

Phenotypes of childhood wheeze in Japanese children: A group-based trajectory analysis

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Abstract

Background: Exploring patterns of childhood wheeze may help to clarify the etiology and prognosis of respiratory diseases. The purpose of this study was to classify phenotypes of wheezing in children up to 9 years of age in Japan and to evaluate the individual and environmental risk factors for these phenotypes.

Methods: Wheeze was evaluated at approximately 1-year intervals based on the mothers' recollection of their child's wheezing or whistling in the chest during the preceding 12 months. The children were aged 1-9 years. In total, 1116 children who had at least five measures of wheezing at all nine time points were used for identifying trajectories. Trajectories were identified with group-based trajectory analysis. A multinomial logit model was built to evaluate the relationships between phenotypes and risk factors.

Results: Five typical trajectories were identified. The probability of group membership was 43.7%, 32.2%, 6.2%, 8.6%, and 9.2% for the never/infrequent wheeze, transient early wheeze, school-age-onset wheeze, early-childhood-onset remitting wheeze, and persistent wheeze trajectories, respectively. Infant tobacco exposure increased the odds of membership in the transient early wheeze trajectory compared to the never/infrequent wheeze trajectory.

Conclusions: Using the group-based trajectory modeling approach, we identified five trajectories of childhood wheeze development in a Japanese population. The trajectories shown here are based on formal statistical modeling rather than on subjective classification, and an assessment of its precision suggested that the model has high assignment accuracy.

KEYWORDS

asthma, birth cohort, phenotypes, trajectory, wheeze

1 | BACKGROUND

Asthma symptoms in childhood are heterogeneous. Exploring patterns of childhood wheeze may reveal clues to its etiology and help to clarify

the prognosis of respiratory diseases. Birth cohort studies provide a good opportunity for exploring the characteristics and heterogeneity of wheeze/asthma occurrence over time. Different phenotypes have been described based on the longitudinal data of childhood wheeze history. The Tucson Children's Respiratory Study made the first effort to classify phenotypes of asthma based on the clinical observations of wheezing. They proposed four trajectories: (i) non-wheeze, (ii) transient wheeze (iii) late-onset wheeze, and (iv) persistent wheeze.¹

Abbreviations: AvePP, average posterior probability; CI, confidence interval; GBTM, group-based trajectory modeling; ISAAC, International Studies of Asthma and Allergies in Childhood; OCC, odds of correct classification; OR, odds ratio; T-CHILD, Tokyo Children's Health, Illness and Development.

With improved statistical techniques, in recent decades, it has become possible to classify wheeze phenotypes objectively based on statistical modeling. For example, two important studies on patterns of wheezing during early childhood using latent class analysis were published in 2008² and 2011.³ Group-based trajectory modeling (GBTM) is a finite mixture modeling approach designed to identify groups of individuals following similar developmental trajectories.^{4–6} This method has been applied in psychology, medicine, and criminology over the past decade.^{7–18}

The purpose of this study was to classify trajectories of wheezing in children up to 9 years of age in Japan and to evaluate the individual and environmental risk factors for these trajectories.

2 | METHODS

2.1 | Data and definition

The data used for analysis were obtained from a hospital-based birth cohort study conducted in Tokyo. The study recruited 1701 pregnant women between 2003 and 2005. In total, 1550 babies were enrolled and followed up until the age of 13 years.¹⁹ Wheeze was assessed using the International Study of Asthma and Allergies in Childhood (ISSAC) questionnaire and evaluated at approximately 1-year intervals based on the mothers' recollection of children's wheezing or whistling in the chest during the preceding 12 months. The children were aged 1–9 years. In total, 1116 children had at least five measures of wheezing at all nine time points, and their data were used to identify trajectories.

2.2 | Statistical analysis

Trajectories were identified with the GBTM approach (see detailed description in Appendix S1). The Bayesian information criterion (BIC) was used for model selection. The model with the larger BIC score was regarded as superior. Model selection consisted of two steps, namely estimating the number of trajectories and deciding the shape of each trajectory. We started searching at the first step by specifying all the groups as cubic trajectories. Statistical and prior knowledge of the wheeze phenotypes was used to decide the number and the order of the trajectories.

