Joint modeling of parentally reported and physician-confirmed wheeze identifies children with persistent troublesome wheezing

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Background: Previous studies have suggested the presence of different childhood wheeze phenotypes through statistical modeling based on parentally reported wheezing.

Objective: We sought to investigate whether joint modeling of observations from both medical records and parental reports helps to more accurately define wheezing disorders during childhood and whether incorporating information from medical records better characterizes severity.

Methods: In a population-based birth cohort (n = 1184), we analyzed data from 2 sources (parentally reported current wheeze at 4 follow-ups and physician-confirmed wheeze from medical records in each year from birth to age 8 years) to determine classes of children who differ in wheeze trajectories. We tested the validity of these classes by examining their relationships with objective outcomes (lung function, airway hyperreactivity, and atopy), asthma medication, and severe exacerbations.

Results: Longitudinal latent class modeling identified a 5-class model that best described the data. We assigned classes as follows: no wheezing (53.3%), transient early wheeze (13.7%), late-onset wheeze (16.7%), persistent controlled wheeze (13.1%), and persistent troublesome wheeze (PTW; 3.2%). Longitudinal trajectories of atopy and lung function differed significantly between classes. Patients in the PTW class had diminished lung function and more hyperreactive airways compared with all other classes. We observed striking differences in exacerbations, hospitalizations, and unscheduled visits, all of which were markedly higher in patients in the PTW class compared with those in the other classes. For example, the risk of exacerbation was much higher in patients in the PTW class compared with patients with persistent controlled wheeze (odds ratio [OR], 3.58; 95% CI, 1.27-10.09), late-onset wheeze (OR, 15.92; 95% CI, 5.61-45.15), and transient early wheeze (OR, 12.24; 95% CI, 4.28-35.03).

Conclusion: We identified a novel group of children with persistent troublesome wheezing, who have markedly different outcomes compared with persistent wheezers with controlled disease. (J Allergy Clin Immunol 2013;132:575-83.)

Key words: *Childhood asthma, asthma endotypes, wheeze phenotypes, longitudinal analysis*

There is growing recognition that asthma might not be a single disease but a collection of diseases with similar clinical presentations.[1,2] The symptoms on which asthma diagnosis is usually made (eg, wheeze) might be a common phenotypic expression of several diseases with separate causes,[3] which are referred to as "asthma endotypes" in recent literature.[2] Although sharing similar observable features (phenotypes), these distinct disease entities (endotypes) arise through different mechanisms. Such heterogeneity is particularly relevant in childhood; wheeze is common in infancy and for many children does not recur,[4] and using the term asthma to describe all childhood wheezing illness is inappropriate.[5] Building on this notion, Martinez et al[4] described different phenotypes of preschool wheezing based on temporal patterns of symptoms ascertained by parental report on the presence/absence of wheezing at ages 3 and 6 years, classifying children as transient early wheezers, late-onset wheezers, and persistent wheezers. In a modification of this approach in the Avon Longitudinal Study of Parents and Children cohort, Henderson et al[6] used longitudinal latent class modeling to describe 2 additional phenotypes (prolonged early and intermediate-onset wheeze). These results were partially replicated in the Prevention and Incidence of Asthma and Mite Allergy birth cohort study (which identified 5 phenotypes but not prolonged early wheeze[7]).

All of the previous studies relied only on parentally reported wheezing. However, parental reports of wheezing might be unreliable.[8] In our previous study, when parents reported that their child had wheezed, the primary care physician or a study physician examined the child on the same day to confirm wheezing.[8]

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Abbreviations used
AHR: Airway hyperreactivity
BIC: Bayesian information criteria
FVC: Forced vital capacity
GP: General practitioner
ICS: Inhaled corticosteroid
LOW: Late-onset wheeze
MWD: Mean wheal diameter
NW: No wheezing
OR: Odds ratio
PCW: Persistent controlled wheeze
PTW: Persistent troublesome wheeze
sIgE: Allergen-specific IgE
SPT: Skin prick test
sRaw: Specific airway resistance
STRA: Severe therapy-resistant asthma
TEW: Transient early wheeze

Approximately one third of parentally reported wheeze was not confirmed by a physician, and these children had identical lung function as those with no history of wheeze; in contrast, children with physician-confirmed wheeze had diminished lung function.[8] These data suggest that almost a third of children assigned as "wheezers" based on parental report might have not wheezed but are incorrectly classified, possibly because of misrepresentation of various respiratory sounds by their parents.[8] Furthermore, reporting bias might be introduced because treatment could suppress wheeze.

