in primary school without a history of wheeze or asthma and the onset of wheeze during a 3-year follow-up period.

Methods: Students in grades 1 to 3 participated in a cross-sectional study in 2000 and again in 2003, creating a prospective cohort. Data were collected using questionnaires in both years. Children without a history of asthma or wheeze in or before 2000 were selected for this analysis (n = 212). Associations between baseline characteristics and an outcome of the onset of new wheeze were evaluated.

Results: Twenty-two children (10.4%) reported new wheeze by 2003. Significant associations were found between new-onset wheeze and body mass index (odds ratio [OR], 1.33; 95% confidence interval [CI], 1.10–1.62) and history of allergic disease (OR, 7.17; 95% CI, 2.48–20.72); significant inverse associations were found with farming exposures in the first year of life (OR, 0.17; 95% CI, 0.05–0.64) and with having a fireplace in the home (OR, 0.20; 95% CI, 0.05–0.83). After stratification by sex, the associations were typically stronger in girls than in boys.

Conclusions: Allergic disease in childhood and early and current exposures affect the development of wheeze. These results support efforts to lead healthy lifestyles and direct continued research into wheeze phenotypes, especially by sex.

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INTRODUCTION

Respiratory disorders such as asthma and wheeze lead to discomfort, activity limitation, and hospitalization.¹ There is a high prevalence in children and adolescents,^{2,3} resulting in a large economic health care burden.¹ Wheeze is often a hallmark of asthma, and in recent years different wheeze phenotypes, including early transient, persistent, and late-onset, have been identified.^{4–6} Examining risk factors for the development of wheeze could help identify the mechanisms of wheeze onset and reduce the morbidity and burden associated with this condition.

In 2000 a cross-sectional study of schoolchildren was conducted. In this small, primarily agricultural community located near coal strip mining and coal-fired power plants

there was a high prevalence of asthma and wheeze.⁷ The distribution of wheeze and asthma by sex was also atypical of that seen in other populations of similar age,⁷ where the prevalence of asthma in this population was not significantly different between boys and girls. There were also differences in the associations between asthma and various risk factors by sex.⁸ This follow-up study examines the association between new-onset wheeze and risk factors present before the onset of wheeze within 3 years in children with no history of wheeze or asthma.

METHODS

Study Design and Population

Cross-sectional studies using identical methods in a primarily agricultural town (population, approximately 10,000) were completed in 2000 and 2003. Methods for the 2000 study have been previously reported.⁷ All students in grades 1 to 6 were approached in each study. Students in grades 1 to 3 in 2000 were potentially studied again in 2003 in grades 4 to 6, creating a prospective cohort. In 2000, 94% (n = 477) of grade 1 to 3 students returned completed questionnaires as part of a cross-sectional study. To examine risk factors for wheeze onset, participants were required to have data available from both 2000 and 2003, to be in grades 1 to 3 in 2000, and to have no report of asthma or wheeze before or at the time of data collection in 2000. Of the 316 students in grades 1 to 3 who would have been eligible, follow-up was available for 212 (67.1%). Reasons for not participating in 2003 were not ascertained but were likely due to families moving and refusal to participate. Data were collected using question-

* Institute of Agricultural, Rural, and Environmental Health, University of Saskatchewan, Saskatoon, Saskatchewan.

† Department of Public Health Sciences, School of Public Health, University of Alberta, Edmonton, Alberta.

‡ College of Nursing, University of Saskatchewan, Saskatoon, Saskatchewan.

§ Department of Public Health Sciences, School of Public Health, University of Alberta, Edmonton, Alberta.

|| Division of Respiratory Medicine, University of Saskatchewan, Saskatoon, Saskatchewan.

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naires in both years. Pulmonary function testing (PFT) was conducted in 2000 but not in 2003. Height and weight collected for the purposes of the PFTs in 2000 were used in the present analysis. In analyses where body mass index (BMI) was included, the sample size was 209 instead of 212 because of missing height and weight. Ethical approval was obtained from the Advisory Committee on Ethics in Biomedical Research at the University of Saskatchewan. Local school and health boards also approved the study. Written consent from the parents and children was obtained.