Model accuracy was evaluated using a 98% CI for the estimated group membership probability, proportion of the sample assigned to the trajectory, average posterior probability of membership (*AvePP*), and odds correct classification (*OCC*; see detailed description in Appendix S1). The threshold for the average posterior probability of group membership was 0.7.⁴ An *OCC* greater than 5 indicated high assignment accuracy.⁴

The profiles of the trajectories were summarized by a cross-table with trajectory assignment and individual characteristics that might be associated with trajectory membership. We used the variables of gender, parental history of asthma, infant tobacco exposure, sensitization to common allergens at 5 and 9 years old, history of asthma, inhaled corticosteroid use, and current asthma

at 9 years old. Data on “sensitization to any common allergen” were obtained from IgE tests of the serum samples from participants. Positive IgE meant an IgE level of ≥ 0.3 ISAC standardized units (ISU). Sensitization was defined as a positive result for any single allergen.¹⁹

Finally, we also built a multinomial logit model linking covariates to evaluate the relationship between the phenotypes and risk factors. In the model extending to covariates, we incorporated gender, parental history of asthma, and infant tobacco exposure. Due to the limited sample size, we only included the three variables in the models and did not perform a variable selection.

All the analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC). SAS Traj, an SAS macro, which estimates a discrete mixture model for clustering of longitudinal data series, was used for all modeling processes (<https://www.andrew.cmu.edu/user/bjones/>).

2.3 | Ethical approval

All participants gave their written informed consent. The Tokyo Children's Health, Illness and Development Study (T-CHILD) was approved by the hospital ethics committee at NCCHD (no. 52).

3 | RESULTS

The basic characteristics of 1116 participants are shown in Table 1. The prevalence of wheeze peaked at 24.2% at 2 years of age and then declined. At age 9 years, the prevalence rate declined to 9.3%.

The trajectories are presented in Figure 1. These trajectories were developed based on equation 4 (Appendix S1) with estimated parameters. The model-estimated group membership probability is shown in Figure 1. We found five typical trajectories. The “never/infrequent wheeze” trajectory comprised children who displayed little or no wheeze during childhood. This trajectory was estimated to comprise 43.7% of the population. A second trajectory, named the “transient early wheeze,” made up 32.2% of the population; wheeze occurred at an early age in this trajectory. The probability of wheezing peaked at age 1–2 years (around 0.4) and almost disappeared after age 5 years. A third trajectory, making up about 6.2% of the population, was labeled “school-age-onset wheeze.” The probability of wheezing remained low before the age of 3 years, increased between the ages of 4 and 5 years, peaked at 7 years (with probability of wheeze around 0.5), and then decreased to 0.2 by 9 years. The fourth trajectory, which included 8.6% of the population, was called “early-childhood-onset remitting wheeze.” The probability of wheezing in this trajectory increased from age 1 year and peaked at age 4 years with a probability of nearly 0.7 and nearly disappeared by school age. Finally, there was the “persistent wheeze” trajectory constituting 9.2% of the population. Members in this trajectory showed a high probability of wheeze throughout the observation period.

TABLE 1 Children with at least 5 responses for wheeze between 1 and 9 y

Characteristic	Children with at least five responses		
	Total	n	%
Gender (girls)	1116	551	49.4
Parental history of asthma	1116	250	22.4
Infant tobacco exposure	1116	375	33.6
Asthma history at 0-6 y old ^a	1030	165	16
Sensitization to common allergens at 5 y old	907	524	57.8
Sensitization to common allergens at 9 y old	706	525	74.4
Current asthma at 9 y old	870	75	8.6
Asthma history at 0-9 y old ^b	871	159	18.3
Inhaled corticosteroid use at 0-9 y old	868	151	17.4
Prevalence of wheeze			
1 y	1099	223	20.3
2 y	1098	266	24.2
3 y	1058	166	15.7
4 y	1056	171	16.2
5 y	1088	184	16.9
6 y	1029	144	14.0
7 y	878	111	12.6
8 y	866	90	10.4
9 y	871	81	9.3

^aA positive answer from the caregiver to the question (child at 6 y old): "Has your child ever received the diagnosis of asthma from a doctor?".

^bA positive answer from the caregiver to the question (child at 9 y old): "Has your child ever had asthma?".

Table 2 shows the assignment accuracy for the trajectories of childhood wheeze. Comparison of a sample proportion of those assigned to the trajectory with the model-estimated membership probability of the trajectories showed good correspondence between the two statistics. The threshold of AvePP of membership (0.7) was achieved for all five trajectories in this study. All OCC were higher than 5 (range: 5.9-110.5), implying a high assignment accuracy of the fitted model.

