Early-Life Risk Factors for Childhood Wheeze Phenotypes in a High-Risk Birth Cohort

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Objective To define longitudinal childhood wheeze phenotypes and identify their early-life risk factors.

Study design Current wheeze was recorded 23 times up to age 7 years in a birth cohort at high risk for allergy (n = 620). Latent class analysis of wheeze responses identified 5 classes. Multinomial logistic regression estimated associations of probability-weighted wheezing classes with early-life factors. All phenotypes were compared with never/infrequent wheezers.

Results Lower respiratory tract infection (LRTI) by 1 year (relative risk [RR], 3.00; 95% CI, 1.58-5.70), childcare by 1 year (RR, 1.51; 95% CI, 1.02-2.22), and higher body mass index (RR, 2.51; 95% CI, 1.09-5.81) were associated with increased risk of early transient wheeze, whereas breastfeeding was protective (RR, 0.54; 95% CI, 0.32-0.90). LRTI (RR, 6.54; 95% CI, 2.55-16.76) and aeroallergen sensitization (RR, 4.95; 95% CI, 1.74-14.02) increased the risk of early persistent wheeze. LRTI (RR, 5.31; 95% CI, 2.71-10.41), eczema (RR, 2.77; 95% CI, 1.78-4.31), aeroallergen sensitization (RR, 5.60; 95% CI, 2.86-10.9), and food sensitization (RR, 2.77; 95% CI, 1.56-4.94) increased the risk of intermediate-onset wheeze, whereas dog exposure at baseline (RR, 0.52; 95% CI, 0.32-0.84) and first-born status (RR, 0.49; 95% CI, 0.32-0.76) were protective. Heavy parental smoking at birth (RR, 3.18; 95% CI, 1.02-9.88) increased the risk of late-onset wheeze, whereas breastfeeding reduced it (RR, 0.34; 95% CI, 0.12-0.96). All wheeze classes except early transient had greater risk of wheeze at age 12 years compared with never/infrequent wheezers.

Conclusion We found distinct early-life risk factor profiles for each wheeze phenotype. These findings provide insight into possible wheeze mechanisms and have implications for identifying preventive strategies and addressing clinical management of early-life wheeze. *(J Pediatr 2014;164:289-94)*.

Childhood asthma is a global problem and the leading cause of childhood morbidity in many Western countries, including Australia. Despite extensive worldwide research, there has been little progress in elucidating causes or developing effective preventive strategies.[1] Asthma is a heterogeneous disorder characterized by phenotypes of variable age of onset and age of remission and possibly associated with different environmental and genetic factors.[1,2] Improved classification of childhood wheeze phenotypes is a preliminary step in focused research on etiology, pathophysiology, and long-term prognosis, along with the possibility of phenotype-specific therapies and preventive strategies.[3]

Birth cohorts have traditionally classified children into 4 wheeze categories based on follow-up time—nonwheezers, early transient wheezers, late-onset wheezers, and persistent wheezers—with different relationships with atopy, lung function, and maternal smoking.[4-7] Recently, childhood wheeze phenotypes have been determined using latent class analysis (LCA), which aims to identify distinct underlying (or latent) groups based on patterns of wheeze over time.[8] These analyses have identified additional phenotypes, such as intermediate-onset wheeze and prolonged early wheeze have not been established. However, the potential etiological factors associated with these newly defined phenotypes have not been established and their clinical relevance is not clear. The Melbourne Atopy Cohort Study (MACS), a high-allergy-risk birth cohort, collected frequent prospective wheeze data over the first 7 years of age, along with follow-up at age 12 years. We aimed to establish wheeze phenotypes using LCA up to age 7 years, based on multiple prospective wheeze assessments in this cohort, and to

BMI	Body mass index
LCA	Latent class analysis
LRTI	Lower respiratory tract infection
MACS	Melbourne Atopy Cohort Study
RR	Relative risk

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investigate the relationships of these phenotypes with early-life exposures and wheeze at age 12 years.

Methods

The MACS began as a randomized controlled trial investigating associations between 3 infant formulas at weaning on subsequent allergies.[9] It comprised 620 infants enrolled by recruiting pregnant women from Melbourne, Australia between 1990 and 1994. Eligible infants had at least 1 first-degree family member with a history of eczema, asthma, allergic rhinitis, and/or severe food allergy. The recruitment process has been described previously.[10] The Mercy Maternity Hospital Ethics Committee approved the study. All mothers provided written informed consent.