Questionnaires

Questionnaires were distributed through the schools in January of both years and were completed by parents, returned to the school, and collected by research staff. Questions were drawn from the American Thoracic Society's Children's Respiratory Disease Questionnaire⁹ and the Student Lung Health Questionnaire.¹⁰ Specific questions of interest were chosen and included in that topic's section (eg, wheeze). Differences between the 2000 and 2003 questionnaires occurred only when questions deemed unusable in 2000 were modified or when additional exposure information was of interest. Additional questions were asked regarding environmental tobacco smoke (ETS). However, the questions used to determine smoking status were the same. Information was collected on sociodemographic characteristics, respiratory health, general health, family history of illness, early-life exposures, rural exposures, and the indoor environment. For this analysis, information used to determine health outcome was identified from the 2003 questionnaire, and risk factors and exclusion criteria were determined from the 2000 questionnaire.

Operational Definitions

Students with no history of wheeze or asthma reported in or before 2000 were included. New-onset wheeze was defined by a positive response to either of the following questions in 2003, both of which were answered negatively in 2000: "Has this child ever had a wheeze or whistling noise that comes from the chest?" "Has your child's chest ever sounded wheezy during or after exercise/sports?" The outcome used in this study was late-onset wheeze, where late onset would be onset after the age of 6 years but before the age of 13 years.

All the information used in this analysis regarding potential risk factors, except for evaluation of farm exposure in the first year of life, was obtained from the initial questionnaire in 2000. History of allergic disease was considered present based on a positive report of respiratory allergy, eczema, or hay fever. Respiratory allergy was based on a positive response to the question, "Has this child ever had an allergy (hives, runny nose, swelling, itchiness, or wheezing) to any of the following: house dust, grain dust, pollen, trees, grasses, mold or mildew, dogs, cats, or birds/feathers?" A history of eczema was considered present when there was a positive response to the question, "Has a doctor ever said that this child has a history of eczema?" A history of hay fever was

considered positive if a physician had ever said that a child had hay fever. A history of early respiratory illness was considered to have occurred if there was a report of any 1 of the following 4 conditions in the first 2 years of life: bronchitis, pneumonia, whooping cough, or croup.

ETS was considered present if either parent smoked in 2000, if cigarettes were smoked in the home, or if the child was exposed to tobacco smoke in a car regularly. The presence of mold or dampness in the home was evaluated by a positive response to either of the following questions: "Does your house have any damage caused by dampness (eg, wet spots on walls or floors)?" "Are there signs of mold or mildew in any living areas in your home?" Premature birth was defined as being born more than 2 weeks before the expected date. Type of dwelling was reclassified as single-family house or as other dwelling type. Current place of residence was defined as rural if the response to the question, "Where is your home located?" was either "farm" or "acreage" and was defined as urban when the response was "in town." A high level of farm exposure in the first year of life was considered present if a child "visited a farm more than 3 times," "visited a farm regularly," or "lived on a farm."

Anthropometric Measures and Lung Function

Height was measured against a wall using a fixed tape measure. Students stood in socks on a hard floor with their heels and backs touching the wall while height was measured. Weight was measured using a calibrated spring scale with children in socks and dressed in normal indoor clothing. From these measures, BMI was calculated as weight in kilograms divided by height in meters squared.¹¹ Pulmonary function was measured by means of forced expiratory maneuvers while seated and wearing a nose clip following American Thoracic Society criteria.

Statistical Analysis

The relationship between various personal and environmental characteristics at baseline (2000) and the onset of new wheeze was examined for children with no history of asthma or wheeze up to 2000. Statistical analysis was completed using a software program (SPSS; SPSS Inc, Chicago, Illinois). Differences between those who were followed up and those who were not were compared using independent-samples *t* tests for continuous variables and χ^2 tests for proportions for categorical variables. Crude analysis using logistic regression was used to examine the association between one independent variable and the onset of new wheeze. Multivariate logistic regression was then performed to control for multiple independent variables and to determine significant predictors of new-onset wheeze. Variables were included in the final model based on statistical significance, clinical importance, and potential confounding. Strengths of associations were determined based on odds ratios (ORs) and 95% confidence intervals (CIs). Because of findings from previous analyses,^{7,8} we repeated the analysis stratified by sex. Goodness-of-fit tests were conducted using Hosmer-Lemeshow

tests. Lung function was reported as percentage of predicted based on equations derived by Knudsen, with statistical testing between the wheeze and no-wheeze groups completed using independent-sample *t* tests.

