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 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; 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

<table>
<thead>
<tr>
<th>Early Wheeze Phenotype, No. (%)</th>
<th>Overall</th>
<th>Sex</th>
<th>City</th>
<th>Study group</th>
<th>Maternal atopy</th>
<th>Firstborn</th>
<th>Household pets</th>
<th>Household smokers</th>
<th>Exclusive breastfeeding ≥4 mo</th>
<th>Atopy before 2 y</th>
<th>Assessed at 15 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>234 (51.0)</td>
<td>220 (56.8)</td>
<td>225 (63.1)</td>
<td>215 (47.4)</td>
<td>99 (57.6)</td>
<td>261 (49.0)</td>
<td>301 (51.2)</td>
<td>357 (53.2)</td>
<td>289 (46.4)</td>
<td>333 (181.4)</td>
<td>116 (50.4)</td>
</tr>
<tr>
<td>Transient Early</td>
<td>127 (27.7)</td>
<td>125 (56.8)</td>
<td>142 (63.1)</td>
<td>102 (47.4)</td>
<td>57 (27.3)</td>
<td>128 (49.0)</td>
<td>154 (51.2)</td>
<td>190 (53.2)</td>
<td>134 (46.4)</td>
<td>181 (54.4)</td>
<td>50 (43.1)</td>
</tr>
<tr>
<td>Late Onset</td>
<td>39 (8.5)</td>
<td>125 (56.8)</td>
<td>142 (63.1)</td>
<td>71 (29.1)</td>
<td>27 (27.3)</td>
<td>79 (30.3)</td>
<td>89 (29.6)</td>
<td>95 (26.6)</td>
<td>86 (29.8)</td>
<td>97 (29.1)</td>
<td>33 (32.4)</td>
</tr>
<tr>
<td>Persistent</td>
<td>59 (12.9)</td>
<td>109 (45.6)</td>
<td>92 (39.3)</td>
<td>132 (54.1)</td>
<td>25 (9.1)</td>
<td>49 (24.7)</td>
<td>89 (29.6)</td>
<td>44 (43.1)</td>
<td>41 (24.3)</td>
<td>28 (24.1)</td>
<td>10 (11.2)</td>
</tr>
</tbody>
</table>

* A total of 459 participants with sufficient wheeze data from birth through age 7 years to classify wheeze phenotype.
* 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.
* Comparisons by 2-tailed χ2 test.
* 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 prenataly 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. 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 wheeze 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>
<thead>
<tr>
<th>Outcome at Age 15 y</th>
<th>Early Wheeze Phenotype&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Never</th>
<th>Transient Early</th>
<th>Late Onset</th>
<th>Persistent</th>
</tr>
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</table>

#### FEV<sub>1</sub>, mL
- **Mean (SD)**
  - Never: 3645 (696)
  - Transient Early: 3492 (743)
  - Late Onset: 3410 (549)
  - Persistent: 3427 (615)
- **β (95% CI)<sup>b</sup>**
  - Never = reference group; all models adjusted for sex, study group, city of residence, exclusive breastfeeding more than 4 months, and atopy before 2 years.
- **Wheeze**
  - No./No. (%)
    - Never: 28/157 (17.8)
    - Transient Early: 20/88 (22.7)
    - Late Onset: 11/30 (36.7)
    - Persistent: 22/45 (48.9)
  - OR (95% CI)<sup>d</sup>
    - Never = reference group; all models adjusted for sex, study group, city of residence, exclusive breastfeeding more than 4 months, and atopy before 2 years.
  - **Asthma**
    - No./No. (%)
      - Never: 8/157 (5.1)
      - Transient Early: 17/88 (19.3)
      - Late Onset: 8/30 (26.7)
      - Persistent: 19/45 (42.2)
    - OR (95% CI)<sup>d</sup>
      - Never = reference group; all models adjusted for sex, study group, city of residence, exclusive breastfeeding more than 4 months, and atopy before 2 years.
  - **Atopic asthma**
    - No./No. (%)
      - Never: 6/154 (3.9)
      - Transient Early: 13/84 (15.5)
      - Late Onset: 8/29 (27.6)
      - Persistent: 16/45 (35.6)
    - OR (95% CI)<sup>d</sup>
      - Never = reference group; all models adjusted for sex, study group, city of residence, exclusive breastfeeding more than 4 months, and atopy before 2 years.
  - **Airway hyperresponsiveness**
    - No./No. (%)
      - Never: 17/147 (11.6)
      - Transient Early: 15/75 (20.0)
      - Late Onset: 11/26 (42.3)
      - Persistent: 18/38 (47.4)
    - OR (95% CI)<sup>d</sup>
      - Never = reference group; all models adjusted for sex, study group, city of residence, exclusive breastfeeding more than 4 months, and atopy before 2 years.
  - **Allergic rhinitis**
    - No./No. (%)
      - Never: 64/157 (40.8)
      - Transient Early: 31/88 (35.2)
      - Late Onset: 13/30 (43.3)
      - Persistent: 24/45 (53.3)
    - OR (95% CI)<sup>d</sup>
      - Never = reference group; all models adjusted for sex, study group, city of residence, exclusive breastfeeding more than 4 months, and atopy before 2 years.
  - **Food allergy**
    - No./No. (%)
      - Never: 9/157 (5.7)
      - Transient Early: 7/88 (8.0)
      - Late Onset: 7/30 (23.3)
      - Persistent: 8/45 (17.8)
    - OR (95% CI)<sup>d</sup>
      - Never = reference group; all models adjusted for sex, study group, city of residence, exclusive breastfeeding more than 4 months, and atopy before 2 years.
  - **Atopy**
    - No./No. (%)
      - Never: 95/155 (61.3)
      - Transient Early: 46/85 (54.1)
      - Late Onset: 23/29 (79.3)
      - Persistent: 32/45 (71.1)
    - OR (95% CI)<sup>d</sup>
      - Never = reference group; all models adjusted for sex, study group, city of residence, exclusive breastfeeding more than 4 months, and atopy before 2 years.
  - **Atopic dermatitis**
    - No./No. (%)
      - Never: 16/157 (10.2)
      - Transient Early: 7/88 (8.0)
      - Late Onset: 3/30 (10.0)
      - Persistent: 4/45 (8.9)
    - OR (95% CI)<sup>d</sup>
      - Never = reference group; all models adjusted for sex, study group, city of residence, exclusive breastfeeding more than 4 months, and atopy before 2 years.

### Abbreviations
- FEV<sub>1</sub>, forced expiratory volume in 1 second; OR, odds ratio.
- Never = non-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.
- 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.
- Significant OR.
- 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. 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, 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-wheeze, 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 hyperreactiveness 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, 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. 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.

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