These problems can be addressed by supplementing information obtained from parents with information from the child's medical records. We hypothesized that joint modeling of observations from both medical records and parental reports would enable us to define wheezing disorders during childhood with greater accuracy and that incorporating information from medical records might provide an added dimension of severity. To test these hypotheses, we used longitudinal latent class modeling[9] in a population-based birth cohort to identify subpopulations (classes) of children who differ in patterns of wheeze during childhood based on both complete medical records and parental assessment of wheeze at different time points. We tested the validity of these classes by examining their relationships with lung physiology, atopy, and clinical outcomes.

METHODS

Study population

The Manchester Asthma and Allergy Study is a population-based birth cohort (details can be found in the Methods section in this article's Online Repository at www.jacionline.org).[10-12] Subjects were recruited prenatally and followed prospectively up to age 8 years. The study was approved by the local ethics committee (registration: ICRCTN72673620). Parents provided written informed consent.

Data sources and definition of variables

Variables used to identify wheeze classes. *Clinical follow-up.* Participants attended follow-up at ages 1, 3, 5, and 8 years. Validated questionnaires were interviewer administered, and *parentally reported current wheeze* was defined as a positive answer to the following question: "Has your child had wheezing or whistling in the chest in the last 12 months?"

Medical records data. A trained pediatrician extracted data from primary care medical records, including the presence of wheeze, asthma diagnosis, all prescriptions (including inhaled corticosteroids [ICSs] and β_2-agonists), unscheduled visits, and hospital admissions for asthma/wheeze during the first 8 years of life. We calculated child's age in days for each event, and defined *physician-confirmed wheeze* for each year from birth to age 8 years.

Variables used to test the validity of wheeze classes. We measured specific airway resistance (sRaw) using plethysmography at ages 3, 5, and 8 years.[10,13] FEV_1 and forced vital capacity (FVC) were measured by using spirometry at age 8 years; we recorded percent predicted FEV_1[14] and the FEV_1/FVC ratio.

Airway hyperreactivity (AHR) was assessed at age 8 years in a 5-step protocol by using quadrupling doses of methacholine[15]; children were categorized as having AHR after a 20% decrease in FEV_1 by the final stage of the challenge (16 mg/mL). We calculated the dose-response slope[16] to include all evaluable data as a continuous variable.

Atopic sensitization was ascertained by using skin prick tests (SPTs; ages 3, 5, and 8 years) and measurement of allergen-specific IgE (sIgE; age 5 and 8 years) to a panel of inhalant and food allergens (details can be found in the Methods section in this article's Online Repository); we defined atopy as a wheal 3 mm larger than that elicited by the negative control to at least 1 allergen. We quantified atopy as the size of the SPT mean wheal diameter (MWD) and absolute levels of sIgE and used the sum of the SPT MWD and sIgE level to all allergens, inhalant allergens, or both in the analysis.[17]

Asthma exacerbations were defined from medical records data as admission to the hospital or emergency department visits, receipt of oral corticosteroids for at least 3 days, or both.[18]

Eczema was defined as a positive answer to the following question: "Has your child had eczema within the past 12 months (ages 1, 3, 5, and 8 years)?"

Statistical analysis

We used a longitudinal latent class item response model (STATA 11.0; StataCorp, College Station, Tex)[9,19] to jointly model data from 2 sources: parentally reported wheeze within the last 12 months at ages 1, 3, 5, and 8 years (from questionnaires) and physician-confirmed wheeze within each year from birth to age 8 years (from medical records; see Fig E1 in this article's Online Repository at www.jacionline.org). We assumed that each child belongs to one of *N* latent classes, with the number and size of classes not known *a priori*. We used a 2-level random coefficient logistic regression model to examine trajectory classes with linear and quadratic change with age.[20] The models were compared for goodness of fit by using the Bayesian information criteria (BIC). For each child, the (posterior) probability of belonging to each of the latent classes was calculated, and children were assigned to the latent class with the largest probability. We tested the validity of classes by examining their relationships to lung function, AHR, atopy, asthma medication use, severe asthma exacerbations, and hospitalizations by using multinomial logistic regression, Cox regression, and longitudinal regression models.

RESULTS

Participant flow

Data on parentally reported current wheeze were available for 1104 participants at age 1 year, 1108 at age 3 years, 1072 at age 5 years, and 1025 at age 8 years. We reviewed medical records of 916 children. Almost 30% of children wheezed in the first year of life; wheeze prevalence decreased to age 8 years (see Fig E2 in this article's Online Repository at www.jacionline.org). There was generally good concordance between parental and physician ratings of wheeze (see Table E1 in this article's Online Repository at www.jacionline.org).

Wheeze classes identified

The optimal model that best described the data was a 5-class model that assumed linear change random coefficients for wheeze

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