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;■■■:■■■-■■■.)

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

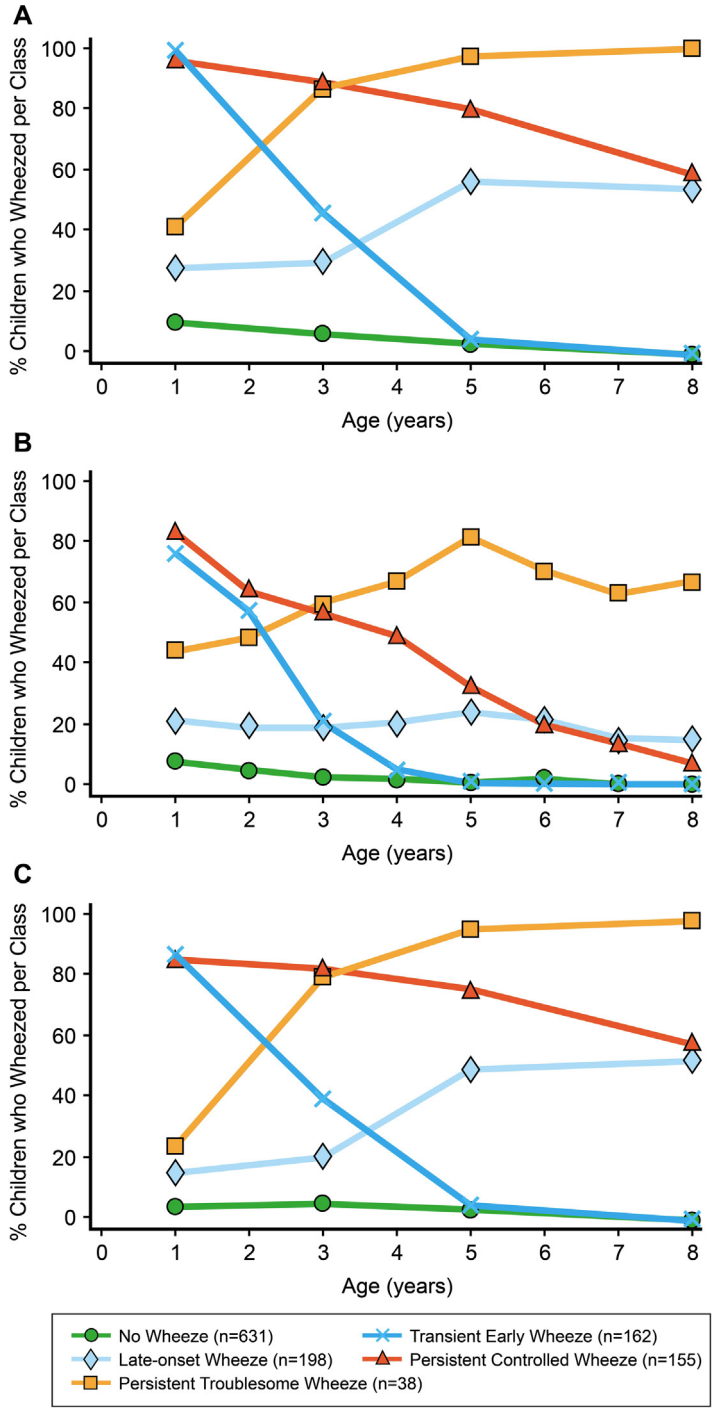

FIG 1. Characteristics of 5 wheeze classes: percentage of participants with reported wheezing according to either parentally reported or physician-confirmed wheeze **(A)**, physician-confirmed wheeze only **(B)**, and parentally reported wheeze only **(C)**. The number of children in each class is denoted in parentheses.

(see Table E2 and Fig E3 in this article's Online Repository at www.jacionline.org). On the basis of our interpretation of their characteristics, we assigned the classes as follows: (1) no wheezing (NW; 53.3%), (2) transient early wheeze (TEW; 13.7%), (3) late-onset wheeze (LOW; 16.7%), (4) persistent controlled wheeze (PCW; 13.1%), and (5) persistent troublesome wheeze (PTW; 3.2%). Fig 1 shows the percentage of children who wheezed annually and growth trajectories for each class over the first 8 years of life. The associates of different classes are presented in Table E3 in this article's Online Repository at www.jacionline.org. By age 6 years, none of the children in the TEW class consulted their general practitioner (GP) with asthma/wheeze, and none had parentally reported wheeze in the eighth year; however, 37.2% received asthma medication in the first year of life. Children in the LOW class had increasing receipt of asthma medication (reaching a maximum of 28.7% at age 8

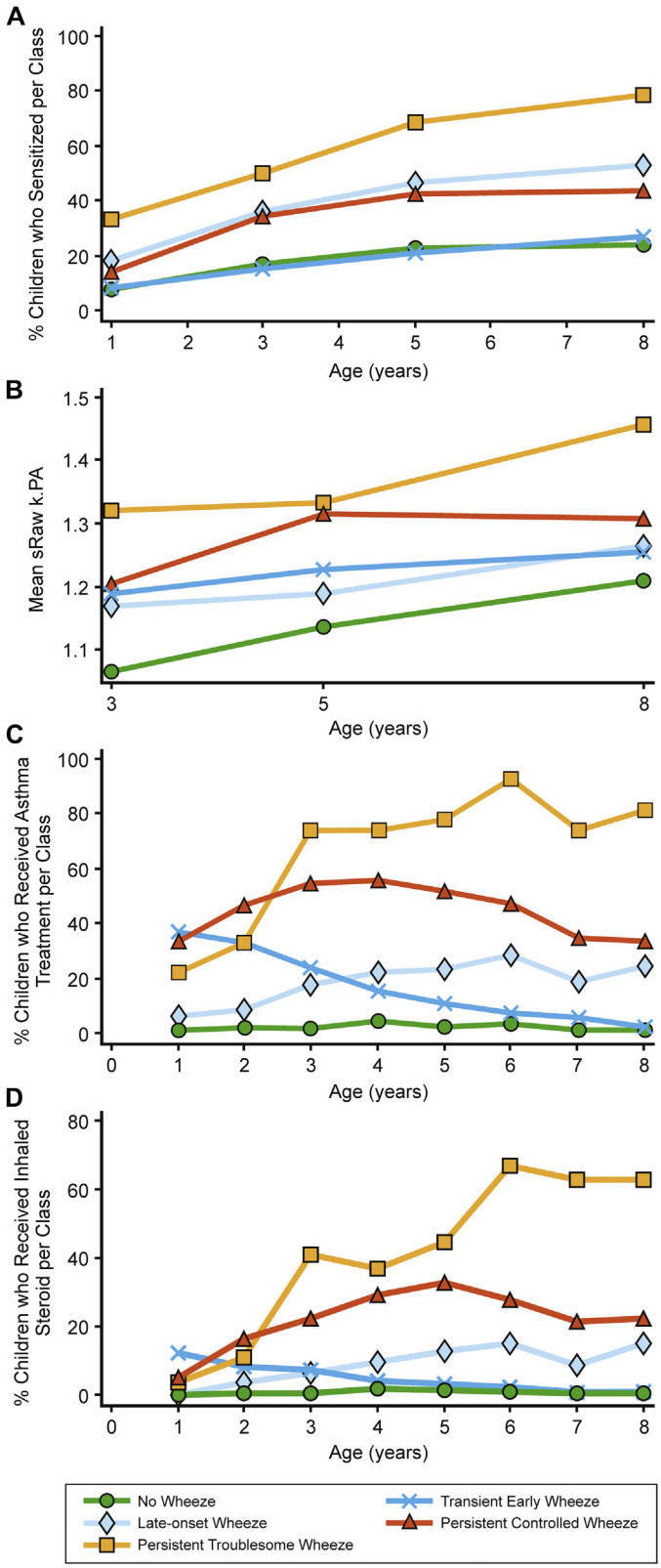

FIG 2. Trajectories of atopy **(A)**, sRaw **(B)**, asthma treatment **(C)**, and ICSs **(D)** over time for each of the wheeze classes.

