

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

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

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/m² according to standard international definitions.¹⁴ Underweight at 4 weeks, previously associated with asthma,¹⁵ was defined as <10 th 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.

Table 1. Characteristics of the study cohort

Characteristic	N	n (%)
Male sex	620	317 (51)
Parental asthma	618	379 (61)
Parental smoking	620	127 (20)
Parental heavy smoking*	566	73 (13)
Parental education	618	175 (28)
First born	620	249 (40)
Cat at birth	605	171 (28)
Dog at birth	605	189 (31)
Breastfeeding ≥ 3 mo	583	517 (89)
Eczema by 6 mo	606	148 (24)
Food allergen sensitization at 1 y [†]	483	80 (17)
Aeroallergen sensitization at 2 y [†]	383	64 (17)
LRTI by 1 y	593	67 (11)

*Mild-moderate smokers excluded.

[†]Individuals sensitized to both food and aeroallergens excluded.

Results

Baseline demographic and clinical characteristics are presented in [Table 1](#). Parents were predominantly Australian born (85%) and of high socioeconomic status (1 or both parents tertiary educated in 72% of couples). Approximately one-half of the children (51%) were male. All children had at least 1 immediate family member with “allergic disease,” and 74% had 2 or more affected family members.

During the first 2 years of life, the 4-week current wheeze prevalence (ie, wheeze in the previous 4 weeks) varied from 2% at 4 weeks to 20% at 78 weeks. There was little variation between yearly current wheeze prevalence (ie, wheeze in the previous 12 months) at age 3–7 years (26%–28%) ([Figure 1](#); available at www.jpeds.com).

The 57 participants (9%) missing surveys until age 2, (33 [58%] missing 1 or 2 surveys from age 18 years) were more

likely to have parents who were not tertiary educated (65% vs 50%; $P = .03$), who smoked (33% vs 19%; $P = .01$), and who smoked heavily (24% vs 12%; $P = .02$). The 18%–33% of participants missing data between age 3 and 7 years were less educated (64% vs 45% with no tertiary education at baseline; $P = .001$). Smokers were overrepresented in those missing data at 3 and 4 years ($P = .04$ and $.03$, respectively) ([Table II](#); available at www.jpeds.com).

Wheeze Phenotypes (4 Weeks to 7 Years)

Five wheeze phenotypes were defined by wheezing patterns from age 4 weeks to 7 years (bootstrap likelihood ratio test P value = .04). [Figure 2](#) shows a graph of probability of wheeze vs time for all classes. The class membership proportions based on the most likely latent class probabilities were as follows: never/infrequent wheeze, relative risk (RR), 42.7% (95% CI, 38.8–46.7); early transient wheeze, RR, 27.5% (95% CI, 24.0–31.2); early persistent wheeze, RR, 5.6% (95% CI, 4.0–7.8); intermediate-onset wheeze, RR, 20.7% (95% CI, 17.6–24.1); and late-onset wheeze, RR, 3.5% (95% CI, 2.1–5.1). Early persistent wheeze appeared in the first 6 months, intermediate-onset wheeze emerged at around 18 months, and late-onset wheeze occurred after age 4 years. Early transient wheeze appeared in the first 12 months and resolved at around 3 years.

Twelve-Year Follow-Up

All wheezing classes except early transient were associated with increased risk of current wheeze at age 12 years. The strongest associations were for intermediate-onset and late-onset wheeze ([Table III](#); available at www.jpeds.com).

