Letters

RESEARCH LETTER

Wheezing Patterns in Early Childhood and the Risk of Respiratory and Allergic Disease in Adolescence

Discerning the clinical relevance of different wheezing patterns in young children is challenging. The landmark Tucson Children's Respiratory Study[1] identified 4 clinically distinct early-life wheezing phenotypes from their 1980 to 1984 population-based birth cohort: never, transient early (wheezing before age 3 years, but not at age 6 years), late onset (wheezing at age 6 years, but not before age 3 years), and persistent (wheezing before age 3 years and at age 6 years). These phenotypes were shown to be associated with respiratory outcomes in adolescence[2]; however, associations with diagnosed disease were not reported, and it is unclear whether these findings apply to genetically predisposed children. To address these unresolved questions, we applied the Tucson Children's Respiratory Study wheeze phenotypes to the

Table 1. Distribution of Early Wheeze Phenotypes in the Canadian Asthma Primary Prevention Study Cohort

		Early Wheeze Phenotype, No. (%)[b]				
	No.[a]	Never	Transient Early	Late Onset	Persistent	*P* Value[c]
Overall	459	234 (51.0)	127 (27.7)	39 (8.5)	59 (12.9)	
Sex						
Female	220	125 (56.8)	59 (26.8)	15 (6.8)	21 (9.5)	.05
Male	239	109 (45.6)	69 (28.9)	23 (9.6)	38 (15.9)	
City						
Vancouver	225	142 (63.1)	45 (20.0)	17 (7.6)	21 (9.3)	<.001
Winnipeg	234	92 (39.3)	83 (35.5)	21 (9.0)	38 (16.2)	
Study group						
Control	215	102 (47.4)	57 (26.5)	20 (9.3)	36 (16.7)	.09
Intervention	244	132 (54.1)	71 (29.1)	18 (7.4)	23 (9.4)	
Maternal atopy						
No	99	57 (57.6)	27 (27.3)	6 (6.1)	9 (9.1)	.36
Yes	360	177 (49.2)	101 (28.1)	32 (8.9)	50 (13.9)	
First born						
No	261	128 (49.0)	79 (30.3)	20 (7.7)	34 (13.0)	.58
Yes	198	106 (53.5)	49 (24.7)	18 (9.1)	25 (12.6)	
Household pets						
No	301	154 (51.2)	89 (29.6)	24 (8.0)	34 (11.3)	.45
Yes	158	80 (50.6)	39 (24.7)	14 (8.9)	25 (15.8)	
Household smokers						
No	357	190 (53.2)	95 (26.6)	31 (8.7)	41 (11.5)	.16
Yes	102	44 (43.1)	33 (32.4)	7 (6.9)	18 (17.6)	
Exclusive breastfeeding ≥4 mo						
No	289	134 (46.4)	86 (29.8)	24 (8.3)	45 (15.6)	.03
Yes	169	100 (59.2)	41 (24.3)	14 (8.3)	14 (8.3)	
Atopy before 2 y[d]						
No	333	181 (54.4)	97 (29.1)	24 (7.2)	31 (9.3)	.002
Yes	116	50 (43.1)	28 (24.1)	13 (11.2)	25 (21.6)	
Assessed at 15 y						
No	139	77 (55.4)	40 (28.8)	8 (5.8)	14 (10.1)	.31
Yes	320	157 (49.1)	88 (27.5)	30 (9.4)	45 (14.1)	

[a] A total of 459 participants with sufficient wheeze data from birth through age 7 years to classify wheeze phenotype.

[b] Never = no wheezing before age 7 years; transient early = wheezing before age 2 years, but not at age 7 years; late onset = wheezing at age 7 years, but not before age 2 years; and persistent = wheezing before age 2 years and at age 7 years.

[c] Comparisons by 2-tailed χ^2 test.

[d] Positive skin prick test result to any allergen at 1 or 2 years.

high-risk Canadian Asthma Primary Prevention Study cohort and evaluated associations with pulmonary function, asthma, and allergic disease in adolescence.

Methods | The Canadian Asthma Primary Prevention Study is a 1994 to 1996 prenatally randomized prevention trial in children at high genetic risk for asthma.The intervention involved avoidance of dust, pets, and tobacco smoke, encouragement of breastfeeding, and delayed introduction of solid foods. [3] Wheeze phenotypes were determined from data collected at 4 months, 8 months, 12 months, 18 months, 24 months, and 7 years, using 2 years and 7 years as the cutoffs for early and late wheezing. At 15 years, 320 participants were assessed for asthma, allergic rhinitis, atopic dermatitis, food allergy (all by pediatric allergist diagnosis), atopy (by skin test), pulmonary function (forced expiratory volume in 1 second), airway hyperresponsiveness (methacholine PC20 <5.5 mg/mL),

At a Glance

- We examined the clinical relevance of early childhood wheezing patterns in the high-risk Canadian Asthma Primary Prevention Study cohort using data collected from birth through 15 years.
- Across early wheezing phenotypes (never, transient early, late onset and persistent), we found a strong gradient of decreasing lung function and increasing asthma risk by age 15 years.
- Early wheezing phenotypes were not associated with atopic dermatitis or allergic rhinitis at age 15 years.
- Atopy before 2 years was associated with persistent wheeze, which in turn was associated with an 11-fold increased risk of asthma.
- Early childhood wheezing patterns provide clinically meaningful information. Strategies to reduce early wheezing and atopic sensitization could have long-term health benefits.

