Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA

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Background: Asthma has its origins in early childhood, but different patterns of childhood wheezing vary in their associations with subsequent asthma, atopy, and bronchial hyperresponsiveness (BHR). Novel wheezing phenotypes have been identified on the basis of analyses of longitudinal data from the Avon Longitudinal Study of Parents And Children (ALSPAC). It is unclear whether these phenotypes can be replicated in other birth cohorts.

Objective: To compare wheezing phenotypes identified in the first 8 years of life in the ALSPAC study and the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study.

Methods: We used longitudinal latent class analysis to identify phenotypes on the basis of repeated reports of wheezing from 0 to 8 years in 5760 children from the ALSPAC study and 2810 children from the PIAMA study. Phenotypes were compared between cohorts. Associations with asthma, atopy, BHR, and lung function were analyzed by using weighted regression analyses.

Results: The model with the best fit to PIAMA data in the first 8 years of life was a 5-class model. Phenotypes identified in the PIAMA study had wheezing patterns that were similar to those previously reported in ALSPAC, adding further evidence to the existence of an intermediate-onset phenotype with onset of wheeze after 2 years of age. Associations with asthma, atopy, BHR, and lung function were remarkably similar in the 2 cohorts.

Conclusion: Wheezing phenotypes identified by using longitudinal latent class analysis were comparable in 2 large birth cohorts. Study of genetic and environmental factors associated with different phenotypes may help elucidate the origins of asthma. (J Allergy Clin Immunol 2011;127:1505-12.)

Key words: *Asthma, preschool children, latent class analysis, phenotype*

It has been reported that the early-life period is important for the development of asthma.[1,2] However, asthma symptoms are heterogeneous in early childhood.[3,4] Identification of different subtypes of asthma in early life is important to study potential pathways of asthma development.[5,6] Different asthma-related phenotypes have been categorized in early childhood by using longitudinal analyses of wheezing history. The Tucson Children's Respiratory Study (TCRS) group identified different patterns of wheeze in early childhood on the basis of clinical observations.[7] They presented 4 wheezing phenotypes (never wheeze, transient early wheeze, late-onset wheeze, and persistent wheeze), and it has been shown by many research groups that these phenotypes differ in risk factors for asthma development,[8-14] lung function,[10,15-19] atopy development,[10,11,19,20] number of encountered viral infections at a young age,[21] genetic polymorphisms,[15,22-24] and gene expression.[25] Although these phenotypes have served as a useful model in the past decade, they may give an incomplete description of the heterogeneity in wheezing phenotypes during childhood.[26]

Two British cohort studies have used latent class analysis to identify distinct phenotypes underlying the observed heterogeneity in asthma symptoms during childhood.[27,28] A population-based cohort from Leicester identified 3 wheezing and 2 coughing phenotypes in 319 children of 0 to 5 years on the basis of characteristics of wheeze and cough, skin prick test results, lung function, and bronchial hyperresponsiveness (BHR).[27] A birth cohort study of 6265 children, the Avon Longitudinal Study of Parents And Children (ALSPAC), identified 6 wheezing phenotypes in childhood from birth to age 7 years and demonstrated that these phenotypes differed in atopy prevalence and lung function levels at 7 to 8 years of age.[28] It is unclear whether phenotypes identified by latent class analysis are comparable between birth cohorts observed in different areas or countries, particularly because the number and timing of measurements, definitions of

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Abbreviations used
ALSPAC: Avon Longitudinal Study of Parents And Children
BHR: Bronchial hyperresponsiveness
BIC: Bayesian information criterion
BLRT: Bootstrap likelihood ratio test
LLCA: Longitudinal latent class analysis
OR: Odds ratio
PIAMA: Prevention and Incidence of Asthma and Mite Allergy
TCRS: Tucson Children's Respiratory Study

wheeze, and population characteristics may differ between studies.

The aim of this study was to classify phenotypes of wheezing up to 8 years of age in the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study and to compare these with wheezing phenotypes of the ALSPAC study. We examined associations of wheezing phenotypes with asthma, atopy, BHR, and lung function at age 8 years in PIAMA and compared these with the associations previously reported in ALSPAC.[28]

METHODS

Study populations: ALSPAC and PIAMA

ALSPAC is a population-based birth cohort study that recruited 14,541 pregnant women resident in Avon, United Kingdom, during 1991 and 1992.[29,30] Study mothers were sent a self-completion questionnaire about the health of their children at 6, 18, 30, 42, 54, 69, 81, and 91 months after birth. The study protocol was approved by the ALSPAC Law and Ethics Committee (Institutional Review Board 00003312) and the local research ethics committee.

PIAMA is a multicenter birth cohort study that selected 4146 pregnant women (1327 with and 2819 without allergy) in The Netherlands in 1996 and 1997.[31] Parents were sent a self-completion questionnaire about the health of their children at 3, 12, 24, 36, 48, 60, 72, 84, and 96 months after birth. At 4 years and 8 years, children participated in a clinical examination. The study protocol was approved by the medical ethics committees of the participating institutions.