Allergy-trained research nurses conducted telephone surveys with the infants' mothers every 4 weeks from birth to age 15 months, once at age 18 months, yearly at age 2-7 years, and once at 12 years. The mothers reported days of cough, rattle, and wheeze experienced during the previous 4 weeks on 18 separate occasions over the first 2 years (following the foregoing schedule). More than 8 days in a 4-week period was considered abnormal, exceeding days of expected symptoms from routine childhood infection,[11] and was defined as wheeze. Wheeze between 3 and 7 years was defined as any positive answer to: "How many episodes of asthma has your child had in the past 12 months?" Current wheeze at 12 years was a positive answer to: "Have you/has your child ever had wheezing or whistling in the chest in the past 12 months?"[12]

Potential early-life risk factors, defined as below, were chosen based on reported associations with early-life wheeze: parental asthma, education, and smoking; infant sex and 4-week weight; breastfeeding for ≥3 months; adiposity (2-year body mass index [BMI]); child atopy, defined as sensitization (food at 1 year, aeroallergen at 2 years, capturing the earliest/most prevalent) and early eczema (6 months as a strong indicator of allergic predisposition); exposure to cats and/or dogs; lower respiratory tract infection (LRTI) in the first year; first-born status; and childcare attendance by age 12 months.

Standardized techniques (Bayer, Spokane, Washington) were used to test for cow's milk, egg white, peanut, house dust mite, rye grass, and cat dander allergies at age 1 and 2 years.[13] A positive skin prick test was defined as a mean wheal diameter of ≥3 mm. Aeroallergen-only and food allergen–only variables excluded those infants sensitive to both.

Parental smoking, parental asthma, presence of pets at birth, first-born status, and parental education were defined by responses to the baseline questionnaire completed at birth. Parental education, as a proxy for socioeconomic status, was defined as neither parent vs 1 or both parents having studied at a tertiary level. Parental smoking was positive if either parent smoked at baseline. Heavy parental smoking was defined as ≥10 cigarettes/day.

LRTI was defined by parental report of a doctor's diagnosis in the first year. Breastfeeding for ≥3 months was defined as any breastfeeding at or beyond 3 months regardless of food intake. Eczema by age 6 months was defined as a doctor's consultation for eczema or any rash treated with steroid cream by 6 months (excluding rashes confined to the scalp or diaper area). Overweight at 2 years was defined as BMI (weight in kilograms/height in meters squared) corresponding to an adult BMI of ≥25 kg/m^2 according to standard international definitions.[14] Underweight at 4 weeks, previously associated with asthma,[15] was defined as <10th percentile using World Health Organization/Centers for Disease Control and Prevention charts. Childcare attendance by 1 year was defined by the questionnaire response.

In randomized controlled trials where the randomization does not affect the outcomes of interest, the study may be considered an observational birth cohort.[16,17] A recently published article from the MACS using an intention-to-treat analysis showed no difference in allergic disease outcomes among the 3 groups (cow's milk formula, soy formula, and partially hydrolyzed whey formula).[9] Despite this, the effect of an intervention formula (by intention to treat at baseline) was considered for inclusion as a confounder in all models.

Two-sample comparison tests were used to calculate the potential differential loss to follow-up. LCA (using Mplus 6; Muthén & Muthén, Los Angeles, California) was performed to determine the optimal number of latent wheeze classes using 23 wheeze data points over the first 7 years of life. LCA fitted a mixture model to the longitudinal data using maximum likelihood estimation via numerical integration. Two sets of variables were estimated: conditional probabilities (ie, probability of wheeze at each time point within a known wheezing class) and posterior probabilities (ie, probability of membership of each class for a given wheeze history). LCA accounted for correlations between repeated measures of wheeze for each child when defining latent classes.

Wheeze models of 1-6 latent classes were assessed for best fit using the bootstrap likelihood ratio test, which measures the difference in model fit between n and n minus 1 classes. This test is considered the most robust of the measures of fit for LCA.[18] Associations between the wheezing classes (nominal outcome) and each early-life risk factor (binary covariate) were analyzed by weighted multinomial logistic regression (using Stata 11.0; StataCorp, College Station, Texas), with weights equal to the probability of membership of each wheeze phenotype for each child (estimated from LCA analysis). A priori confounders were sex and parental education. Multinomial logistic regression was used to examine potential mediation between early-life factors.

Mediation describes an intervening condition between exposure and outcome necessary for the outcome to occur. Mediation analysis was undertaken for specific early-life variables for which both temporality of associations and biologic mechanisms were plausible. It is rarely possible to disentangle mediation from confounding. The principal mediator tested was aeroallergen sensitization as an intermediary between LRTI and wheeze. Allergen sensitization in the context of eczema and wheeze was tested as well. Missing information on wheeze was handled as missing completely at random.