Table 2. Respiratory and Allergic Disease at Age 15 Years According to Early Wheeze Phenotype in the Canadian Asthma Primary Prevention Study Cohort

	Early Wheeze Phenotype[a]			
Outcome at Age 15 y	Never	Transient Early	Late Onset	Persistent
FEV_1, mL				
Mean (SD)	3645 (696)	3492 (743)	3410 (549)	3427 (615)
β (95% CI)[b]	1 [Reference]	−219 (−378 to −59)[c]	−304 (−538 to −71)[c]	−335 (−539 to −130)[c]
Wheeze				
No./No. (%)	28/157 (17.8)	20/88 (22.7)	11/30 (36.7)	22/45 (48.9)
OR (95% CI)[d]	1 [Reference]	1.25 (0.64-2.42)	2.51 (1.05-6.01)[c]	3.97 (1.87-8.44)[c]
Asthma				
No./No. (%)	8/157 (5.1)	17/88 (19.3)	8/30 (26.7)	19/45 (42.2)
OR (95% CI)[d]	1 [Reference]	3.94 (1.59-9.78)[c]	6.01 (1.96-18.39)[c]	11.81 (4.45-31.35)[c]
Atopic asthma				
No./No. (%)	6/154 (3.9)	13/84 (15.5)	8/29 (27.6)	16/45 (35.6)
OR (95% CI)[d]	1 [Reference]	4.10 (1.45-11.58)[c]	7.90 (2.38-26.25)[c]	10.70 (3.67-31.20)[c]
Airway hyperresponsiveness				
No./No. (%)	17/147 (11.6)	15/75 (20.0)	11/26 (42.3)	18/38 (47.4)
OR (95% CI)[d]	1 [Reference]	1.67 (0.75-3.71)	6.04 (2.21-16.52)[c]	7.94 (3.19-19.76)[c]
Allergic rhinitis				
No./No. (%)	64/157 (40.8)	31/88 (35.2)	13/30 (43.3)	24/45 (53.3)
OR (95% CI)[d]	1 [Reference]	1.00 (0.56-1.79)	1.22 (0.54-2.79)	1.90 (0.92-3.95)
Food allergy				
No./No. (%)	9/157 (5.7)	7/88 (8.0)	7/30 (23.3)	8/45 (17.8)
OR (95% CI)[d]	1 [Reference]	1.49 (0.48-4.58)	5.58 (1.56-19.96)[c]	2.74 (0.84-8.88)
Atopy				
No./No. (%)	95/155 (61.3)	46/85 (54.1)	23/29 (79.3)	32/45 (71.1)
OR (95% CI)[d]	1 [Reference]	1.00 (0.54-1.83)	2.64 (0.94-7.38)	1.73 (0.77-3.91)
Atopic dermatitis				
No./No. (%)	16/157 (10.2)	7/88 (8.0)	3/30 (10.0)	4/45 (8.9)
OR (95% CI)[d]	1 [Reference]	0.97 (0.37-2.55)	1.15 (0.30-4.41)	1.19 (0.35-4.02)

Abbreviations: FEV_1, forced expiratory volume in 1 second; OR, odds ratio.

[a] Never = no wheezing before age 7 years; transient early = wheezing before age 2 years, but not at age 7 years; late onset = wheezing at age 7 years, but not before age 2 years; and persistent = wheezing before age 2 years and at age 7 years.

[b] Associations determined by linear regression with never-wheezers as the reference group; all models adjusted for sex, study group, city of residence, exclusive breastfeeding more than 4 months, and atopy before 2 years.

[c] Significant OR.

[d] Associations determined by logistic regression with never-wheezers as the reference group; all models adjusted for sex, study group, city of residence, exclusive breastfeeding more than 4 months, and atopy before 2 years.

and wheeze (self-reported). Analyses were adjusted for study group because the intervention reduced the incidence of early wheezing.[3] We had insufficient power to test for effect modification; however, we did not expect the impact of early wheezing to differ by study group. The study was approved by the University of Manitoba Research Ethics Board, and written informed consent was obtained from parents.

