Published in final edited form as:

Ann Allergy Asthma Immunol. 2009 January ; 102(1): 29–34. doi:10.1016/S1081-1206(10)60104-4.

Is Early Life Wheeze Associated with Lung Function at Age 6 Years?

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Abstract

Background—The incidence of wheeze is unknown and the role of early life wheeze in subsequent health is not clearly understood. Our goal was to calculate the age-specific incidence of wheeze and determine whether wheezing at particular times in early life was predictive of abnormal airway hyperresponsiveness (AHR), percent predicted FEV1 and current asthma at age 6 years.

Methods—Using data from a birth cohort study with annual report of wheezing (Childhood Allergy Study) and spirometry and methacholine challenge at age 6 years, the age-specific incidence of wheeze was determined using Kaplan-Meier estimates. Logistic and linear regression models were used to assess the associations between the presence of age-specific wheezing and the outcomes of current asthma, AHR and percent predicted FEV1 at age 6 years.

Results—The 6-year cumulative incidence of wheezing was higher for boys (66.2%, 95% CI 59.8%, 72.6%) than girls (47.6% 95% CI 41.4%, 53.8%). There was no age when wheezing was more strongly associated with either AHR or percent predicted FEV1 at 6 years. Only wheeze in the fifth year among males and in females, both wheezing in the fourth and fifth years were positively predictive of current asthma at age 6. This is likely due to the definition of current asthma (ever doctor diagnosis and either medication or symptoms in last year). Eczema, parental asthma history and total cord blood IgE did not affect these associations.

Conclusions—Wheezing at any particular time in early life may not be predictive of early childhood lung function.

INTRODUCTION

Researchers have studied patterns of early-life wheeze using various methodologies to examine its association with the development of asthma – the most common chronic childhood disease in the United States.¹ Wheezing has been used in asthma predictive indices^{2,3} and others have followed the lead of the Tucson researchers who examined outcomes among children grouped by their wheezing patterns.^{4–6} The age-specific incidence of wheeze and whether wheezing at any particular age(s) is more strongly associated with later lung function is not known. Using annual reports of wheeze in our birth cohort of

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All work performed at Henry Ford Hospital.

Financial disclosure: D.R. Ownby has received honoraria from CR Bard and Genetech. G. Wegienka has no interests to disclose. S. Havstad has no interests to disclose. E. Zoratti has no interests to disclose. C. Cole Johnson has no interests to disclose.

children with and without family histories of asthma, we calculated age-specific incidence rates of wheeze and determined whether wheezing at any particular age was associated with early-life lung function (airway hyperresponsiveness - AHR, percent predicted FEV1, current asthma) at age 6–7 years.

METHODS

Study Population

We examined the patterns of wheezing through age six to seven years in the Childhood Allergy Study (CAS) birth cohort. Briefly, CAS is an ongoing study evaluating the environmental determinants of pediatric allergy and asthma. All pregnant women at least 18 years of age living in the northern Detroit suburbs, that had an estimated date of confinement between April 15, 1987 and August 31, 1989, who were seeing Henry Ford Health System (HFHS) providers as part of a health maintenance organization, were invited to participate in the study. Only full term infants were included in the study. Further details have been published.⁷

Of the 953 women who consented to participate, 106 of their infants were later excluded from the study because their cord blood was not collected per the original protocol. Of the remaining 847 infants, 841 had valid cord blood measures and six more were determined to be ineligible at subsequent review of eligibility criteria. Mothers of the remaining 835 children were asked to complete interviews annually about their child's health in the previous year; 724 children had at least the first annual interview completed.

Data Collection

For the child, a family history of asthma was indicated when either parent had a prior asthma diagnosis as reported by the mother in the enrollment interview. Annual interviews were conducted when the children were approximately 1, 2, 3, 4, 5 and 6 years of age. Parents were asked whether in the previous year, their child had eczema or wheezing ("In the past 12 months, did your child have wheezing?"). Data were not collected on the frequency, severity or duration of wheeze.