TABLE I. Lung function and airway hyperresponsiveness at age 8 years and sIgE antibody levels to common inhalant allergens (dust mite, cat, and dog) at ages 5 and 8 years among children in different wheeze classes using children with "no wheezing" as the reference class

	NW (53%)	TEW (13.7%)	LOW (17.0%)	PCW (13.1%)	PTW (3.2%)	Total	*P* value
Percent predicted FEV_1 (L)						790	<.001
Mean	101.3	95.5	96.9	95.5	95.5		
95% CI	100.3-102.3	93.1-97.9	94.9-99.0	93.1-97.9	89.8-101.3		
P value		<.001	<.001	<.001	.008		
FEV_1/FVC ratio (%)						789	<.001
Mean	87.8	86.3	85.5	85.5	82.1		
95% CI	87.3-88.3	85.2-87.4	84.4-86.7	83.2-85.8	79.1-85.0		
P value		.019	<.001	<.001	<.001		
Methacholine dose-response slope						627	.024
Mean	5.98	8.21	11.14	10.8	19.06		
95% CI	5.32-6.71	6.53-10.26	8.97-13.85	8.24-14.26	12.88-29.80		
P value		.021	<.001	<.001	<.001		
sIgE to mite, cat, and dog							
Age 5 y						603	<.001
Geometric mean	0.8	0.7	2.2	2.7	13.9		
95% CI	0.71-0.86	0.62-0.84	1.50-3.33	1.71-4.29	4.35-44.33		
P value		.41	<.001	<.001	<.001		
Age 8 y						581	<.001
Geometric mean	0.3	0.4	2.0	1.8	10.6		
95% CI	0.29-0.41	0.26-0.53	1.16-3.55	0.91-3.67	2.80-40.46		
P value		.77	<.001	<.001	<.001		
sIgE to mite, cat, and dog in atopic children							
Age 5 y						205	<.001
Geometric mean	1.7	1.4	8.5	10.1	53.4		
95% CI	1.22-2.33	0.75-2.56	4.60-15.72	5.47-18.61	19.36-147.12		
P value		.61	<.001	<.001	<.001		
Age 8 y						255	<.001
Geometric mean	1.3	2.1	9.8	10.3	54.2		
95% CI	0.88-1.95	0.98-4.38	5.24-18.24	4.66-22.61	19.5-147.13		
P value		.33	<.001	<.001	<.001		

years). All children in the PCW class visited their GPs on at least 2 occasions, and the proportion receiving asthma treatment peaked at age 4 years (56.0%), after which it reached a plateau (Fig 2); 85.2% wheezed in the first year of life. In the smallest class (PTW) 44.4% of the children visited their GPs for wheezing in the first year of life, and at age 8 years, 92.6% were receiving asthma treatment.

At age 8 years, 112 (11.2%) of 1000 children had current physician-diagnosed asthma; of these, 1 (0.90%) was in the NW class, 3 (2.68%) were in the TEW class, 35 (31.25%) were in the LOW class, 47 (41.96%) were in the PCW class, and 26 (23.21%) were in the PTW class.

Wheeze classes, lung function, airway reactivity, and atopy

Children in all wheezing classes had significantly lower FEV_1 at age 8 years than nonwheezers, with no difference between wheezing classes (Table I). However, the FEV_1/FVC ratio (indicating airway narrowing) was significantly lower in the PTW class compared with the TEW and LOW classes ($P < .01$, Table I), with a trend compared with the PCW class ($P = .08$). There were striking differences in AHR between the classes. Children in the PTW class were at the highest risk of AHR ($P < .001$, Table E3) and had significantly more hyperreactive airways compared with all other classes (Table I).

Children in the LOW, PCW, and PTW classes were significantly more likely to be atopic compared with those in the NW class ($P < .01$), with no difference between the NW and TEW classes. At ages 5 and 8 years, the PTW class had the highest sIgE levels to inhalant allergens (Table I); furthermore, even among atopic children, sIgE levels were significantly higher in those in the PTW class compared with children in any other class. Similarly, children in the PTW class had significantly higher SPT wheal sizes compared with the PCW class and other wheeze classes (see Table E4 in this article's Online Repository at www.jacionline.org), both in the whole population and among atopic children only.

Longitudinal analyses

Longitudinal analyses revealed marked differences in the development trajectories of atopy and lung function throughout childhood between different classes (Fig 2 and Table II). Children with PTW had a higher probability of sensitization compared with those with LOW (odds ratio [OR], 2.56 [95% CI, 1.35-5.12]; $P = .004$) and PCW (OR, 3.12 [95% CI, 1.64–6.25]; $P = .001$). The trajectories of sRaw (longitudinal random coefficients model) also differed significantly between classes (Fig 2, *B*). At age 3 years, sRaw was significantly higher (ie, lung function was diminished) in all wheezing classes compared with the NW class; by age 8 years, these differences in sRaw decreased for all but the

TABLE II. ORs (95% CIs) showing longitudinal association of atopy, eczema, and markers of asthma severity of different wheeze classes compared with PTW as the reference class in a longitudinal logistic regression model

	NW (n = 632), OR (95% CI)	TEW (n = 162), OR (95% CI)	LOW (n = 198), OR (95% CI)	PCW (n = 155), OR (95% CI)
sRaw				
Mean difference (95% CI)	−0.26 (−0.33 to −0.19)	−0.17 (−0.25 to −0.10)	−0.19 (−0.27 to −0.12)	−0.09 (−0.17 to −0.02)
P value	<.001	<.001	<.001	.015
Sensitization (SPT)				
Yes	0.14 (0.07 to 0.25)	0.13 (0.06 to 0.25)	0.39 (0.20 to 0.74)	0.32 (0.16 to 0.61)
P value	<.001	<.001	.004	.001
Eczema (1-8 y)				
Yes	0.22 (0.14 to 0.36)	0.28 (0.16 to 0.47)	0.36 (0.22 to 0.61)	0.53 (0.31 to 0.90)
P value	<.001	.02	<.001	.018
Hospital admissions for asthma/ wheeze (0-8 y)				
Yes	0.02 (0.01 to 0.05)	0.23 (0.11 to 0.46)	0.12 (0.06 to 0.24)	0.42 (0.21 to 0.82)
P value	<.001	<.001	<.001	.011
ICSs (age 0-3 y)				
Yes	0.00 (0.00 to 0.01)	0.03 (0.01 to 0.07)	0.05 (0.02 to 0.13)	0.24 (0.10 to 0.55)
P value	<.001	<.001	<.001	.001
Asthma exacerbation (age 0-8 y)				
Yes	0.00 (0.00 to 0.01)	0.07 (0.03 to 0.14)	0.06 (0.03 to 0.12)	0.28 (0.15 to 0.53)
P value	<.001	<.001	<.001	<.001
No. of asthma exacerbations (age 0-8 y)				
Yes	0.00 (0.00 to 0.01)	0.12 (0.06 to 0.22)	0.09 (0.05 to 0.17)	0.46 (0.25 to 0.85)
P value	<.001	<.001	<.001	.013

PTW class, in which sRaw further increased (eg, at age 3 years, there was no significant difference between the PTW and PCW classes [$P = .17$], but at age 8 years, sRaw differed significantly between these 2 classes [$P = .015$]). To allow the comparison of the differences noted in lung function at age 3 years with those noted at age 8 years, we have also presented the results as *z* scores (see Table E5 in this article's Online Repository at www.jacionline.org).