RESULTS

Children who participated in both years who met the inclusion criteria (*n* = 212) were similar to those who did not participate in 2003 (*n* = 104) regarding demographic characteristics, BMI, and health indicators (Table 1). However, those not followed up were less likely to have lived in a single-family home in 2000 and to have lived their whole life in the area.

Twenty-two children (10.4%) reported new-onset wheeze by 2003. Of those who reported wheeze during the 3-year follow-up, 2 had shortness of breath associated with the wheeze, 14 had experienced wheeze after exercise or sports, and 2 were currently taking breathing medications. In the 12 months before completion of the 2003 survey, 18 children had at least 1 episode of wheeze; of these, 3 had also been diagnosed as having asthma by a physician. The PFT results were not significantly different between those who developed wheeze and those who did not (Table 2). Sixteen children without wheeze and 1 with wheeze did not have lung function data available.

Mean (SD) age at baseline was 7.1 (0.9) years for those who did not develop wheeze and 7.3 (1.0) years for those who

Table 2. Pulmonary Function Test Results by Wheeze Outcome

	Results, mean (SD), % of predicted		<i>P</i> value
	No wheeze (<i>n</i> = 174)	New-onset wheeze (<i>n</i> = 21)	
FVC	114.0 (13.0)	111.3 (15.9)	.37
FEV ₁	110.0 (12.2)	106.9 (13.5)	.28
FEF _{25%-75%}	98.4 (23.4)	95.9 (25.0)	.66
PEFR	105.5 (22.0)	106.3 (21.7)	.88

Abbreviations: FEF_{25%-75%}, forced expiratory flow between 25% and 75% of FVC; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEFR, peak expiratory flow rate.

did (*P* = .48). Children with new-onset wheeze had a higher BMI in 2000 than those without wheeze (mean [SD], 18.5 [4.0] vs 16.7 [2.1], respectively; OR, 1.25; 95% CI, 1.08–1.44; *P* < .01). A total of 11.1% of boys and 9.7% of girls developed wheeze.

In crude analyses, onset of wheeze was associated with history of allergic disease, eczema, early-life respiratory illness, and prenatal smoking, with an inverse relationship between onset of wheeze and visiting a farm more than 3 times in the first 12 months of life or having a fireplace in the home (Tables 3 and 4). In the multivariate analysis, increased BMI and history of respiratory allergy increased the risk of new-onset wheeze, whereas high early-life farm exposure and presence of a fireplace in the home were protective (Table 5). After stratification by sex, the patterns of association were generally the same as in the overall analysis (Table 5). However, the association between history of allergic disease and new wheeze was stronger in boys, whereas the associations between early-life farm exposure and home fireplace with new wheeze were statistically significant in girls only, although the association between presence of a home fireplace and early-life farm exposure in boys was directionally similar.

DISCUSSION

We found that early-life farm exposure was inversely associated with the development of wheeze, whereas higher BMI and history of allergic disease were associated with increased risk of wheeze. In analyses stratified by sex, associations with new wheeze were stronger in girls, except for history of allergic disease. This study population did not have a history of wheeze or asthma in early childhood, and development of wheeze during the next 3 years could be considered late-onset wheeze, defined as the onset of wheeze in late childhood. Late-onset wheeze has been defined as no wheeze until the age of 3 years with the presence of wheeze at the age of 6 years.⁵ However, other studies^{6,12,13} have incorporated their own definition of late-onset wheeze, similar to ours.