Factors Associated with Wheeze Phenotypes

The RRs, adjusted for sex and parental education level, comparing early transient, early persistent, intermediate-

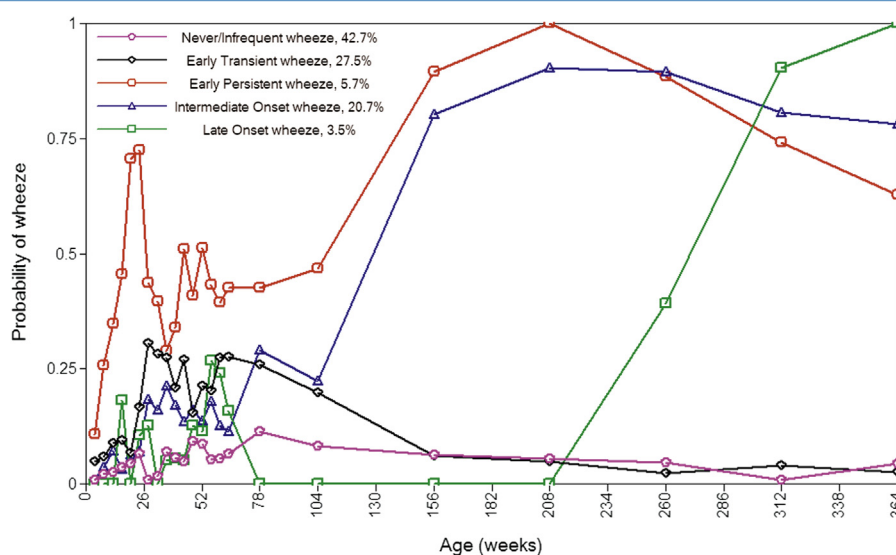
**Figure 2.** Probability of wheeze at each time point for each wheeze class from LCA.

Table IV. Associations of wheeze phenotypes with early-life characteristics

Characteristic	RR (95% CI)			
	Early transient wheeze	Early persistent wheeze	Intermediate-onset wheeze	Late-onset wheeze
Baseline factors				
Parental asthma	1.13 (0.80-1.59)	1.64 (0.78-3.45)	1.38 (0.91-2.09)	1.27 (0.54-3.01)
Heavy smoking at birth	1.05 (0.60-1.84)	1.14 (0.39-3.31)	0.89 (0.45-1.74)	3.18 (1.02-9.88)
First child	0.77 (0.55-1.08)	0.54 (0.26-1.12)	0.49 (0.32-0.76)	0.84 (0.37-1.93)
Cat at birth*	0.91 (0.62-1.33)	1.43 (0.70-2.92)	0.90 (0.56-1.44)	0.93 (0.37-2.36)
Dog at birth*	0.99 (0.69-1.42)	0.95 (0.46-1.97)	0.52 (0.32-0.84)	1.28 (0.52-3.15)
Early-life factors				
Breastfed $\geq$ 3 mo	0.54 (0.32-0.90)	0.60 (0.21-1.71)	1.04 (0.50-2.18)	0.34 (0.12-0.96)
Eczema $\leq$ 6 mo	1.00 (0.66-1.52)	1.41 (0.63-3.14)	2.77 (1.78-4.31)	1.08 (0.38-3.03)
Food SPT (3 mm) at 1 y	1.28 (0.76-2.14)	0.68 (0.18-2.63)	2.77 (1.56-4.94)	1.42 (0.44-4.51)
Aeroallergen SPT (3 mm) at 2 y	1.17 (0.60-2.29)	4.95 (1.74-14.02)	5.60 (2.86-10.93)	3.28 (0.87-12.31)
LRTI by 1 y	3.00 (1.58-5.70)	6.54 (2.55-16.76)	5.31 (2.71-10.41)	1.10 (0.15-7.94)
Overweight at 2 y	2.51 (1.09-5.81)	1.19 (0.20-6.94)	2.56 (0.96-6.84)	0.00
Childcare by 12 mo	1.51 (1.02-2.22)	1.37 (0.63-2.95)	1.41 (0.91-2.18)	0.48 (0.17-1.34)

SPT, skin prick test.

Reference category: never/infrequent wheeze. All models controlled for sex and parent education level.

*The cat and dog models also controlled for each other.

onset, and late-onset wheeze (baseline category, never/infrequent wheeze) between children with and without each early-life risk are presented in **Table IV**. The presence of LRTI by age 1 year was associated with a 3-fold increase in the risk of early transient wheeze. Attendance at childcare by 1 year and being overweight by 2 years were also associated with an increased risk of early transient wheeze. A reduced risk of early transient wheeze was observed in children who were breastfed for 3 or more months, and a modest decrease in risk was seen in first-born children.