Longitudinal trajectories of asthma medication and severe exacerbations

Nearly all children in the PCW and PTW classes received asthma medication by age 8 years (see Table E3). However, at age 8 years, the proportion of children receiving asthma treatment was significantly higher in the PTW class (81.5%) compared with any other class (Fig 2, *C*; eg, 33.6% in the PCW class, $P < .001$). Different classes had significantly different trajectories of ICS prescriptions over time (Fig 2, *D*). Initially, the TEW class had a high probability of receiving ICSs, but with each year, the odds of receiving ICSs decreased by 41%. In contrast, the initial OR of receiving ICSs in the PCW and PTW classes was lower compared with that in the TEW class, with no change over time in the PCW class but a significant increase in the PTW class (the odds of receiving ICSs in patients with PTW increased by 63% per year). Of all ICSs prescribed in the first year of life, 68.2% were prescribed to the TEW class, although this class accounted for only 33.7% of children who wheezed in the first year of life.

There were striking differences in the pattern of exacerbations, hospital admissions, and unscheduled visits for asthma between different classes (Fig 3). The risk of exacerbation in the first 8 years of life was higher in the PTW class compared with the PCW class (OR, 3.58 [95% CI, 1.89-6.67]; $P < .001$), the LOW class (OR, 16.67 [95% CI, 8.33-33.34]; $P < .001$), and the TEW class (OR, 14.29 [95% CI, 7.14-35.03]; $P < .001$). The risk of hospital admission was also significantly higher in the PTW class compared with any other wheeze class (PCW: OR, 2.83 [95% CI, 1.20-6.67; $P = .02$]; LOW: OR, 7.82 [95% CI, 3.20-19.13; $P < .001$; and TEW: OR, 7.61 [95% CI, 3.01-19.26; $P < .001$]). When investigating time to the first hospital admission and asthma exacerbation, children with PTW had a significantly higher risk of events (see Fig E4 in this article's Online Repository at www.jacionline.org). These differences persisted when predicting the risk of events occurring after age 3 years, with patients with PTW having a significantly higher risk of exacerbation and hospital admission compared with those with PCW ($P < .001$, see Fig E3).

Early identification of troublesome wheezers

We proceeded to investigate whether we can distinguish between children with troublesome wheeze from those in other wheeze classes at age 3 years (see Table E6 in this article's Online Repository at www.jacionline.org). Among children with a history of wheeze in the first 3 years, those with PTW were significantly more likely to have diminished lung function (sRaw, >1.6 $kPa \cdot s^{-1}$ [corresponding to a *z* score of 1.7]; OR, 6.48 [95% CI, 1.87–22.46]; $P = .003$), eczema (OR, 4.04 [95% CI, 1.79–9.10]; $P = .001$), an SPT MWD (sum of all allergens) of 10 mm or greater (OR, 8.14 [95% CI, 3.22–20.62]; $P < .001$), and 3 or more exacerbations by age 3 years (OR, 12.38 [95% CI, 4.35–35.21]; $P < .001$). Children who had 3 of these 4 features (exacerbations, eczema, SPT MWD ≥10 mm, and/or sRaw >1.6 kPa) were at markedly higher risk to be in the PTW class compared with other wheezers (OR, 39.74 [95% CI, 8.84-178.65]; $P < .001$). Using 3 features provided overall good discrimination

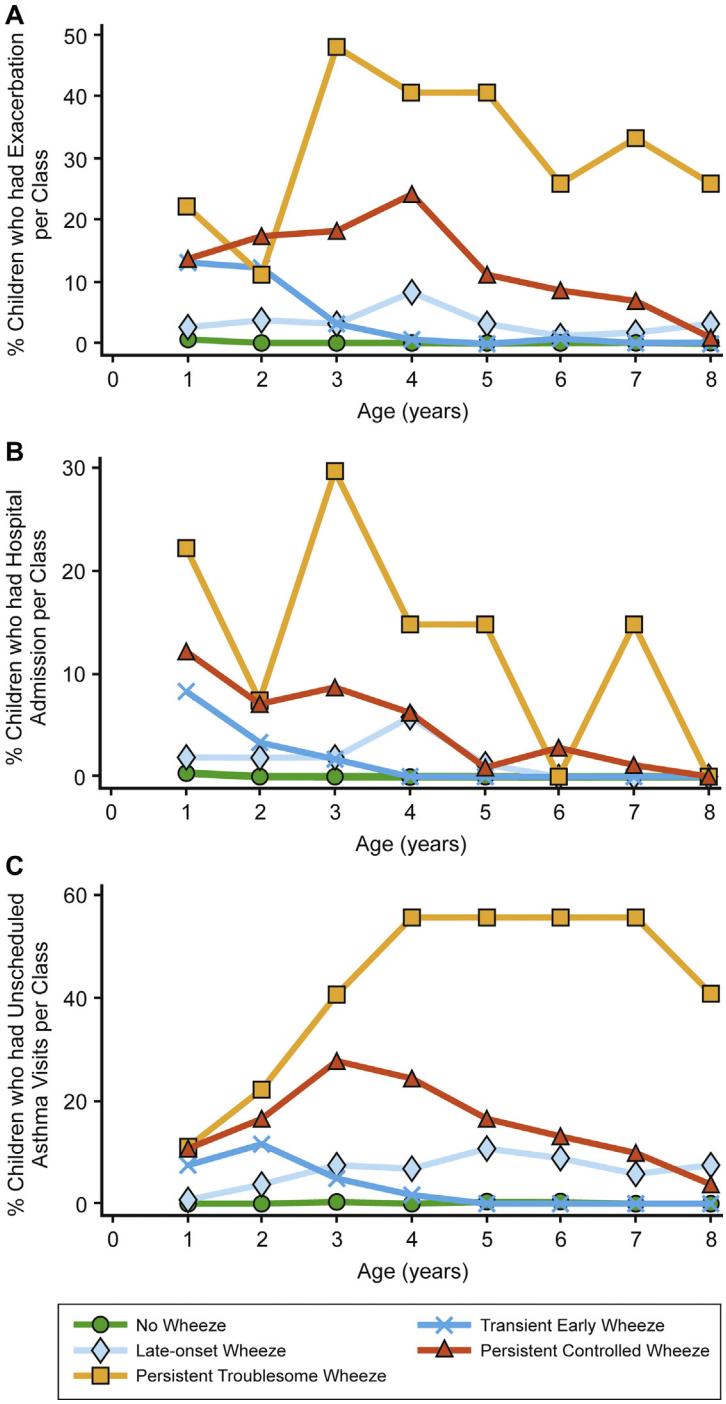

FIG 3. Trajectories of severe exacerbations **(A)**, hospital admissions **(B)**, and unscheduled visits for asthma **(C)** over time for each of the wheeze classes.

between children who were in the PTW class and those with other wheeze phenotypes (area under the curve, 0.81), with 95.4% of children correctly classified, and the positive predictive value was 42.9%. A stepwise regression approach revealed an SPT MWD of 10 mm or greater and a history of exacerbations by age 3 years as significant independent predictors of PTW, distinguishing them from other children who wheezed in the first 3 years of life.