Blood for IgE analyses was collected periodically. The serum from the cord blood and 2 year and 4 year samples was separated and stored at –20°C. Details of total IgE quantification have been published.^{7,8} Briefly, the assay was a biotin-avidin amplified ELISA with a fluorescent substrate. The antibody used in both the capture and detecting steps was affinity-purified antihuman IgE (Kirkegaard & Perry Laboratories, Gaithersburg, MD). Anti-IgE was labeled with biotin when used as a detecting antibody. Cord blood samples with sera with IgA levels >30 µg/ml were considered potentially contaminated with maternal blood and excluded.

Children were asked to undergo clinical examination between the ages 6–7 years. Children who underwent clinical evaluation (n=484, 58 percent) were not different with respect to parental allergy and asthma history, the presence of cats/dogs in the home, and parental education when compared with those who did not undergo examination.⁹ Children who had ever wheezed were neither more nor less likely to participate in the clinical examination than those who never wheezed (data not shown).

During clinical evaluation, all performed by a single pediatric allergist (DRO), children underwent pulmonary function testing and methacholine challenge which serve as outcomes in our investigation.

Spirometry and Methacholine Challenge—Lung function was measured with a spirometer (KoKo; Pulmonary Data Service; Louisville, CO) in accordance with American Thoracic Society (ATS) standards.¹⁰ Children were coached to engage in maximal forced expiratory maneuvers while standing without noseclips. Predicted values were calculated with the equations of Polgar and Promadhat.¹¹ Spirometry findings were accepted if the child made a good effort and two forced exhalation maneuvers indicated reproducibility ($\pm 5\%$) for FVC and FEV₁.

Children with FEV₁ $\geq 70\%$ predicted and reproducible measurements underwent methacholine challenge with normal saline diluent and then five sequential doses of methacholine (0.025, 0.25, 2.5, 10 and 25 mg/mL) administered with a nebulizer (model 646; DeVilbiss Health Care Inc., Somerset, PA) connected to a French-Rosenthal-type dosimeter (Pulmonary Data Service). Three minutes after each dose was administered, spirometry was repeated. Methacholine administration was stopped after the maximum methacholine concentration was reached or after the FEV₁ fell to $<80\%$ of the best post saline solution value and remained below this level for at least two minutes.

Measurements from children who could not successfully complete the maneuvers were excluded. The results were classified into AHR groups using ATS criteria: normal responsiveness (provocative concentration of a substance causing a 20% fall in FEV₁ [PC₂₀], >16 mg/mL); borderline positive result (PC₂₀, 4 to 16 mg/mL); mild AHR (PC₂₀, 1 to <4 mg/mL); and moderate-to-severe AHR (PC₂₀, <1 mg/mL).^{12, 13} Due to small numbers, we combined subgroups into abnormal AHR (borderline positive, mild AHR and moderate-to-severe AHR) versus normal AHR.

Methacholine challenge and spirometry results from children with current asthma (defined below) were excluded from analyses

Current Asthma at Age 6 Years—Current asthma was defined as the child ever had a doctor diagnosis of asthma and either had symptoms of asthma (wheezing/asthma attack) or used asthma medication in the prior year. Doctor diagnosis was defined using two methods: first, by medical chart review for those who saw HFHS physicians and second, by parental report at interviews in years 4 and 6.

Statistical Analyses

Survival analysis methods (Kaplan Meier curves) were used to examine age-specific incidence and cumulative incidence of wheeze. Logistic and linear regression models were built to examine whether reported wheezing at certain ages was predictive of current asthma and lung function outcomes (AHR, percent predicted FEV₁) at age 6 years. Only children with complete data (interviews/complete lung function tests) were included in modeling. A significant association was defined as an indicator with at least marginal statistical significance ($p < 0.10$) and a large parameter estimate. For each outcome we created two sets of three models each (1 model each for all children, females only, males only). The first set, or Model A approach, includes an indicator variable for wheezing in each year. The second approach, Model B, groups any wheezing in the first three years together and any wheezing in the fourth and fifth years together to facilitate comparison to other publications.⁴

Stratified models were used to evaluate whether parental history of asthma or parental report of the child having eczema were effect modifiers. The sample size was not large enough to evaluate whether having high IgE (greater than the calculated upper 95% confidence interval boundary on logarithmically transformed data) at any age was an effect modifier. We examined whether cord IgE, total IgE at age 2 years, total IgE at age 4 years, parent ever reported eczema for the child or parental history of asthma were confounders based on

change in effect criteria (15%). Given the observed gender differences in wheeze incidence, we created separate final models for boys and girls.