Sensitization to aeroallergen by 2 years and LRTI by 1 year were both associated with an increased risk of early persistent wheeze.

Numerous factors were associated with an increased risk of intermediate-onset wheeze, including eczema by age 6 months, food allergen sensitization by 1 year, aeroallergen sensitization by 2 years, and LRTI in the first year of life. A reduced risk was observed for first-born children and those who owned a dog at baseline.

Heavy parental smoking was associated with an increased risk of late-onset wheeze. A reduced risk was observed in children who were breastfed for at least 3 months. There was no association of wheezing phenotype with randomized controlled trial formula allocation, parental asthma, parental

education level, weight $\leq$ 10th percentile at 4 weeks, or cat ownership at baseline.

Mediation by Allergen Sensitization

Adjustment for aeroallergen sensitization reduced the association between LRTI and early persistent wheeze by 52%, indicating possible mediation (**Table V**). Similarly, introducing allergen sensitization into the model for early eczema and intermediate-onset wheeze reduced the effect by 41% for food and by 32% for aeroallergen sensitization. Aeroallergen sensitization also reduced the association between heavy parental smoking and late-onset wheeze by 16%.

Discussion

This study established a distinct profile of potentially etiologically important early-life risk factors for each childhood wheeze phenotype identified using LCA. All wheeze phenotypes except early transient predicted current wheeze at age 12 years, the time at which children have outgrown transient wheeze and remaining wheeze is likely to persist.¹⁹ Importantly, the risk factor profiles, in combination with existing mechanistic hypothesis, identify possible causative mechanisms for each of these phenotypes, including: (1) childhood

Table V. Mediation by allergen sensitization

Exposure	Adjusted RR (95% CI) for wheeze	Potential mediator	Adjusted RR (95% CI) for wheeze	% change in RR
Early persistent wheeze				
LRTI	6.54 (2.55-16.76)	Aeroallergen sensitivity at 2 y	3.13 (0.69-14.33)	−52%
Intermediate-onset wheeze				
Eczema by 6 mo	2.77 (1.78-4.31)	Food allergen sensitivity at 1 y	1.63 (0.92-2.88)	−41%
	2.77 (1.78-4.31)	Aeroallergen sensitivity at 2 y	1.87 (1.01-3.47)	−32%
	2.77 (1.78-4.31)	Both	1.77 (0.87-3.60)	−36%
Late-onset wheeze				
Heavy smoking parent	3.18 (1.02-9.88)	Aeroallergen sensitivity at 2 y	2.69 (0.55-13.19)	−16%

All models controlled for parent education level and sex.

viral respiratory infections causing early transient wheeze; (2) the interaction of early-life respiratory infection and allergen sensitization (the “2-hit hypothesis”²⁰), which may result in early persistent wheeze; (3) the atopic march (ie, progression of atopic disease from eczema to hay fever and asthma²¹), which describes the associations found for the recently discovered phenotype of intermediate-onset wheeze; and (4) passive cigarette smoke exposure, which may explain the phenotype of late-onset wheeze. Given that both LRTI and aeroallergen sensitization increased the risk of early persistent wheeze, we postulate that this group may reflect the 2-hit hypothesis, in which respiratory infections and sensitization are thought to act synergistically on the risk of asthma.²² Early severe infections may result in lung damage, remodeling, permanent scarring, and asthma,²³ which may compromise epithelial integrity, facilitating aeroallergen sensitization.²⁰ We were able to confirm previous research suggesting that early persistent wheeze is associated with sensitization,^{4,5} and also demonstrated that aeroallergen sensitization may mediate the risk of early persistent wheeze associated with LRTI, indicating that sensitization may lie on the causal pathway.

Many atopic characteristics, including eczema and sensitization to food and aeroallergens, are associated with an increased risk of the intermediate-onset wheeze phenotype recently revealed by LCA.⁸ Intermediate-onset wheeze may be a phenotype in which defective lung,^{22,24} skin,²⁵ and gut epithelial barriers result in lung infections, eczema, and allergen sensitization. Defective skin and mucous membrane barriers may promote sensitization to environmental allergens and subsequent asthma, suggesting a mechanism for the atopic march.²¹ Our finding of mediation of asthma risk by allergen sensitization in children with eczema provides support for this theory.