DISCUSSION

By jointly modeling longitudinal observations of wheezing from parentally completed questionnaires and information transcribed from medical records, we have identified 4 distinct classes of wheezing with different longitudinal trajectories of atopy and lung function. We identified a novel class of children with persistent troublesome wheezing, who have markedly different outcomes compared with children of all other wheeze classes,

including persistent wheezers with controlled disease. The airways of children in this class were significantly more obstructed and hyperreactive, and despite all children receiving asthma medication by age 8 years, they had markedly more exacerbations, hospitalizations, and unscheduled medical visits. Importantly, there was a loss of lung function in this group between ages 3 and 8 years. Children in this class had markedly larger skin test responses and higher sIgE levels (even among atopic children). We identified strong predictors of subsequent troublesome wheezing among symptomatic children as early as age 3 years, namely diminished lung function, large SPT responses (sum of wheal diameters to inhalant and food allergens ≥10 mm), current eczema, and a history of 3 or more exacerbations in the first 3 years of life.

A strength of this study is that we used not only parentally reported data but also the information from medical records detailing each child's contact with health care professionals. We capitalized on a unique feature of the health care system in the United Kingdom in that GPs are required to maintain accurate records of all health care encounters of their patients, including hospital admission, outpatient appointments, and all prescriptions. These dual sources of information enabled more precise definitions of wheeze events than studies that relied on questionnaires only.[6,7] Importantly, the medical records contained accurate information on medication prescriptions, asthma exacerbations, unscheduled primary care visits, and hospital admissions. These outcomes provided additional validation that the 4 wheeze classes are not only different from the NW class but are importantly different from each other. However, a limitation of our study is that although we have accurate records of the collected prescriptions, we have no confirmation that children took the medication.

Our results suggest similar structure to that proposed by the Tucson Children's Respiratory Study.[4] However, an important difference is that our analysis identified 2 distinct classes within what is commonly considered a single phenotype of persistent wheeze: one with symptoms that are well controlled and the other with troublesome symptoms and frequent exacerbations (despite high levels of treatment). This suggests that children in the PTW class are either undertreated or poorly responsive to currently available anti-inflammatory treatments. Phenotypic characteristics of children in this class (including high atopy rates, high sIgE levels and large SPT wheal diameters; persistent symptoms; and severe exacerbations despite treatment) are consistent with the recently proposed term "problematic severe asthma"[21,22] and appear similar to patients with severe therapy-resistant asthma (STRA).[23] Children in this class experience significant morbidity, and given the high exacerbation rate and high level of unscheduled medical visits and hospital admissions, these children are likely to consume a disproportionate amount of health care resources. Our data suggest that despite having phenotypic markers that are commonly considered indicators of good therapeutic response to ICSs (eg, atopy and eczema), children in this class might be relatively resistant to currently available treatments. In this context it is of note that recent studies have demonstrated that pediatric STRA is characterized by airway remodeling and markers of T_H2 inflammation (eosinophilia) but without T_H2 cytokines[24] and that a cardinal feature of bronchial epithelial cells from highly atopic children with STRA is impaired IFN-β and IFN-λ induction by rhinovirus, with no relationship between atopy/T_H2-mediated inflammation with impaired interferons.[25] These and our data suggest a possibility of 2 independent mechanisms (atopy related and virus related) in causation of troublesome wheezing in childhood.

Our observational data indicate that almost 70% of all ICSs prescribed in the first year of life were prescribed to children in the TEW class, although this class accounted for only approximately 34% of children who wheezed in the first year. Randomized controlled trial data suggest that use of ICSs in young wheezing children has no effect on the natural history of asthma later in childhood[26-28] and that symptomatic benefits in infants are minimal,[26,28] suggesting overtreatment in this class in early life. This highlights the importance of efforts to identify predictors of different wheeze classes in infancy, so that, for example, we can reduce unnecessary use of ICSs among very young children with transient wheezing.

Several recent publications have demonstrated the utility of unbiased clustering approaches to multidimensional data to identify phenotypes of childhood[29-31] and adult[32,33] asthma. A principal component analysis applied to more than 100 questions relating to wheeze/other respiratory symptoms suggested the existence of 5 different clusters in preschool children.[31] A recent cluster analysis with 19 variables (including personal/family history, atopy, inflammatory markers, and lung function) in 315 asthmatic children identified 3 clusters,[30] one of which had characteristics similar to the clinical phenotype of STRA[34] and to the PTW class in our study. Cluster analysis among children from the US Severe Asthma Research Program identified clusters that did not corresponded entirely to definitions of severe asthma proposed by national and international guidelines.[29] However, potential problems of the cross-sectional approach to unbiased clustering used in the above studies include the recent observation that some of the variables commonly used to cluster the patients are unstable[35] and that analysis does not include the important dimension of time. We propose that if we are to improve asthma classification and identify true latent endotypes, an added dimension of time is essential to take into account the longitudinal changes in observable characteristics.

In conclusion, using joint modeling of observations from medical records and parental reporting of wheeze during the first 8 years of life, we have identified 4 latent phenotypes of childhood wheezing that significantly differed in their relationships with atopy, lung function, and airway reactivity, suggesting (but not proving) that different classes might be underpinned by different biological mechanisms (ie, that they represent different endotypes). We identified a novel class of persistent troublesome wheezers characterized by significant airway obstruction and hyperreactivity, very high levels of atopy, and, despite receiving ICSs, high rates of exacerbations, hospitalizations, and unscheduled medical visits for wheezing. At age 3 years, predictors of subsequent troublesome symptoms among children with wheezing were large skin test wheal diameters (≥10 mm), history of previous exacerbations, diminished lung function, and current eczema.

We thank the children and their parents for their continued support and enthusiasm. We greatly appreciate the commitment they have given to the project. We also acknowledge the hard work and dedication of the study team (postdoctoral scientists, research fellows, nurses, physiologists, technicians, and clerical staff).

Key messages

- **The joint modeling of longitudinal observations of wheezing from parental questionnaires and transcribed from primary medical care records enabled us to identify 4 distinct classes of wheezing, with an important novel class of children with PTW.**
- **Children with PTW have airways that are significantly more obstructed and hyperreactive and have a markedly higher probability of severe asthma exacerbations and, when atopic, markedly higher levels of specific serum IgE and larger SPT responses.**
- **At age 3 years, predictors of subsequent troublesome symptoms among children with wheezing were a large skin test wheal diameter (≥10 mm), a history of previous exacerbations, diminished lung function, and current eczema.**

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METHODS

Study design

The study design was an unselected birth cohort study.

Setting

The maternity catchment area was Wythenshawe and Stepping Hill Hospitals, comprising 50 square miles of South Manchester and Cheshire, United Kingdom, a stable mixed urban-rural population.

Screening and recruitment

All pregnant women were screened for eligibility at antenatal visits (8th-10th week of pregnancy). Of the 1499 couples who met the inclusion criteria (≤10 weeks of pregnancy, maternal age ≥18 years, and questionnaire and skin test data available for both parents), 288 declined to take part in the study, and 27 were lost to follow-up between recruitment and the birth of a child. A total of 1184 participants had at least some evaluable data.

Clinical follow-up

Children attended review clinics at ages 1, 3, 5, and 8 years (±4 weeks). A validated International Study of Asthma and Allergies questionnaire was interviewer administered; according to parentally reported history of wheeze, *current wheeze* was defined as a positive response to the following question: "Has your child had wheezing or whistling in the chest in the last 12 months?"

