

Sex-specific risk factors for childhood wheeze and longitudinal phenotypes of wheeze

Sze Man Tse, MDCM, MPH,^a Sheryl L. Rifas-Shiman, MPH,^b Brent A. Coull, PhD,^c Augusto A. Litonjua, MD, MPH,^d Emily Oken, MD, MPH,^b and Diane R. Gold, MD, MPH^d *Montreal, Quebec, Canada, and Boston, Mass*

Background: Although sexual dimorphism in wheeze and asthma prevalence are well documented, sex-specific risk factors for wheeze and longitudinal wheeze phenotypes have not been well elucidated.

Objective: By using a large prebirth cohort, this study aimed to identify sex-specific risk factors for wheeze from birth through midchildhood and identify distinct longitudinal wheeze phenotypes and the sex-specific risk factors associated with these phenotypes.

Methods: Mothers reported child wheeze symptoms over the past year approximately yearly on 9 occasions starting at age 1 year. We identified sex-specific predictors of wheeze, wheeze phenotypes, and sex-specific predictors of these phenotypes by using generalized estimating equations, latent class mixed models, and multinomial logistic analysis, respectively.

Results: A total of 1623 children had information on wheeze at 1 or more time points. Paternal asthma was a stronger predictor of ever wheezing in boys (odds ratio [OR], 2.15; 95% CI, 1.74-2.66) than in girls (OR, 1.53; 95% CI, 1.19-1.96; *P* for sex by paternal asthma interaction = .03), whereas being black or Hispanic, birth weight for gestational age *z* score, and breast-feeding duration had stronger associations among girls. We identified 3 longitudinal wheeze phenotypes: never/infrequent wheeze (74.1%), early transient wheeze (12.7%), and persistent wheeze (13.1%). Compared with never/infrequent wheeze, maternal asthma, infant bronchiolitis, and atopic dermatitis were associated with persistent wheeze in both sexes, but paternal asthma was associated with persistent wheeze in boys

only (OR, 4.27; 95% CI, 2.33-7.83; *P* for sex by paternal asthma interaction = .02), whereas being black or Hispanic was a predictor for girls only.

Conclusion: We identified sex-specific predictors of wheeze and longitudinal wheeze patterns, which might have important prognostic value and allow for a more personalized approach to wheeze and asthma treatment. (*J Allergy Clin Immunol* 2016;■■■:■■■-■■■.)

Key words: Asthma, sex differences, parental asthma, bronchiolitis

Sexual dimorphism in wheeze and asthma prevalence and their associated morbidities are well documented, with a higher male/female ratio in childhood and a reversal of this ratio during adolescence that persists into adulthood.¹⁻⁷ It has been suggested that dysynapsis and the relative collapsibility and size of airways might predispose male infants to wheeze more than female infants.⁸ Other hypotheses include female and male hormonal influences⁹⁻¹¹ and differences in consultation practices.¹²

Although several large cross-sectional and longitudinal studies have identified risk factors for wheeze and asthma, few have looked specifically at sex-specific risk factors. Instead, most simply adjust for sex in their multivariate analytic models. The identification of sex-specific risk factors has important implications for asthma prediction and prevention, as well as for our understanding of the genetic determinants of asthma. Using a large birth cohort of children with a parental history of allergy or asthma and follow-up to age 14 years, we found that paternal asthma and infant bronchiolitis were risk factors for wheeze in boys only, whereas maternal asthma was a risk factor for both sexes.¹³ Interestingly, the magnitude of the associations of paternal asthma and infant bronchiolitis with wheeze in boys persisted throughout childhood, suggesting that the long-term effect of these factors on the longitudinal trajectory of wheeze might also be sex specific.

Recently, trajectories of wheeze have been identified by using longitudinal latent class analyses in large birth cohorts.¹⁴ These trajectories are consistent with previously documented patterns,¹⁵ and a few studies have identified risk factors associated with these trajectories.¹⁶⁻¹⁸ For example, in models including boys and girls, parental asthma and aeroallergen sensitization were stronger predictors of persistent wheeze, whereas early respiratory tract infections, breast-feeding, and day care attendance were predictors of early transient wheeze.^{17,18} However, sex-specific risk factors, which are important from a prognostic point of view, have not been examined.