Heavy parental smoking was associated with increased risk of late-onset wheeze. Smoking previously has been associated with wheeze and asthma; however, this is the first study to link early life smoke exposure uniquely with increased risk of late-onset wheeze. We postulate that this phenotype may arise in late childhood secondary to the effects of long-term passive smoke exposure. Furthermore, when respiratory function declines in later life, this group may contribute to the smoking-related early-life origins of chronic obstructive pulmonary disease that we reported in a previous study.²⁶

Breastfeeding for longer than 3 months was associated with reduced risk of both early transient and late-onset wheeze. The relationship between breastfeeding and allergic disease in children remains unclear, likely related to methodological issues, including inconsistencies of exposure and outcome definitions, along with failure to account for the possible effects of reverse causation.²⁷ Our present results provide good prospective evidence that breastfeeding may protect against the development of wheeze in childhood, possibly by modifying the immune response to early-life infections associated with both of these phenotypes. Major strengths of the present study include the abundance and completeness of information available for the first 2 years of life. Multiple

data points provided a solid base for pattern recognition LCA. In contrast to previously reported LCAs,^{8,28} we targeted high-risk children with multiple early wheeze assessments, permitting a more comprehensive picture of wheeze in early childhood as a basis for establishing phenotypes.

This study has some limitations. The results are based on a high-risk cohort, and thus the phenotype prevalence estimates might not be applicable to the general population. Regardless, however, the identified phenotypes are similar to those found in unselected birth cohorts,⁸ and the risk factors associated with each phenotype are likely to be similar between populations. Although we have incorporated objective measurements in terms of skin prick testing and BMI, our data on wheeze were based on survey responses. There is a large body of evidence suggesting that surveys based on wheeze are valid proxy measures for the presence of asthma.²⁹

In conclusion, our findings provide novel insights into potential causative or aggravating environmental exposures for different childhood wheeze phenotypes. Investigating the long-term outcomes of these phenotypes to establish their clinical relevance is now critical. We have shown that wheeze tracks up to age 12 years, and will present a detailed analysis of respiratory outcomes including lung function in this cohort at both 12 and 18 years of age in future work. Clinicians should continue to promote breastfeeding and tobacco avoidance. ■

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Table II. Baseline characteristics of those missing and not-missing at each follow-up

Characteristic	Baseline	2 y	2 y missing (9%)	3 y	3 y missing (33%)	4 y	4 y missing (18%)	5 y	5 y missing (20%)	6 y	6 y missing (21%)	7 y	7 y missing (28%)	2 y BMI (41%)	2 y BMI missing (59%)
Male sex	317/620 (51)	288/562 (51)	28/57 (59)	221/419 (53)	96/201 (48)	257/508 (51)	60/112 (54)	251/496 (51)	66/124 (53)	249/489 (51)	68/131 (52)	228/442 (52)	89/178 (50)	143/257 (56)	174/363 (48)
Parental asthma	379/618 (61)	338/560 (60)	40/57 (70)	254/417 (61)	125/201 (62)	310/506 (61)	69/112 (62)	304/494 (62)	75/124 (60)	303/487 (62)	76/131 (58)	271/440 (62)	108/178 (61)	149/255 (58)	230/263 (63)
Parental smoking	127/620 (20)	107/562 (19)	19/57 (33)	77/419 (18)	50/201 (25)	96/508 (19)	31/112 (28)	96/496 (19)	31/124 (25)	96/489 (20)	31/131 (24)	86/442 (19)	41/178 (23)	47/257 (22)	80/363 (18)
Parental heavy smoking	73/566 (13)	61/516 (12)	12/50 (24)	45/387 (12)	28/179 (16)	59/471 (13)	14/95 (15)	60/460 (13)	13/106 (12)	59/451 (13)	14/114 (12)	56/411 (14)	17/154 (11)	27/236 (11)	46/327 (14)
Parental education	319/619 (52)	281/561 (50)	37/57 (65)	190/418 (45)	129/201 (64)	245/507 (48)	74/112 (66)	239/495 (48)	80/124 (65)	237/488 (49)	82/131 (63)	218/441 (49)	101/178 (57)	125/256 (49)	194/363 (53)
First born	249/620 (40)	223/562 (40)	25/57 (44)	172/419 (41)	77/201 (38)	197/508 (39)	52/112 (46)	196/496 (40)	53/124 (43)	189/489 (39)	60/131 (46)	173/442 (39)	76/178 (43)	95/257 (37)	154/363 (42)
Dog	189/605 (31)	177/547 (32)	12/57 (21)	126/406 (31)	63/199 (32)	157/495 (32)	32/110 (29)	157/483 (33)	32/122 (26)	154/476 (32)	35/129 (27)	143/431 (33)	46/128 (26)	68/253 (27)	121/352 (34)
Cat	171/605 (28)	157/547 (29)	14/57 (25)	115/406 (28)	56/199 (28)	138/495 (28)	33/110 (30)	133/483 (28)	38/122 (31)	132/476 (28)	39/129 (30)	123/431 (29)	48/174 (28)	78/253 (31)	93/252 (26)