Atopic sensitization

Atopic sensitization was ascertained by means of SPTs at ages 3 and 5 years for 7 allergens (*Dermatophagoides pteronyssinus*, cat, dog, grass pollen, molds, milk, and egg [Bayer, Elkahrt, Ind]). At age 8 years, SPTs were additionally performed for tree pollen and peanut (total of 9 allergens tests). We defined sensitization as a mean wheal diameter 3 mm larger than that elicited by the negative control to at least 1 of the allergens tested. We also measured specific serum IgE levels to mite, cat, dog, grasses, milk, egg, and peanut by means of ImmunoCAP (Phadia, Uppsala, Sweden) at ages 5 and 8 years.

Lung function measurement

Children were asymptomatic at the time of assessment of lung function. Short-acting β_2-agonists were withheld for at least 6 hours, and long-acting β_2-agonists were withheld for at least 24 hours before testing.

sRaw. At ages 3, 5, and 8 years, we carried out measurements of sRaw to assess airway function in all children who were willing to cooperate. Measurements were made with a constant-volume whole-body plethysmograph (Masterscreen Body 4.34; Jaeger, Würzburg, Germany). sRaw was measured by using a single-step procedure from the simultaneously measured changes in respiratory flow and changes in plethysmographic pressure, omitting the measurement of thoracic gas volume. Measurements were carried out during tidal breathing with an adapted facemask. Once a stable breathing pattern was established, at least 3 measurements of sRaw were performed, and each was calculated from the means of 5 consecutively measured technically acceptable loops. The median of these 3 measurements of effective sRaw was used in the analysis. The measured values were corrected for the influence of the pneumotachograph screen and for the volume displacement caused by the subject (or subject plus parent).

Spirometry. Spirometry was performed at age 8 years according to American Thoracic Society guidelines with a Lilly pneumotachograph system with animated incentive software (Jaeger). FEV_1 and FVC were recorded, and the data were expressed as FEV_1 percent predicted and FEV_1/FVC ratio.

AHR

At the 8-year follow-up, airway reactivity was assessed by means of methacholine challenge with a 5-step protocol performed according to American Thoracic Society guidelines. Quadrupling doses of methacholine (0.0625-16.0 mg/mL) were delivered to subjects through a DeVilbiss 646 nebulizer (Sunrise Medical HHG, Somerset, Pa) and a KoKo dosimeter (Pulmonary Data Services, Doylestown, Pa) calibrated to deliver 0.009 mL per 0.6-second actuation. The predicted FEV_1 was calculated, and if the measured value was less than 1.0 L or less than 60% of the predicted value, the test was not performed. FEV_1 was measured 30 and 90 seconds after 5 inhalations of each dose of methacholine. The challenge was stopped when either a 20% decrease in FEV_1 was observed or the maximum methacholine concentration had been administered.

Data from primary care medical records

Eligible practices were contacted and invited to participate in the study either by means of both postal information packs and telephone calls (GP practices with ≥2 children) or by post only (GP practices with a single study participant). Data access and manual extraction were performed during arranged visits to each GP practice. A trained pediatrician extracted data from electronic and paper-based primary care medical records, including prescriptions, acute wheeze episodes, oral steroid prescriptions, and hospital admissions for asthma or wheeze during the first 8 years of life. Timing, type of visit, symptoms, indication, and prescriptions for each encounter were noted. We calculated the child's age in days for each event.

Data analysis

We analyzed data from questions assessing the presence of wheeze using 2 complementary measures: a parental rating, in which parents were asked whether their child wheezed within the 12-month interval before their first, third, fifth, and eighth birthdays, and a GP rating of wheeze events, which was reported from medical records, assessing whether a child, on being presented to the GP, was given a diagnosis of having wheezed within a given year. We used a longitudinal latent class item response model to determine wheeze phenotypes (latent classes) for homogenous groups of children.[E1] Each class is estimated as having a particular pattern of development of underlying wheeze, which at each age is reported subject to error by the parent and the GP. A factor-loading parameter is included to allow the reliability of parent and GP reports to have differing reporting reliabilities. Conditional on the level of wheeze of each underlying wheeze class, the errors in reporting are assumed to be independent. Fig E1 shows the type of relationship that has been modeled.

The model can be described algebraically for measure j (parent or GP) and for participant i ($i = 1,\ldots,N$) at measurement occasion t by using the following equation:

$$\Pr\left(y_{ijt}=1\right)=\sum_k \pi_k \frac{\exp\left\{\lambda_j\left(\alpha_k+\beta_k age_{it}+\gamma_k age_{it}^2\right)\right\}}{1+\exp\left\{\lambda_j\left(\alpha_k+\beta_k age_{it}+\gamma_k age_{it}^2\right)\right\}} \quad \text{for } k=1,\ldots,K,$$

where π_k is the prevalence of class k among K classes, and λ_j is a factor loading. The model was estimated by using maximum likelihood with gllamm in Stata 11.0 software (StataCorp, College Station, Tex).[E1,E2] We examined both linear change trajectory models and models with quadratic effects. The models allow us to hypothesize that there might be subgroups of children who have changing wheeze responses over time. We specified this as a 2-level random-coefficient logistic regression model[E3] for the dichotomous variable representing the answer to the question "Has the child wheezed within the given time period?," with level 1 units as the yearly measurement occasions and level 2 units as children. Children were assigned to the latent class with the largest posterior probability.[E4]

Choosing the number of latent classes that best described the data

The models were compared for goodness of fit by using the BIC, which is a measure that combines the log-likelihood value with the number of parameters,[E5] penalizing complex models with additional parameters. The model with the smallest BIC value was considered the best-fitting model.

Early identification of troublesome wheezers

Cut-offs for sRaw and the size of SPT MWD were based on the distribution of data as the upper quartile on a log-transformed scale.

RESULTS

Participant flow

A total of 987 participants registered with 185 different GP practices provided informed consent for medical records data collection. Of 130 GP practices with more than 1 child on the register, 125 were visited, and data were successfully collected. Three practices (with 7 participating children) did not reply after 5 attempts, and 1 practice (with 2 children) declined the invitation. One GP practice did not agree to provide access at their premises but posted copies of the medical records. Of the 55 GP practices with only 1 registered child, 42 provided copies of children's medical records; the remaining 13 practices did not send the required information after 2 postal contacts and were classified as "failed to reply." One child could not be traced, 9 moved away from the area during the data collection, and 22 changed GPs during the collection period, moving into a practice that had already been visited. We retrieved and reviewed medical records of 925 study participants. Nine of these records were only partially accessed (missing paper or electronic records) and were therefore excluded.

All children with available clinical outcomes were included at each time point. There was no difference in parental asthma/atopy between children with or without missing data on clinical outcomes.

The prevalence of wheeze according to the validated questionnaire and medical records is shown in Fig E2.

Trajectory modeling of the developmental pathways of wheeze

Table E2 shows the values of the BIC and the log-likelihood for 3-class, 4-class, 5-class, 6-class, and 7-class solutions using both linear and quadratic time-varying models.

According to the BIC, the optimal model with respect to number of classes and time complexity was a 5-latent-class model that assumed a linear change trajectory for wheeze. Neither adding further classes nor allowing for a higher-order change trajectory improved the fit.

Two-fold cross-validation with 20 random data splits into equal partitions of 592 children to ascertain the robustness of these latent classes using a smaller subgroup of children confirmed a 5-latent-class model, which assumed a linear change trajectory for wheeze (Fig E3 shows the average BIC for each of the test sets and the overall average).

Descriptive characteristics of the 5 classes in the linear trajectory model

The largest class (NW) comprised 53.3% of the cohort. Although some of these children wheezed within the first year of life, 88.5% had no parentally reported wheeze, and 81.2% never presented to the GP with wheeze symptoms. These children had a maximum of 2 physician-diagnosed wheeze episodes, with only 1.2% of this class visiting the GP with wheeze more than once. Children in this class tended not to receive asthma treatment.