Data on wheezing were collected at approximately 12-month intervals on the basis of parental recall of wheezing during the preceding 12 months. In ALSPAC, wheezing definitions were used as reported previously.[28] A total of 11,740 children (80.7% of the original population) had at least 2 measures of wheezing, and 5,760 (39.6% of the original population) had complete reports of wheeze at all 8 time points. In PIAMA, wheezing was defined to be present when 2 subsequent questions were answered positively: "Has your child ever had wheezing or whistling in the chest at any time in the past?" and "Has your child had wheezing or whistling in the chest in the past 12 months?" A total of 3789 children (91.4% of the original population) had returned at least 2 questionnaires in PIAMA, and 2810 (67.8% of original population) had complete reports of wheeze at all 8 time points.

For comparison of PIAMA with ALSPAC, we used wheezing reports at 8 time points in PIAMA (12, 24, 36, 48, 60, 72, 84, and 96 months). These are offset from the ALSPAC time points by a maximum of 6 months (6, 18, 30, 42, 54, 69, 81, and 91 months). Outcome measures of asthma in the PIAMA study are described in the Methods section in this article's Online Repository at www.jacionline.org.

Statistical analysis

Longitudinal latent class analysis (LLCA) attempts to explain the associations between wheeze at different time points by identifying population phenotypes (latent classes) within which the occurrence of wheeze at each time point is statistically independent of wheeze at other times. A latent class model estimates 2 sets of parameters: (1) conditional probabilities of wheeze at each time point given membership of a phenotype, and (2) the posterior probabilities of phenotype membership for each child given the child's wheezing history. A full description of LLCA modeling is given in the Online Repository. We plotted the conditional probability of wheeze over time for each phenotype.

We compared phenotypes in PIAMA with those in ALSPAC in a 2-step approach: (1) derivation of the best fitting model (optimal model) by unrestricted LLCA of PIAMA data and (2) derivation of a constrained model by fixing a subset of the parameters to correspond to the phenotypes found in ALSPAC (see the Online Repository for additional details). To assess model fit, we used (1) the Bayesian information criterion (BIC), a function of the likelihood that rewards parsimony; (2) entropy, an assessment of model classification based on the posterior class membership probabilities; and (3) the bootstrap likelihood ratio test (BLRT),[32] a test of an improvement in fit between the *n* and *n-1* class models (see the Online Repository for details). Models derived by using PIAMA data were compared with those in ALSPAC in terms of goodness-of-fit statistics, wheezing patterns assigned to each phenotype, trajectories of the conditional probability of wheezing for each phenotype, and the prevalence of corresponding wheezing phenotypes.

It is important that statistical analyses account for correlations between repeated measurements made over time. Our approach accounted for repeated reports of wheezing up to age 96 months by using longitudinal latent class analyses, which model correlations between wheezing at different times and account for these in defining the latent classes (phenotypes).

Associations of wheezing phenotypes with subsequent asthma, atopy, and BHR were examined by using regression models that were weighted according to each individual's posterior probability of belonging to each phenotype. For example, a child might have a posterior probability 0.9 of persistent wheeze and a posterior probability 0.1 of transient early wheeze. In regression analyses, this child would contribute 2 lines of data, the first for persistent wheeze with weight 0.9 and the second for transient early wheeze with weight 0.1. For binary (dichotomous) outcomes, odds ratios (ORs) with 95% CIs were estimated by using weighted logistic regression models, whereas for continuous outcomes, mean differences with 95% CIs were estimated by using weighted linear regression models. Bronchial responsiveness was transformed to a dose-response slope by regressing FEV_1 change from baseline against dose of methacholine. The resulting slopes were log-transformed for regression analyses. Means of log slopes and mean differences between phenotypes were exponentiated and presented as geometric means and ratios of geometric means, respectively. In all regression models, never/infrequent wheeze was the reference group. Latent class analyses were performed with Mplus 4.1 software (2006; Muthen & Muthen, Los Angeles, Calif), and weighted linear and logistic regression models were fitted by using Stata/MP 10.0 (2007; StataCorp, College Station, Tex; see the Online Repository for further detailed descriptions).

Primary analyses reported in the main manuscript were based on children with complete reports of wheezing at each time. To evaluate potential bias as a result of children with missing reports of wheeze, we repeated all analyses in children with at least 2 observations of wheeze. For comparison, we present repeated analyses in the Online Repository including children with a minimum of 2 reports of wheeze.

RESULTS

Characteristics of the study population of the ALSPAC study and the PIAMA study are shown in Table I. In ALSPAC, 11,740 children returned at least 2 questionnaires, and 5760 (49.1%) had complete reports of wheeze at all 8 time points. Children with complete data were less likely than children with incomplete data to wheeze during childhood and to have a mother with atopy. In PIAMA, 3789 children returned at least 2 questionnaires, and 2810 (74.2%) had complete reports of wheeze. Children with complete data were less likely to wheeze during childhood, to have had asthma by 8 years, or to have a mother with asthma and/or atopy compared with children with incomplete data.