Table 3 shows the summary statistics of the individual characteristics by individual-level trajectory assignments. Some 45.9% of individuals in the persistent wheeze trajectory had a family history of asthma. Conversely, this figure was only 17.6% in the "never/infrequent wheeze" trajectory. Compared with other trajectories, tobacco exposure in the infant period was more prevalent in the transient early wheeze and persistent wheeze trajectories with a proportion of 38.6% and 36.7%, respectively, vs approximately 30% in the three other trajectories. Children among the early-childhood-onset remitting wheeze and persistent wheeze trajectories were more likely to have a history of asthma and inhaled corticosteroid use. Some 44.9% of individuals in the persistent wheeze trajectory suffered asthma at age 9 years, whereas the other trajectories showed a rate below 20%. In the persistent wheeze trajectory, 80.2% of individuals were found to have become sensitized to common allergens at age 5 years.

Table 4 shows the results of the association of the risk factors with trajectory membership. The never/infrequent wheeze trajectory was the comparison group. Infant tobacco exposure increased the odds of classification in the transient early wheeze trajectory and persistent trajectory rather than the never/infrequent wheeze trajectory (OR = 1.49, 95% CI (1.02-2.20) and 1.59 (0.94-2.62), respectively). Children whose parents had asthma were more likely to belong to the "early-childhood-onset remitting" (OR = 2.22, 95% CI (1.17-4.22)) and "persistent wheeze" trajectories (OR = 4.77, 95% CI (2.83-8.05)) than the never/infrequent trajectory; the magnitude of the effect size was largest for the persistent wheeze and smallest for early-transient wheeze.

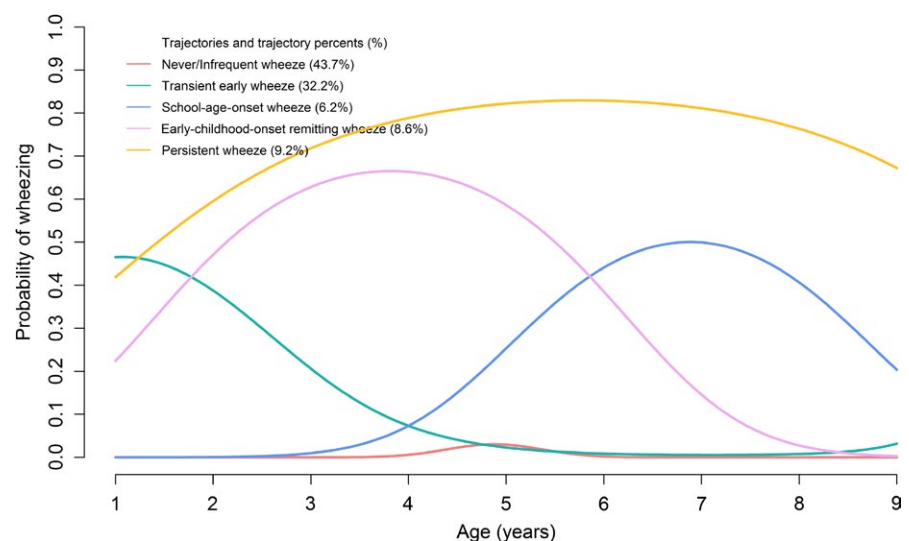
FIGURE 1 Estimated prevalence of wheezing at each time point from 1 to 9 y for each of the 5 wheezing phenotypes identified by group-based trajectory analysis of 1116 children

TABLE 2 Diagnostics of assignment accuracy

Trajectories	Estimated group membership- probability (π_j) %	98% CI for π_j %	Proportion of the sample assigned to the trajectory %	Average posterior probability of membership (AvePP _j) %	Odds correct classification (OCC _j)
Never/Infrequent wheeze	43.7	38.8-48.6	52.7	82.1	5.9
Transient early wheeze	32.2	26.4-38.1	25.5	92.0	24.2
School-age-onset	6.2	3.5-8.9	5.2	82.4	70.8
Early-childhood-onset remitting	8.6	4.5-12.8	7.8	77.1	35.8
Persistent wheeze	9.2	7.0-11.3	8.8	91.8	110.5

4 | DISCUSSION

Childhood is an important time for the development of asthma. Clarifying phenotypes of asthma in this period is important for understanding the pathways of the development of this disease.^{20,21} Although childhood wheezing phenotypes have been described by other research groups, this is the first study to use GBTM to clarify wheezing trajectories in a Japanese population.