In the TEW class 37.2% of children received asthma treatment in the first year of life compared with only 2.5% in the eighth year of life. By the time they reached age 6 years, none of these children presented to the GP with asthma/wheeze, and they have a maximum of 4 visits for asthma/wheeze symptoms, the majority of which (95.0%) took place within the first 4 years of life. This trend was consistent with the pattern of parental reports of wheeze, with no parents reporting wheeze in the eighth year of life.

Children in the LOW class had increasing prevalence of wheeze and receipt of asthma medication in parental reports (reaching a maximum of 28.7% at age 8 years).

All children in the PCW class visited the GP with asthma/wheeze symptoms on at least 2 occasions. Although the proportion of children in this class visiting the GP for asthma/wheeze decreased over time, the proportion of these children receiving asthma treatment increased between age 1 (33.6%) and 4 (56.0%) years, after which it reached a plateau (Fig 2). Most (85.2%) of these children were reported to have wheezed by their parents at age 1 year, decreasing to 56.8% at age 8 years.

The smallest class (PTW) represented 3.2% of the cohort. In the first year of life, 44.4% were recorded as having wheezed by the GP, and 23.7% wheezed according to parental reports. By the fifth year of life, 94.7% of these children wheezed according to parental reports, and 81.5% wheezed according to GP reports. Most (92.6%) of the children in this class received asthma treatment in the eighth year of life.

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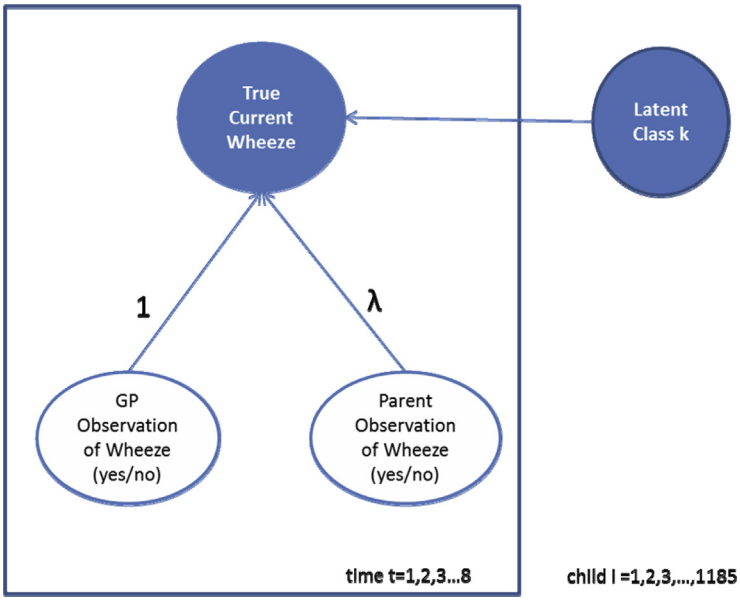

FIG E1. Linear trajectory model based on parentally reported and physician-confirmed wheeze. Plates represent variables repeated over different measurements. *Unshaded circles* represent observed variables, and *shaded circles* represent unobserved or latent variables to be inferred. Because we used binary variables, the *arrows* in the figure represent a logistic regression model for these variables.

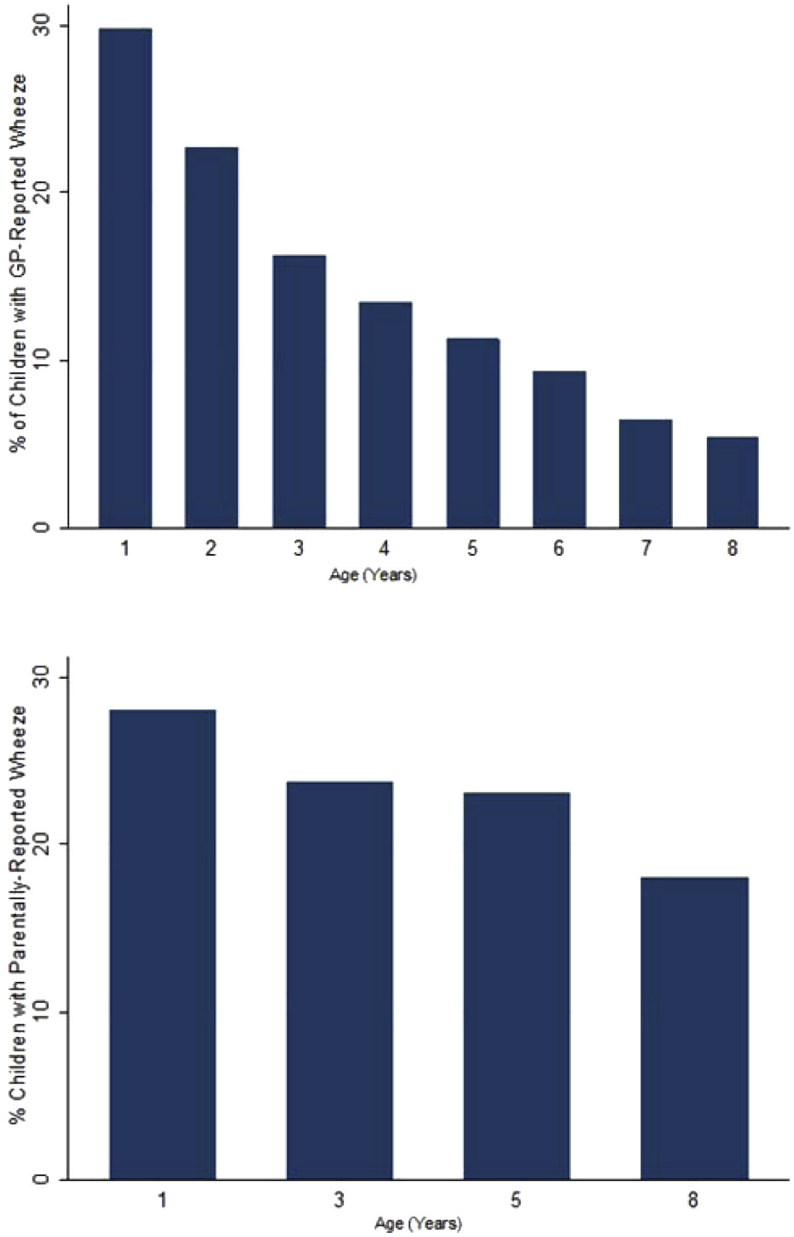

FIG E2. Prevalence of wheeze according to GP records and parental questionnaire information.

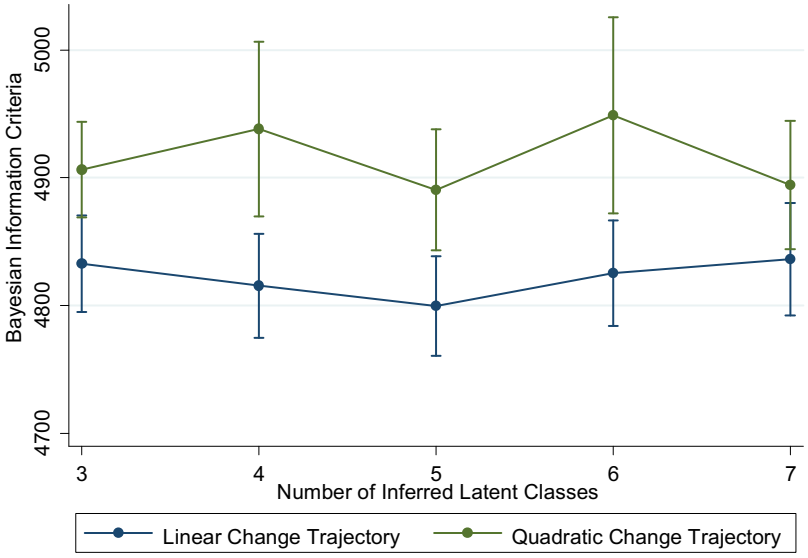

FIG E3. Plot showing change in BIC for the linear and quadratic change trajectory model when different numbers of latent classes are assumed.