The models assume independence of the predictor variables (the wheeze indicator variables in this case). While they are probably not completely independent, we think collinearity between the indicator variables is limited as indicated by a variance inflation factor <1.7 for all the covariates (>2.5 might suggest concern).¹⁴

The institutional review board at HFHS approved this research. Each family provided written informed consent.

RESULTS

Wheeze Incidence

Of the 724 children whose parents completed at least the first annual interview, a slight majority were female (51.9%, n=376), 16.8% (n=101 of 600 children with interview data on this question) had ever had eczema, and 16.2% (n=112 of 690 children with interview data on this question) had a family history of asthma. Most children were born to mothers who identified themselves as White (92.8%).

Annual age- and gender-specific wheeze incidences are presented in Table 1. At every age, boys had a higher incidence rate of wheeze compared with girls. The greatest incidence for both boys and girls was in the first year of life (27.2/100 children, 95% confidence interval=CI 23.5/100, 31.3/100). By the age of 6 years, more than half of the parents had reported that their child had wheezed (56.5%; 95% CI 52.0%, 61.0%). The cumulative incidence was higher for boys (66.2%, 95% CI 59.8%, 72.6%) than girls (47.6%; 95% CI 41.4%, 53.8%) (Figure 1).

Wheeze and Lung Function at Age 6 Years

Data from children with interviews completed for ages 1–5 years and with completed clinic visit data were used in statistical modeling. Of the 302 children with complete data for modeling, 157 (52%) were female, 59 (19.5%) had a parental history of asthma, and 53 (17.5%) ever had parental reported eczema. Those included in the models were similar to those who were not included (n=422) with respect to rates of eczema and gender. Those included in modeling were slightly more likely to have ever wheezed (49% versus 43%, p=0.12) and have a family history of asthma (20% versus 14%, p<0.05). Those not included were excluded for refusing the clinic visit at age 6 years (n=284, 67%), or for having a missing annual interview (n=104, missed 1 interview; n=29, missed 2 interviews; n=5, missed >2 interviews).

Neither parental history of asthma nor child's eczema history was an effect modifier of the associations (data not shown). Parental asthma history, child eczema, cord blood IgE, total IgE at 2 years and total IgE at 4 years did not confound the associations between wheezing and the outcomes (data not shown).

Twenty-two children (7.3%) had current asthma at age 6 years (15 males, 7 females) (Table 2). Of the 269 children without current asthma who completed methacholine challenge at age 6–7 years, 35.7% (n=96) were classified as having abnormal airway hyperresponsiveness (Table 2). Among the 20 children with current asthma who completed the methacholine challenge, 75% were classified as have abnormal airway hyperresponsiveness (Table 2). Of the 270 children without current asthma who successfully completed spirometry, the mean percent predicted FEV1 was 94.5 (SD=11.5) (Table 2). The

mean percent predicted FEV₁ was 87.9 (SD=11.5) among the 22 children with current asthma (Table 2).

To analyze the outcome of current asthma, we created 3 logistic regression models: one for all children (n=302) and separate models for girls (n=157) and boys (n=145) (Table 3). The first model for all children shows that more recent wheezing (wheeze in fifth year) was a large and statistically significant positive predictor of current asthma at age 6 years (controlling for all other wheezing). Among females, in addition to wheezing in the fifth year, wheeze in the fourth year was also positively predictive (both marginally statistically significant while controlling for all other wheezing). Comparatively, only wheeze in the fifth year among males was predictive (statistically significant while controlling for all other wheezing).

Using the approach of grouping any early and late wheezing, later wheezing (age 4 or 5 years) was strongly associated with current asthma compared to early wheezing (first 3 years) for all children regardless of gender (Table 3).