The GBTM approach model repeatedly measured wheezing data rather than subjective definitions of subtypes of wheeze, allowing researchers to find unexpected potential trajectories that may have been overlooked.⁴ Expanding the GBTM with covariates also allows researchers to estimate the effect of risk factors on a specific trajectory.⁴ In addition, the profile characteristics of trajectories are presented in a tabular format, which can be easily understood and facilitates discussion with other researchers.⁴

Published studies have reported 4–6 wheeze/asthma phenotypes. For example, Caudri et al studied wheezing phenotypes in the first 8 years of life and showed five wheezing phenotypes. The never/infrequently wheezing subgroup included 75% of all children. Some 16.7% of children belonging to the largest group had transient early wheeze. The three other subtypes included intermediate-onset wheeze (3.1%), persistent wheeze (3.5%), and late-onset wheeze (1.7%).²² Henderson et al² identified six phenotypes among children in the first 6 years of life. Savenije et al³ reported a six-class model with data obtained from 5760 children followed from birth to 8 years of age and a 5-class model based on 2810 children from another cohort study. Another study classifying wheeze type was conducted by Chen et al,²³ who analyzed 689 U.S. children aged 3–108 months and identified four wheeze phenotypes: never/infrequent (47.1%), early-transient (37.5%), early-persistent (7.6%), and late-onset (7.8%). In 2017, Sbihi et al reported asthma trajectories based on a population-based birth cohort of more than 65 000 children in Canada. They distinguished four trajectories for children aged 0–10 years: (i) no asthma, representing 88.8% of the cohort, (ii) transient asthma (5.6% of the cohort), (iii) early-onset chronic asthma (<1 year; 1.5%), and (iv) late-onset chronic asthma (<3 year; 4.1%) during early childhood.⁶ Although we used a different model and data, we validated these published phenotypes in the current study. In keeping with the previously published wheeze phenotype taxonomy, we defined these trajectories as never/infrequent wheeze, transient early wheeze, school-age-onset, early-childhood-onset remitting wheeze, and persistent wheeze.

We believe these trajectories, based on the profiles of the trajectories and the models with covariates, are sound. For example, as shown in Table 3, we found that “a history of asthma,” “current asthma at 9 years old,” and “inhaled corticosteroid use” each comprised a very small proportion of the never/infrequent wheeze trajectory but a high proportion of the early-childhood-onset remitting and persistent wheeze trajectories. In addition, the transient early wheeze and persistent wheeze trajectories had a high proportion of infant tobacco exposure, implying that tobacco exposure during early life had a larger effect on these trajectories. The model with risk factors further confirmed this implication. The coefficients of the model indicated that

TABLE 3 Patient characteristics by trajectory

	N	Never/Infrequent wheeze	Transient early wheeze	School-age-onset	Early-childhood-onset remitting	Persistent wheeze
Gender (girls)	1116	54.8%	45.6%	44.8%	43.7%	35.7%
Parental history of asthma	1116	17.2%	22.5%	31.0%	25.3%	45.9%
Infant tobacco exposure	1116	31.5%	38.6%	29.3%	31.0%	36.7%
Asthma history at 0-6 y old ^a	1030	1.7%	10.3%	31.5%	53.0%	76.4%
Sensitization to common allergens at 5 y old	907	51.4%	53.9%	72.9%	75.0%	80.2%
Sensitization to common allergens at 9 y old	706	66.9%	75.4%	85.4%	87.7%	89.7%
Current asthma at 9 y old	870	2.5%	4.0%	15.2%	11.1%	44.9%
Asthma history at 0-9 y old ^b	871	1.4%	11.5%	41.3%	52.8%	78.7%
Inhaled corticosteroid use at 0-9 y old	868	3.0%	8.5%	37.0%	45.8%	78.4%

^aA positive answer from the caregiver to the question (child at 6 y old): "Has your child ever received the diagnosis of asthma from a doctor?".

^bA positive answer from the caregiver to the question (child at 9 y old): "Has your child ever had asthma?".

TABLE 4 Predictors and trajectory in multinomial logit model linking group membership to covariates (N = 1116)

	Transient early wheeze ^a		School-age-onset ^a		Early-childhood-onset remitting ^a		Persistent wheeze ^a	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Gender (girls vs boys)	0.62 (0.43-0.90)	.01	0.62 (0.32-1.20)	.15	0.53 (0.30-0.95)	.03	0.37 (0.22-0.64)	<.001
Parental history of asthma	1.43 (0.88-2.33)	.15	2.07 (0.92-4.68)	.08	2.22 (1.17-4.22)	.02	4.77 (2.83-8.05)	<.001
Infant tobacco exposure	1.49 (1.02-2.20)	.04	1.04 (0.50-2.15)	.92	0.88 (0.46-1.71)	.71	1.57 (0.94-2.62)	.08

OR, odd ratio; CI, confidence interval.

^aNever/infrequent wheeze was the reference group

infant tobacco exposure significantly increased the likelihood of membership in the transient early wheezing trajectory. Increased odds also occurred in the persistent wheeze group.