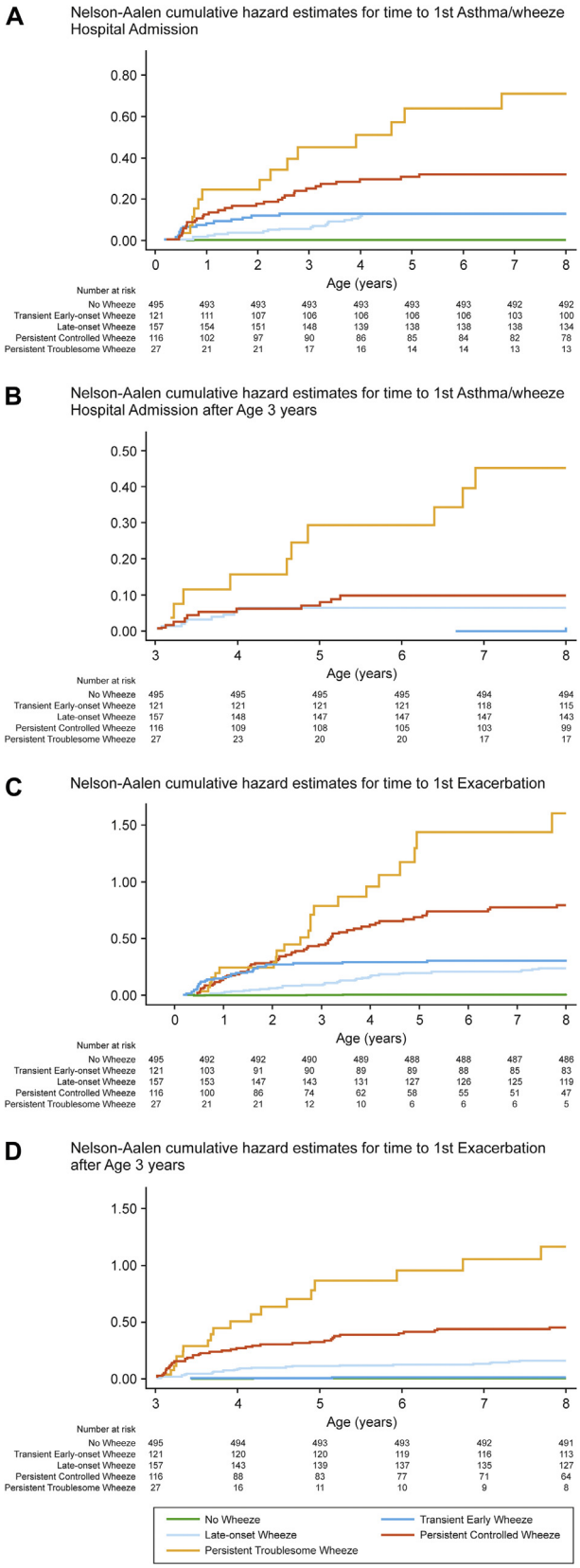

FIG E4. Nelson-Aalen cumulative hazard plots for time to first severe asthma exacerbation within the first 8 years of life **(A)**, time to first severe asthma exacerbation after age 3 years **(B)**, time to first asthma/wheeze-related hospital admission within the first 8 years of life **(C)**, and time to first asthma/wheeze-related hospital admission after age 3 years **(D)**.

TABLE E1. Cross-tabulations indicating correlation between physician-confirmed wheeze and parentally reported current wheeze at different time points

Parentally reported current wheeze	Physician-confirmed wheeze			
	Age (y)	Yes	No	Total
	1			
	Yes	160 (61.5%)	100 (38.5%)	870
	No	75 (12.3%)	535 (87.7%)	
	3			
	Yes	79 (60.8%)	51 (39.2%)	879
	No	122 (16.3%)	627 (83.7%)	
	5			
	Yes	69 (69.7%)	30 (30.3%)	885
	No	131 (16.7%)	655 (83.3%)	
	8			
	Yes	36 (75.0%)	12 (25.0%)	879
	No	117 (14.1%)	714 (85.9%)	

TABLE E2. Model fit results for the linear growth trajectory model and the quadratic growth trajectory model (log-likelihood, BIC, and number of model parameters or *df*) used

	Linear change trajectory			Quadratic change trajectory		
No. of classes	**LL**	**BIC**	***df***	**LL**	**BIC**	***df***
3	−4692.7	9573.4	20	−4641.8	9490.4	22
4	−4600.4	9417.0	23	−4585.3	9415.0	26
5	−4583.3	9411.1	26	−4573.6	9429.3	30
6	−4575.9	9424.4	29	−4550.6	9420.8	34
7	−4571.4	9443.5	32	−4538.0	9433.1	38

LL, Log-likelihood.

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TABLE E3. Relative risk ratios (95% CIs) of associates of different wheeze classes using children with "no wheezing" as the reference class in multinomial logistic regression

	NW (n = 632), baseline	TW (n = 162)		LOW (n = 198)		PCW (n = 155)		PTW (n = 38)				
Characteristics	**No. (%)**	**No. (%)**	**RRR (95% CI)**	**No. (%)**	**RRR (95% CI)**	**No. (%)**	**RRR (95% CI)**	**No. (%)**	**RRR (95% CI)**	**Total**	**χ_4^2 Statistic**	***P* value**
Sex										1185	35.76	<.001
Male	290 (45.9)	104 (64.1)	2.11 (1.48-3.02)	119 (60.1)	1.78 (1.28-2.46)	106 (68.4)	2.55 (1.76-3.70)	23 (60.5)	1.81 (0.93-3.53)			
P value			<.001		.001		<.001		.1			
Maternal asthma										1180	26.70	<.001
Yes	63 (10.0)	26 (16.1)	1.73 (1.05-2.83)	43 (21.9)	2.54 (1.66-3.89)	34 (22.4)	2.60 (1.64-4.13)	7 (18.4)	2.04 (0.86-4.82)			
P value			.030		<.001		<.001		.11			
Paternal asthma										1177	4.82	.306
Yes	43 (6.8)	7 (4.4)	0.62 (0.27-1.41)	19 (9.8)	1.48 (0.84-2.61)	12 (7.8)	1.16 (0.60-2.26)	4 (10.5)	1.61 (0.55-4.74)			
P value			.26		.17		.66		.39			
AHR at age 8 y										627	55.80	<.001
Positive	33 (9.9)	14 (16.9)	1.86 (0.94-3.66)	35 (31.8)	4.27 (2.49-7.32)	27 (35.5)	5.04 (2.79-9.11)	11 (47.8)	8.39 (3.43-20.50)			
P value			.073		<.001		<.001		<.001			
Doctor-diagnosed asthma (ever)										993	412.48	<.001
Yes	19 (3.4)	41 (31.5)	13.02 (7.23-23.5)	67 (45.0)	23.1 (13.2-40.4)	91 (72.2)	73.5 (40.3-134)	29 (90.6)	273 (76.4-976)			
P value			<.001		<.001		<.001		<.001			
Doctor-diagnosed asthma (age 8 y)										1000	300.86	<.001
Yes	1 (0.2)	3 (2.2)	12.8 (1.32-124)	35 (22.9)	165 (22.5-1222)	47 (38.8)	355 (48.3-2611)	26 (81.3)	2422 (281-20862)			
P value			.028		<.001		<.001		<.001			
Asthma treatment ever (GP)										916	417.14	<.001
Yes	79 (16.0)	79 (65.3)	12.4 (7.88-19.6)	113 (72.0)	12.4 (8.13-18.8)	107 (92.2)	72.7 (36.1-146.4)	27 (100.0)	NA (100%)			
P value			<.001		<.001		<.001					
Inhaled steroid ever										916	302.61	<.001
Yes	21 (4.2)	31 (25.6)	7.77 (4.28-14.1)	55 (35.0)	12.2 (7.05-21.1)	73 (62.9)	38.3 (21.5-68.2)	26 (96.3)	586 (76.0-4533)			
P value			<.001		<.001		<.001		<.001			

RRR, Relative risk ratio.