The present results confirm those of other studies^{6,12} of wheeze onset where history of allergic disease has been reported as a risk factor for late-onset wheeze. It has been suggested that early-life atopic disease predicts subsequent

Table 1. Characteristics of Participants Without a History of Asthma or Wheeze in or Before 2000 Studied in 2000 and 2003 Compared With Those Who Were Lost to Follow-up^a

Characteristic	Follow-up information (<i>n</i> = 212)	No follow-up information (<i>n</i> = 104)	<i>P</i> value
Age, mean (SD), y	7.2 (0.9)	7.2 (1.0)	.95
BMI, mean (SD) ^b	16.9 (2.4)	16.9 (2.5)	.59
Girls, %	53.3	49.0	.48
White race, %	97.6	96.2	.46
Parents with >high school education, %	55.2	59.6	.46
Reporting a respiratory allergy, %	11.3	12.5	.76
Living in a single-family home, %	89.2	80.8	.04
Parental history of asthma, %	7.1	13.5	.07
Parental history of allergy, %	34.4	35.6	.84
Spending whole life in the area, %	72.0	53.8	.001
Reporting ever cough, %	19.3	13.5	.20
Reporting ever phlegm or congestion, %	6.1	2.9	.22
Reporting breathing medication use in the past 12 mo, %	4.2	1.0	.12

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

^a Based on characteristics from the 2000 survey.

^b Based on a sample size of 101 for those who were not followed up and 209 for those who were followed up owing to missing height and weight information.

Table 3. Crude Associations Between Personal Characteristics and New-Onset Wheeze

Baseline (2000) characteristic	Children, No. (n = 212)	Children with new-onset wheeze, %	OR (95% CI)	P value
Sex				
Male	99	11.1	1 (Reference)	
Female	113	9.7	0.86 (0.36–2.07)	.74
Parent's educational level				
≤High school	95	13.7	1 (Reference)	
>High school	117	7.7	0.53 (0.21–1.29)	.16
Type of home				
Single parent	22	22.7	1 (Reference)	
Two parent	190	9.0	0.33 (0.11–1.02)	.05
Family history of asthma				
Absent	197	10.2	1 (Reference)	
Present	15	13.3	1.36 (0.29–6.47)	.70
Allergic disease				
No	188	7.4	1 (Reference)	
Yes	24	33.1	6.21 (2.27–17.03)	<.001
Early-life respiratory illness				
No	191	8.9	1 (Reference)	
Yes	21	23.8	3.20 (1.04–9.82)	.04
Born premature				
No	175	10.9	1 (Reference)	
Yes	37	8.1	0.73 (0.20–2.59)	.62
Birth weight <2,500 g				
No	200	10.0	1 (Reference)	
Yes	12	16.7	1.80 (0.37–8.80)	.47
Breastfed				
No	54	13.0	1 (Reference)	
Yes	158	9.5	0.70 (0.27–1.83)	.47

Abbreviations: CI, confidence interval; OR, odds ratio.

development of aeroallergen sensitization later in life.¹⁴ This may have resulted in wheeze in this population.

Several studies^{15–18} have suggested a protective effect of farm exposure on wheeze, but this relationship is not consistent.^{19,20} Although some studies¹⁶ have considered the association between early-life farm exposure and wheeze in children, we are unaware of any other study that has examined the association between early-life farm exposure and development of wheeze in late childhood in children with no wheeze or asthma in early childhood. This suggests that a protective effect against the development of wheeze may continue into the preteen years. The association of early-life farm exposure with allergy has typically been stronger and more consistent than that with wheeze. However, early-life exposures may promote an immune system resistant to allergic disease, as described by the hygiene hypothesis,²¹ and result in a lower incidence of wheeze.

Obesity in children often leads to obesity in adults²² and predicts adverse health outcomes in adulthood.²³ Others have reported that children without wheeze or asthma had an increased risk of developing wheeze²⁴ or asthma with wheeze²⁵ within a few years when they were obese or had an increased BMI at baseline. The present findings confirm these results. Mechanisms that have been suggested to help explain the association between obesity and wheeze have

included mechanical constraints due to excess body size, obesity as a marker of lifestyle, and effects on hormone levels.²⁶

BMI should be used cautiously in studies of children because of differences in growth rates and onset of puberty, leading to variability in the relationship between BMI and adiposity.²⁷ However, BMI seems to approximate body fat in children on average, although not reliably at an individual level.²⁸ To address potential confounding, we adjusted for age and sex in the analyses and completed an analysis stratified by sex. Also, BMI has been used in several studies of children and allows for comparisons across studies. We conducted an analysis using the overweight definitions based on international standards²⁹ and found strong and directionally similar associations, although they did not reach statistical significance (data not shown). Related to body size, age at onset of puberty has been associated with the persistence of wheeze, with those with younger age at onset having greater risk,³⁰ but has been less studied regarding development of wheeze. We did not collect information on age at puberty onset.