Data are n/N (%). At baseline, some questions were missed on some surveys, accounting for discrepancy in starting numbers. The heavy smoking variable excludes mild smokers. Bold typeface indicates that the followed up and missing variables are significantly different for the those parameters.

Table III. Associations of wheeze phenotypes with current wheeze at age 12 years

Wheeze phenotype	Current wheeze at 12 y, aOR (95% CI)*
Early transient wheeze	0.95 (0.51-1.78)
Early persistent wheeze	4.63 (1.94-11.09)
Intermediate-onset wheeze	11.13 (6.11-20.29)
Late-onset wheeze	11.47 (3.44-38.26)
Never/frequent wheeze	1

*Adjusted for sex and education level.

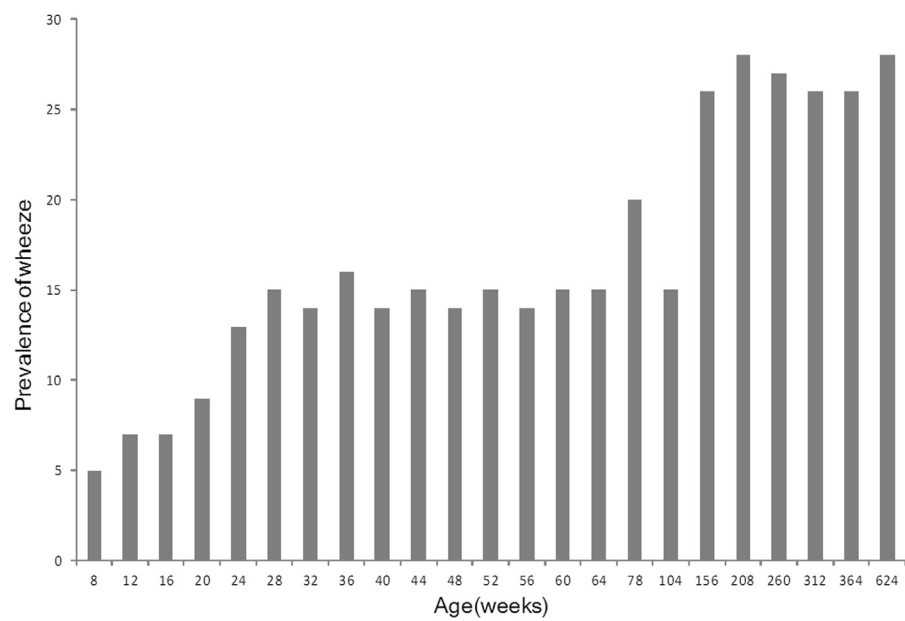


Figure 1. Prevalence of wheeze at each time point in the cohort.