TABLE E4. MWDs for each wheeze class with 95% CIs

MWD	PTW (n = 38)	NW (n = 632)	TEW (n = 162)	LOW (n = 198)	PCW (n = 155)	Total	*P* value
Age 3 y							
All allergens						994	<.001
Mean MWD (mm)	6.62	1.09	1.08	2.82	2.86		
95% CI	2.88 to 10.36	0.85 to 1.33	0.58 to 1.58	2.03 to 3.61	1.80 to 3.91		
P value		<.001	<.001	.009	.013		
Inhalant allergens						994	<.001
Mean MWD (mm)	5.38	0.98	1	2.55	2.44		
95% CI	2.26 to 8.50	0.75 to 1.20	0.53 to 1.47	1.87 to 3.23	1.62 to 3.26		
P value		<.001	<.001	.018	.016		
Food allergens						992	.001
Mean MWD (mm)	1.24	0.12	0.08	0.27	0.42		
95% CI	0.20 to 2.28	0.06 to 0.18	0.00 to 0.17	0.07 to 0.48	0.04 to 0.80		
P value		<.001	.009	.032	.109		
Age 5 y							
All allergens						975	<.001
Mean MWD (mm)	8.89	1.67	1.25	3.75	4.5		
95% CI	5.48 to 12.27	1.32 to 2.02	0.70 to 1.80	2.82 to 4.68	3.24 to 5.76		
P value		<.001	<.001	.001	.009		
Inhalant allergens						975	<.001
Mean MWD (mm)	7.84	1.62	1.23	3.56	4.04		
95% CI	4.98 to 10.70	1.29 to 1.96	0.69 to 1.77	2.73 to 4.39	2.99 to 5.09		
P value		<.001	<.001	.001	.007		
Food allergens						955	<.001
Mean MWD (mm)	1.03	0.05	0.02	0.19	0.47		
95% CI	0.28 to 1.78	0.01 to 0.09	−0.02 to 0.07	0.01 to 0.37	0.05 to 0.89		
P value		<.001	.03	.044	.264		
Age 8 y							
All allergens						946	<.001
Mean MWD (mm)	9.83	1.64	2.01	4.83	4.07		
95% CI	6.34 to 13.33	1.32 to 1.96	1.18 to 2.84	3.77 to 5.89	2.78 to 5.37		
P value		<.001	<.001	.004	.001		
Inhalant allergens						946	<.001
Mean MWD (mm)	8.53	1.47	1.76	4.13	3.33		
95% CI	5.57 to 11.49	1.18 to 1.75	1.04 to 2.48	3.27 to 4.99	2.40 to 4.26		
P value		<.001	<.001	.002	<.001		
Food allergens						945	<.001
Mean MWD (mm)	1.3	0.17	0.25	0.7	0.75		
95% CI	0.23 to 2.37	0.09 to 0.25	0.04 to 0.47	0.35 to 1.05	0.20 to 1.30		
P value		<.001	.019	.249	.326		

P values indicate association of MWDs at ages 3, 5, and 8 years with different wheeze classes using children with PTW as the reference class in multinomial logistic regression.

TABLE E5. Mean *z* score for specific airway conductance (sGaw) at age 3 years and for FEV_1/FVC ratio at age 8 years for different wheeze classes using children with PTW as the reference class in multinomial logistic regression

	NW (53%)	TEW (13.7%)	LOW (17.0%)	PCW (13.1%)	PTW (3.2%)	Total	*P* value
z Score, sGaw (age 3 y)						629	<.001
Mean	−0.25	−0.27	−0.19	−0.33	−0.81		
95% CI	−0.33 to −0.16	−0.47 to 0.07	−0.44 to −0.07	−0.56 to −0.10	−1.50 to −0.12		
P value		<.001	<.001	<.001	<.001		
z Score, FEV_1/FVC (age 8 y)						697	<.001
Mean	0.18	−0.08	−0.13	−0.35	−0.85		
95% CI	0.09 to 0.27	−0.28 to 0.12	−0.33 to 0.08	−0.59 to −0.11	−1.35 to −0.34		
P value		.02	.002	<.001	<.001		

Results are presented as *z* scores to track change of impairment to lung function over time. sGaw is the reciprocal of sRaw, with lower sGaw values indicating poorer lung function.

TABLE E6. Relative risk ratios (95% CIs) showing associates at age 3 years of different wheeze classes using children with PTW as the reference class in multinomial logistic regression

	PTW (n = 38)	NW (n = 632)		TEW (n = 162)		LOW (n = 198)		PCW (n = 155)			
	No. (%)	No. (%)	RRR (95% CI)	No. (%)	RRR (95% CI)	No. (%)	RRR (95% CI)	No. (%)	RRR (95% CI)	Total	*P* value
Sex										1185	<.001
Male	23 (60.5)	290 (45.9)	0.55 (0.28-1.08)	104 (64.2)	1.17 (0.57-2.42)	119 (60.1)	0.98 (0.48-2.00)	106 (68.4)	1.41 (0.68-2.94)		
P value			.08		.67		.96		.36		
Eczema										1088	<.001
Yes	16 (61.5)	114 (19.1)	0.15 (0.07-0.33)	33 (21.6)	0.17 (0.07-0.41)	53 (30.1)	0.27 (0.11-0.63)	57 (42.2)	0.46 (0.19-1.08)		
P value			<.001		<.001		.003		.074		
Exacerbation										916	<.001
Yes	15 (55.6)	4 (0.8)	0.02 (0.01-0.07)	30 (24.8)	0.51 (0.37-0.72)	14 (8.9)	0.26 (0.16-0.41)	42 (36.2)	0.73 (0.54-0.98)		
P value			<.001		<.001		<.001		.037		
Sensitization											
Mite										980	<.001
Yes	8 (33.3)	44 (8.2)	0.18 (0.07-0.44)	14 (10.0)	0.22 (0.08-0.61)	34 (21.3)	0.54 (0.21-1.37)	21 (17.8)	0.43 (0.16-1.14)		
P value			<.001		.004		.19		.09		
Dog										982	<.001
Yes	7 (29.2)	17 (3.2)	0.08 (0.03-0.22)	5 (3.6)	0.09 (0.03-0.32)	15 (9.4)	0.25 (0.09-0.70)	17 (14.3)	0.40 (0.15-1.21)		
P value			<.001		<.001		.008		.08		
Cat										977	<.001
Yes	7 (29.2)	19 (3.5)	0.09 (0.03-0.24)	5 (3.6)	0.09 (0.03-0.32)	18 (11.4)	0.31 (0.11-0.86)	11 (9.3)	0.25 (0.09-0.73)		
P value			<.001		<.001		.024		.012		

RRR, Relative risk ratio.