Results | The distribution of early wheeze phenotypes was 51.0% never, 27.7% transient early, 8.5% late onset, and 12.9% persistent. The distribution differed significantly by sex, city, and breastfeeding (**Table 1**). Atopy before 2 years was strongly associated with persistent wheeze ($P < .001$). As reported previously,[3] wheezing was reduced in the intervention group ($P=.001$). Independent of these factors, early wheeze phenotypes were associated with lung function in adolescence (**Table 2**): compared with never-wheezers, forced expiratory volume in 1 second was significantly lower among transient early (−219 mL, $P = .007$), late-onset (−304 mL, $P = .01$), and persistent (−335 mL, $P = .001$) wheezers. Asthma was also associated with early wheeze phenotypes: prevalence was 5%, 19%, 27%, and 42% among never, transient early, late-onset, and persistent wheezers, respectively, with corresponding adjusted odds ratios of 3.94 (95% CI, 1.59-9.78) for early transient, 6.01 (95% CI, 1.96-18.39) for late onset, and 11.81 (95% CI, 4.45-31.35) for persistent. Food allergy risk was elevated with late-onset wheeze (adjusted odds ratio, 5.58; 95% CI, 1.56-19.96), but was not associated with transient early wheeze. Similarly, late-onset and persistent (but not transient early) wheeze were associated with an increased risk of wheeze and airway hyperresponsiveness at age 15 years. No associations were observed for atopic dermatitis or allergic rhinitis.

Discussion | Our results validate the Tucson Children's Respiratory Study early childhood wheezing phenotypes in a high-risk population and further clarify their associations with pulmonary function and diagnosed asthma in adolescence. Across wheezing phenotypes, we found a strong gradient of decreasing lung function and increasing asthma risk by age 15 years. We further identified early atopy (by age 2 years) as being strongly associated with persistent wheeze, which in turn was associated with a nearly 12-fold increased risk of asthma. Although we could not classify more recently defined phenotypes requiring data between ages 2 years and 7 years,[4,5] our results are consistent with other cohorts where children experiencing intermediate, late-onset, and persistent wheeze were more likely to develop asthma and bronchial hyperreactivity by middle childhood.[4,6] Our study extends these findings through adolescence in a high-risk cohort and demonstrates that asthma-associated deficits in lung function are already present at a young age. Collectively, these data show that early wheezing patterns provide clinically meaningful information and suggest that strategies to reduce early-life wheezing and atopic sensitization could have long-term health benefits.

Meghan B. Azad, PhD
Moira Chan-Yeung, MB
Edmond S. Chan, MD
Amy M. Dytnerski, RNBN
Anita L. Kozyrskyj, PhD
Clare Ramsey, MD
Allan B. Becker, MD

Author Affiliations: Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada (Azad, Dytnerski, Becker); Department of Community Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada (Azad, Dytnerski, Ramsey, Becker); Children's Hospital Research Institute of Manitoba, Winnipeg, Manitoba, Canada (Azad, Dytnerski, Becker); Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada (Chan-Yeung); Division of Allergy and Immunology, Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada (Chan); Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada (Kozyrskyj); Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba, Canada (Ramsey).

Corresponding Author: Meghan B. Azad, PhD, Children's Hospital Research Institute of Manitoba, Department of Pediatrics and Child Health, University of Manitoba, 501G – 715 McDermot Ave, Winnipeg, MB R3E 3P4, Canada (meghan.azad@umanitoba.ca).

Published Online: February 8, 2016. doi:10.1001/jamapediatrics.2015.4127.

Author Contributions: Dr Azad had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Chan-Yeung, Kozyrskyj, Becker.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Azad, Chan, Dytnerski.
Critical revision of the manuscript for important intellectual content: Azad, Chan-Yeung, Chan, Kozyrskyj, Ramsey, Becker.
Statistical analysis: Azad.
Obtained funding: Chan, Kozyrskyj, Becker.
Administrative, technical, or material support: Chan-Yeung, Chan, Dytnerski, Becker.
Study supervision: Chan-Yeung, Chan, Kozyrskyj, Ramsey, Becker.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was supported by Canadian Institutes of Health Research.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the Canadian Asthma Primary Prevention Study families, study coordinators (Rishma Chooniedass, RN, BN, CAE, Department of Pediatrics and Child Health, University of Manitoba; Marilyn Lilley, RN, Department of Pediatrics and Child Health, University of Manitoba; and Roxanne Rousseau, BSc, CCRP, Department of Medicine, University of British Columbia), and the Canadian Asthma Primary Prevention Study research team, whose commitment and hard work have made this research possible. Mss Chooniedass, Lilley, and Rousseau were compensated for their work as study staff.

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ; The Group Health Medical Associates. Asthma and wheezing in the first six years of life. *N Engl J Med*. 1995;332(3):133-138.

2. Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med*. 2005;172(10):1253-1258.

3. Chan-Yeung M, Ferguson A, Watson W, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol*. 2005;116(1):49-55.

4. Savenije OE, Granell R, Caudri D, et al. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J Allergy Clin Immunol*. 2011;127(6):1505-12.e14.

5. Collins SA, Pike KC, Inskip HM, et al; Southampton Women's Survey Study Group. Validation of novel wheeze phenotypes using longitudinal airway function and atopic sensitization data in the first 6 years of life: evidence from the Southampton Women's survey. *Pediatr Pulmonol*. 2013;48(7):683-692.

6. Henderson J, Granell R, Heron J, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax*. 2008;63(11):974-980.