We modeled abnormal AHR as a dichotomous dependent variable using logistic regression models for the 269 children (143 females and 126 males) without current asthma who completed methacholine challenge at age 6–7 years. Of the 269 children, 173 were classified as normal, 79 as borderline AHR, and 17 as mild AHR. No children were classified as moderate-severe AHR. Among all children without current asthma, as well as for only boys and only girls, wheeze was not associated with AHR (Table 4).

We modeled the log transformed percent predicted FEV₁ as a continuous dependent variable using linear regression models for the 270 children (143 females and 127 males) without current asthma who completed spirometry at age 6–7 years. Among these children, wheeze at any age was not associated with the outcome and this was also true for models for only girls and only boys (Table 5).

DISCUSSION

Parents may bring their wheezing young child to visit a physician because they are concerned that their child has or is developing asthma. What should a physician tell the parents? While there is no definitive answer, our analyses provide some evidence on incidence and cumulative incidence of wheeze, as well as information on whether wheezing at any specific age or age group was more strongly associated with subsequent lung function. Most children wheeze at least once before the age of 6–7 years and wheezing is more common among boys than girls. With the exceptions of wheezing between the age of 3 to 4 years or 4 to 5 years in females and between age 4 and 5 years in males, no time points were more strongly associated with the outcomes at age 6–7 years. The fact that we found associations with later wheezing timepoints may be at least partly due to the definition of current asthma (wheeze in the last year and a doctor's diagnosis of asthma which may overlap with wheeze just prior to that time period). Additionally, wheezing and wheeze patterns don't appear to translate to actual lung function for most children.

Perhaps early life wheezing, given its frequency, is not indicative of subsequent asthma or lung function. Patterns of early life wheeze and its association with biological milestones in the allergic march have been studied among several cohorts of children, including the cohort from Tucson.⁴ Like ours, this birth cohort comprised a study population that was selected from the general population rather than from referral clinics or from families with asthma histories. After the Tucson results were published, others groups followed with similar analyses of their cohorts of similarly unselected populations.^{5,6,15} The results often paralleled the Tucson findings. However, no study was able to examine annual reports of

wheeze and its association with subsequent asthma and lung function. We have tried to further the study of early life wheeze by looking for specific time periods of wheezing onset that might be more strongly associated with later health outcomes.

Due to methodological differences, our age- and gender-specific incidence rates of wheeze are difficult to compare to those published by the research group at the Mayo Clinic in 1992.¹⁶ Unlike our work that focused on early life and annual wheeze, they grouped individuals by ages and determined incidence rates throughout the life course, as well as used groupings of definite asthma case, probable asthma case or only a single wheeze episode.

Few data are available on the annual incidence of wheeze for each of the first 6 years of life thus making it difficult to know whether the increased incidence of wheeze at age 6 we report is unusual. Given the point estimates and 95% CIs, the CIs at age 6 years do overlap with multiple previous years. Thus, we cannot say the rates are different. If the incidence rate at age 6 years is truly an increase over the previous few years, there would be no clear explanation. However, in Michigan, children enter school within the year after turning age 5 years. A child may experience their first major viral infection once they start school as they are also likely exposed to new environmental and microbial exposures in the school setting. Any of these things could trigger incident wheezing.

Our work has limitations. We used parental report of wheeze. Recognition and interpretation of wheezing likely varies among parents and physicians and has multiple etiologies and varying severity. Further, we did not ask the parents to report details of their child's wheezing. More information on frequency, duration, and severity could have provided more specific estimates of associations between wheezing and subsequent lung function. Also, methacholine challenge test results do not necessarily indicate that the child has asthma just as children with an asthma diagnosis do not necessarily have airway hyperresponsiveness.^{17, 18}

While our cohort was relatively large, we were still limited in our sample size due to missing data. Confidence intervals are provided to allow assessment of the precision of our estimates. Despite these limitations, the work presented covers new analyses and suggests a different approach for evaluating the role of wheeze in subsequent health.