The findings of this report should be interpreted cautiously. First, identification of the wheeze trajectory was based on parents' reports, which are subject to recall bias. Inhaled corticosteroid use might have influenced the symptoms of wheeze, and although this treatment intervention might have affected group classification of wheeze trajectories, we do not think it led to substantially biased results as only a few subjects used inhaled corticosteroids without

reporting wheeze symptoms in this cohort. Second, although the profile of trajectory membership implied risk factors for the trajectories, traditional statistical methods such as the *F* test and chi-square test cannot be used to test for significance of cross-group differences because of the uncertainty of the classifications. However, the association of individual-level covariates with trajectory membership and trajectory parameters was estimated simultaneously.⁴ Therefore, there was no problem with classification errors in the modeling process linking covariates. Third, the small sample size limited our ability to include more variables in the expanding model with risk factors.

Other demographic and socioeconomic factors associated with these trajectories remain to be studied. In addition, this is a hospital-based study; as such, generalization of the results to the entire population must be done with caution.

5 | CONCLUSION

Using the group-based trajectory modeling approach, we identified five trajectories of childhood wheeze development in a Japanese population. The trajectories shown here are based on formal statistical modeling rather than on subjective classification, and an assessment of its precision suggested that the model had high assignment accuracy.

CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design and concept, statistical analysis, and writing/review of manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supplement

Statistical details of building group-based trajectory model

Trajectories were identified with the GBTM approach (1). Parameters of the model were estimated based on maximum likelihood estimation. Let $Y_i = \{y_{i1}, y_{i2}, \dots, y_{it}\}$ denote a longitudinal observation of measurement of individual i over T periods. $P(Y_i)$ denotes the unconditional probability of Y_i . $P(Y_i)$ is the sum of all groups with the probability of Y_i given membership in group j ($P^j(Y_i)$) multiplying the probability of belonging to a group for an individual from the population (π_j).

$$P(Y_i) = \sum_j^J \pi_j P^j(Y_i) \quad 1)$$

For a given j , conditional independence is assumed for y_{it} over T periods of measurement. Thus the $P^j(Y_i)$ can be written as a product of a sequence of terms with the probability distribution function of y_{it} conditional on membership in group j ($p^j(y_{it})$).

$$P^j(Y_i) = \prod_1^T p^j(y_{it}) \quad 2)$$

The likelihood of all individuals (N) is the product of the each unconditional individual likelihood ($P(Y_i)$).

$$L = \prod_1^N P(Y_i) \quad 3)$$

In the current study, the dependent variable Y_i was a longitudinal observation of wheezing in individual i at each survey (children aged 1-9 years). The probability distribution of Y_i was specified as the binary logit distribution due to a dichotomous outcome variable, and the subjects who met the wheeze definition at each measurement point during follow-up were the outcome event.

The model comprised two components: one was the expected trajectory for each group (probability of wheezing in the current study), and the other was the probability of group membership in each group (π_j). Trajectory shape was determined in terms of a polynomial function of age defined by the parameters. For example, for a cubic trajectory, there are four parameters, $\beta_0^j, \beta_1^j, \beta_2^j, \beta_3^j$, and the trajectory for a binary logistic model can be calculated by

$$P^j(y_t = wheezing) = \frac{e^{\beta_0^j + \beta_1^j Age_{it} + \beta_2^j Age_{it}^2 + \beta_3^j Age_{it}^3}}{1 + e^{\beta_0^j + \beta_1^j Age_{it} + \beta_2^j Age_{it}^2 + \beta_3^j Age_{it}^3}} \quad 4)$$

The Bayesian Information Criterion (BIC) was used for model selection. Model accuracy was evaluated using a 98% CI for estimated-group membership probability, the proportion of the sample assigned to the trajectory, average posterior probability of membership (*AvePP*), and odds correct classification (*OCC*). The posterior probability of group membership ($\hat{P}(j|Y_i)$) predicted the probability of membership of individual i 's in each group (j), given the observed outcome in each of the t assessment periods (Y_i). The posterior probability of group membership was calculated after the model parameters were decided.

$$\hat{P}(j|Y_i) = \frac{\hat{P}(Y_i|j)\hat{\pi}_j}{\sum_j \hat{P}(Y_i|j)\hat{\pi}_j} \quad 5)$$

where $\hat{P}(Y_i|j)$ can be calculated directly based on coefficients of the fitted model. Odds of correct classification is defined as the ratio of the odds of a correct classification based on the maximum probability classification rule to the odds of a correct classification based on random assignment with the probability of the estimated population based rate (1).

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