A previous study³¹ found no association between fireplace use and wheeze, and the associations we found were of borderline significance. A limitation with this variable was that we did not collect information on the frequency and duration of fireplace use. The presence of a fireplace may

Table 4. Crude Associations Between Indoor Environmental Characteristics and Early-Life Farm Exposure and New-Onset Wheeze

Baseline (2000) characteristic	Children, No. (n = 212)	Children with new-onset wheeze, %	OR (95% CI)	P value
ETS exposure				
Absent	102	12.8	1 (Reference)	
Present	110	8.2	1.64 (0.67–4.02)	.28
Residence				
Urban	203	10.3	1 (Reference)	
Rural	9	11.1	1.08 (0.13–9.09)	.94
Home mold or dampness				
Absent	159	10.7	1 (Reference)	
Present	53	9.4	0.87 (0.31–2.49)	.80
Ever owned a pet				
No	86	8.1	1 (Reference)	
Yes	126	11.9	1.53 (0.59–3.91)	.38
Home humidifier				
Absent	67	6.0	1 (Reference)	
Present	145	12.4	0.45 (0.15–1.38)	.16
Home fireplace				
Absent	147	12.9	1 (Reference)	
Present	65	4.6	0.33 (0.09–1.14)	.08
Dwelling type				
Single family	23	8.7	1 (Reference)	
Not single family	189	10.6	1.24 (0.27–5.70)	.78
Farm visits in the first 12 mo of life				
≤3 visits	87	5.8	1 (Reference)	
>3 visits	125	13.6	0.39 (0.14–1.09)	.07

Abbreviations: CI, confidence interval; ETS, environmental tobacco smoke; OR, odds ratio.

have been a surrogate for other characteristics that are inversely associated with wheeze. Similarly, presence of a home humidifier was of borderline significance in its association with new-onset wheeze. In a prospective study³² of children without wheeze there was an increased risk of asthma at follow-up. However, in a case-control study³³ increased risk of asthma was present only if the humidifier was in the child's bedroom. Again, we had no information regarding frequency of use or humidifier location. Thus, the differences in associations are difficult to explain. We did not find an association between ETS and wheeze. Typically there is an increased risk of asthma or wheeze associated with ETS.

Differences between the sexes in the determinants of late-onset wheeze have been infrequently studied. One study¹³ reported differences in the association with adolescent-onset wheeze (>10 years of age) between boys and girls, with the differences typically being related to allergy, airways responsiveness, and lung function. Adolescent-onset wheeze was found to be associated with atopy in boys but not in girls.¹³ In the present study, the association between allergic disease and new-onset wheeze was stronger in boys, although it was also strong in girls. We found that except for history of allergic disease, associations with new wheeze were stronger in girls. Girls in the preteen years may respond more to body size and environmental exposures, whereas wheeze in boys may be largely attributable to allergic predisposition. This may help explain the wheeze sex switch that occurs. Despite

these differences, interaction terms between sex and the other variables in the model were not statistically significant, and the direction was similar between the sexes despite the differences in the strength of association.

In a previous study⁸ we found that respiratory allergy, early-childhood respiratory illness, family history of asthma, and home mold or dampness were associated with an increased risk of asthma, whereas home air-conditioning was associated with a reduced risk. Consistent with these results was the association between new-onset wheeze and history of allergic disease. Differences in the associations with new-onset wheeze in the present analysis and the previous analysis may be due to the design or outcomes considered in the studies.