We chose to analyze the data in ways that would investigate a heretofore unexplored area, but also take advantage of annual interviews. Every cohort study has collected or is collecting different types of data in different ways at different time points. Our annual data allowed us the unique opportunity to explore wheeze in individual time periods while adjusting for wheeze in other time periods. We look forward to repeating these analyses with outcomes at age 18 years in these children as this data collection is underway.

Acknowledgments

Original data collection was funded by NIAID and the Fund for Henry Ford Hospital.

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Figure 1.
The Cumulative Incidence of Wheeze for Male and Female Children Based on Kaplan-Meier Estimates from Annual Parental Reports, The Childhood Allergy Study, Detroit, MI. The solid line represents the experience of male children. The dashed line represents the experience of female children.
The X axis represents the age of the child in years.
The Y axis represents the cumulative incidence of wheeze expressed as a percentage.

Table 1

The Age-Specific Incidence (First Occurrence) Rates of Wheeze per 100 Children Based on Annual Parental Reports, The Childhood Allergy Study, Detroit, MI. *

Age of Interview	Incidence Rates (95% CI)	Females Incidence Rates (95% CI)	Males Incidence Rates (95% CI)
One year	27.2 (23.5, 31.3)	23.9 (19.2, 29.4)	30.7 (25.2, 37.2)
Two year	12.2 (9.2, 15.9)	10.4 (6.8, 15.2)	14.5 (9.6, 21.0)
Three year	9.1 (6.2, 13.0)	6.1 (3.1, 10.9)	12.8 (7.7, 19.9)
Four year	9.0 (6.2, 12.8)	7.7 (4.3, 12.8)	10.7 (6.1, 17.4)
Five year	5.8 (3.4, 9.1)	2.8 (0.1, 6.5)	9.8 (5.2, 16.8)
Six year	13.4 (9.0, 19.1)	11.9 (6.8, 19.4)	15.6 (8.5, 26.1)

* Rates represent the number of children experiencing their first wheeze episode among all those children who have not had any prior episodes of wheeze. Children are removed from the risk set/subsequent rate calculations (right truncated) once they have a missing annual interview.

Table 2
Outcomes of Lung Function at Age 6–7 Years, The Childhood Allergy Study, Detroit, MI.

	All Children		Female Subjects		Male Subjects	
	N		N		N	
Current Asthma at Age 6–7 Years (%)	302	7.3%	157	4.5%	145	10.3%
Abnormal airway hyperresponsiveness*						
- Has Current Asthma	20	75.0%	6	83.3%	14	71.4%
- Does not Have Current Asthma	269	35.7%	143	41.3%	126	29.4%
Percent Predicted FEV ₁ † (Mean, SD)						
- Has Current Asthma	22	87.9% (11.5%)	7	84.2% (10.8%)	15	89.7% (11.7%)
- Does not Have Current Asthma	270	94.5% (11.5%)	143	92.9% (10.4%)	127	96.3% (12.3%)

* Abnormal airway hyperresponsiveness is defined as anything that was not normal (provocative concentration of substance causing a 20% fall in FEV₁ [PC₂₀], > 16 mg/mL).

† Percent predicted FEV₁ adjusted for height, weight and gender.

Table 3
A Logistic Regression Model of Current Asthma at Age 6–7 Years, The Childhood Allergy Study, Detroit, MI.*

		All subjects (N=302)		Females (N=157)		Males (N=145)	
Models:		aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Model A:							
Wheeze in:							
1 yr		0.6 (0.2, 2.1)	0.41	0.6 (0.1, 5.4)	0.66	0.5 (0.1, 2.6)	0.39
2 yr		2.0 (0.5, 7.5)	0.29	2.3 (0.2, 22.8)	0.47	2.3 (0.4, 13.8)	0.38
3 yr		1.4 (0.4, 5.0)	0.63	1.9 (0.1, 25.6)	0.64	1.0 (0.2, 4.5)	0.97
4 yr		2.1 (0.6, 7.8)	0.26	13.8 (0.7, 259)	0.078	1.0 (0.2, 4.8)	0.95
5 yr		20.1 (5.8, 70.3)	<0.05	7.6 (0.7, 78.3)	0.089	26.5 (5.4, 131)	<0.05
Model B: †							
Early wheeze		0.9 (0.3, 2.4)	0.82	1.7 (0.3, 11.3)	0.58	0.7 (0.2, 2.2)	0.51
Late wheeze		33.2 (9.2, 120)	<0.05	41.7 (4.4, 400)	<0.05	23.2 (4.9, 111)	<0.05

* Referent group for both models is children with no reported wheezing. aOR=odds ratio adjusted for other specified wheeze covariates.

† Early wheeze is defined as wheeze in at least the first 3 years. Late wheeze is defined as any wheeze during ages 4–5 years.

Table 4

A Logistic Regression Model of Abnormal Airway Hyperresponsiveness among Children without Current Asthma at Age 6–7 Years, The Childhood Allergy Study, Detroit, MI.*

		All subjects (N=269)		Females (N=143)		Males (N=126)	
Models:		aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Model A:							
Wheeze in:							
1 yr		1.3 (0.7, 2.3)	0.46	1.7 (0.8–3.9)	0.19	0.8 (0.3–2.1)	0.70
2 yr		0.8 (0.4, 1.7)	0.61	0.8 (0.3–2.3)	0.63	1.0 (0.4–2.9)	0.97
3 yr		2.0 (0.9, 4.6)	0.11	2.9 (0.7–13.0)	0.16	1.8 (0.6–5.4)	0.26
4 yr		1.6 (0.7, 4.0)	0.29	1.8 (0.4–8.2)	0.43	1.7 (0.5–5.4)	0.38
5 yr		0.8 (0.3, 2.1)	0.58	0.5 (0.1–3.6)	0.51	1.2 (0.3–4.2)	0.77
Model B:†							
Early wheeze		1.1 (0.6, 1.8)	0.82	1.4 (0.7–2.9)	0.34	0.8 (0.4–1.9)	0.67
Late wheeze		1.3 (0.7, 2.7)	0.39	1.9 (0.6–5.8)	0.28	1.4 (0.6–3.5)	0.45

* Abnormal airway hyperresponsiveness (AHR) is defined as AHR that is not normal (provocative concentration of a substance causing a 20% fall in FEV₁ [PC20]. >16 mg/mL). aOR=odds ratio adjusted for other specified wheeze covariates.

† Early wheeze is defined as wheeze in at least the first 3 years. Late wheeze is defined as any wheeze during ages 4–5 years.

Table 5

A Linear Regression Model of Percent Predicted FEV₁ among Children without Current Asthma at Age 6–7 Years, The Childhood Allergy Study, Detroit, MI.*

		All subjects (N=270)		Females (N=143)		Males (N=127)	
Models:		β (s.e.)	p-value	β (s.e.)	p-value	β (s.e.)	p-value
Model A:							
Wheeze in:							
1 yr		-2.1 (1.7)	0.21	-1.1 (2.1)	0.61	-3.4 (2.6)	0.18
2 yr		-0.4 (2.0)	0.84	-1.3 (2.7)	0.63	0.3 (3.0)	0.93
3 yr		-2.9 (2.4)	0.24	-5.9 (3.9)	0.11	-2.0 (3.3)	0.54
4 yr		1.0 (2.6)	0.69	-0.1 (3.8)	0.98	0.7 (3.5)	0.85
5 yr		1.4 (2.8)	0.61	-2.8 (4.5)	0.54	1.9 (3.7)	0.61
Model B:[†]							
Early wheeze		-1.4 (1.5)	0.34	-2.0 (1.9)	0.29	-1.4 (2.2)	0.53
Late wheeze		1.0 (1.9)	0.62	-2.7 (3.0)	0.36	1.7 (2.7)	0.51

* Referent group for both models is children with no reported wheezing. aOR=odds ratio adjusted for other specified wheeze covariates.

[†] Early wheeze is defined as wheeze in at least the first 3 years. Late wheeze is defined as any wheeze during ages 4–5 years.