The major limitation of this study was the small number of "new-onset wheezers." However, despite the small numbers, the participation rate at baseline was good. Although we did not know the reasons for loss to follow-up, the differences between those who were and were not followed up indicated that the families who were not followed up may be more transient. The lack of differences in sociodemographic and health indicators would not suggest that the health of families was a cause of lack of participation.

Another limitation was the lack of severity information collected on the wheeze group. The population considered likely represents a population with mild wheeze, as indicated by the few students with new wheeze who were either newly

Table 5. Multivariate Analysis of New-Onset Wheeze and Demographic, Health, and Exposure Variables in 2000 Overall and for Boys and Girls^a

Baseline (2000) characteristic	Overall (N = 209)		Boys (n = 97) ^b		Girls (n = 112) ^b	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.21 (0.70–2.10)	.49	1.05 (0.44–2.51)	.91	1.45 (0.65–3.22)	.36
BMI	1.33 (1.10–1.62)	<.01	1.27 (1.00–1.62)	.05	1.42 (1.02–1.98)	.04
Sex						
Male	1 (Reference)		NA		NA	
Female	1.17 (0.42–3.27)	.77	NA	NA	NA	NA
Allergic disease						
No	1 (Reference)		1 (Reference)		1 (Reference)	
Yes	7.17 (2.48–20.72)	<.001	9.75 (2.04–46.61)	<.01	7.99 (1.55–41.08)	.01
Home humidifier						
Absent	1 (Reference)		1 (Reference)		1 (Reference)	
Present	0.32 (0.09–1.16)	.08	0.67 (0.11–4.07)	.67	0.14 (0.02–1.03)	.05
Home fireplace						
Absent	1 (Reference)		1 (Reference)		1 (Reference)	
Present	0.20 (0.05–0.83)	.03	0.38 (0.07–2.21)	.28	0.08 (0.01–0.95)	.05
Farm exposure in the first 12 mo of life						
≤3 visits	1 (Reference)		1 (Reference)		1 (Reference)	
>3 visits	0.17 (0.05–0.64)	<.01	0.31 (0.06–1.50)	.18	0.07 (0.01–0.61)	.02
ETS exposure						
Absent	1 (Reference)		1 (Reference)		1 (Reference)	
Present	0.74 (0.24–2.24)	.59	0.44 (0.09–2.23)	.32	1.05 (0.20–5.52)	.95

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; ETS, environmental tobacco smoke; NA, not applicable; OR, odds ratio.

^a The models are adjusted for all the variables in the table.

^b Model fit was adequate for boys and girls as indicated by the nonsignificant values for the Hosmer-Lemeshow tests ($\chi^2_8 = 9.495$; $P = .30$ for boys and $\chi^2_8 = 6.86$; $P = .55$ for girls).

diagnosed as having asthma or taking breathing medications. Late-onset wheeze, however, may have long-term consequences because findings from the Children's Respiratory Study in Tucson suggest that onset of wheeze at the age of 6 years is associated with increased prevalence of wheeze up to the age of 16 years.³⁴ Also, the mean lung function values from the present study were within the reference range. Despite this, lung function may be normal, even in children with asthma, when they are not experiencing an episode.³⁵

This analysis did not account for exposure characteristics in 2003. The objective was to investigate whether variables that were already present were associated with new-onset wheeze. The characteristics in 2003 could have occurred after the onset of wheeze because wheeze may have occurred at any point during 3-year follow-up.

In conclusion, these findings indicate a reduced risk of developing wheeze in the preteen years associated with farm exposure in the first year of life and an increased risk of developing wheeze with higher BMI and a history of allergic disease. These findings suggest that efforts should be made to study wheeze development throughout childhood and adolescence and that specific exposures should be considered, including early-life exposures. Findings regarding differences by sex support the notion that the mechanisms of wheeze development may be different between boys and girls and that these differences should be investigated.

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Requests for reprints should be addressed to:

Joshua A. Lawson, MSc
 Institute of Agricultural, Rural, and Environmental Health
 Royal University Hospital
 University of Saskatchewan
 3641-103 Hospital Dr
 Saskatoon, SK, Canada S7N 0W8
 E-mail: josh.lawson@usask.ca