By using a large birth cohort of children not selected for atopy risk, this study examined sex-specific risk factors for wheeze from birth through midchildhood. Furthermore, distinct longitudinal phenotypes of wheeze were identified, and sex-specific risk factors for these trajectories were examined.

From ^athe Division of Respiratory Medicine, Department of Pediatrics, Sainte-Justine University Hospital Center and University of Montreal; ^bthe Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston; ^cthe Department of Biostatistics, Harvard School of Public Health, Boston; and ^dthe Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston.

This article is subject to the National Institutes of Health (NIH) Public Access Policy (<http://publicaccess.nih.gov>). Project Viva is funded by R01 HL064925, R01 AI102960, and R37 HD 034568. E.O. received funding from the NIH (K24 HD069408 and P30 DK092924).

Disclosure of potential conflict of interest: S. L. Rifas-Shiman, E. Oken, and D. R. Gold have received research support from the National Institutes of Health (NIH). B. A. Coull has received research support from the NIH, US Environmental Protection Agency, and Health Effects Institute and is employed by Harvard University. A. A. Litonjua has received research support from the NIH and receives royalties from UpToDate and Springer Humana Press. S. M. Tse declares no relevant conflicts of interest.

Received for publication October 17, 2015; revised April 5, 2016; accepted for publication April 13, 2016.

Corresponding author: Sze Man Tse, MDCM, MPH, Division of Respiratory Medicine, Department of Pediatrics, Sainte-Justine University Hospital Center and University of Montreal, 3175 chemin de la Côte-Sainte-Catherine, Montréal, Québec H3T 1C5, Canada. E-mail: sze.man.tse@umontreal.ca.

0091-6749/\$36.00

© 2016 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2016.04.005>

Abbreviations used

GEE: Generalized estimating equations
OR: Odds ratio

METHODS**Subjects**

Project Viva is a prospective prebirth cohort study the goal of which is to examine associations of prenatal and perinatal factors with maternal and child health.¹⁹ Mothers were recruited at their first prenatal appointment at Atrius Harvard Vanguard Medical Associates, a multispecialty group practice in Massachusetts. This cohort consisted of 2128 singleton live-born infants. At in-person visits and on mailed questionnaires, mothers were invited to respond to a questionnaire about the child's health at birth, 6 months and 1 year of age, and approximately 1-year intervals thereafter.

Ascertainment of wheeze and exposures

For this study, we used maternal reports of child wheeze for questionnaire years 1 through 9 inclusively, corresponding approximately to yearly assessments between the ages of 1 and 9 years. Wheeze was considered present if the parent answered yes to the following question: "Since your child was [age at last questionnaire], had he/she ever had wheezing (or whistling in the chest)?" Children with at least 1 wheeze outcome available from questionnaire years 1 through 9 were included ($n = 1623$). We ascertained most demographics data, parental medical history, and the child's characteristics through maternal reports at enrollment in the study or at the child's birth and assessed bronchiolitis and atopic dermatitis before 1 year of age at questionnaire year 1. Environmental smoke exposure before age 1 year was considered present if the parents reported that the child was exposed to at least 1 hour of cigarette smoke per week on the 6-month or 1-year questionnaires.

Statistical analysis

We performed a descriptive analysis of the baseline characteristics of the entire cohort and by sex. We used generalized estimating equations (GEE) to identify predictors of wheeze longitudinally stratified by sex and incorporating all observed outcomes. An independent correlation structure was used, and this model was compared with the unstructured and exchangeable structures by using the quasi-Akaike information criterion. We included the following exposures in the final model based on our previous study and results from other studies^{13,20-23}: maternal and paternal asthma, household income ($>\$70,000/\text{y}$ vs $\leq \$70,000/\text{y}$), child's age at the time of wheeze ascertainment, child's race/ethnicity, season of birth, gestational length, birth weight for gestational age z score, breast-feeding duration, environmental smoke exposure before age 1 year, and bronchiolitis and atopic dermatitis before age 1 year. Given the variation in age at the time of yearly questionnaires, we used the exact age in years for each ascertainment time point for all analyses. Other covariates that we considered but did not include in the final model were as follows: maternal smoking during pregnancy, maternal and paternal eczema and hay fever, and child care at 6 months of age. These did not independently predict wheeze (parental eczema and maternal smoking during pregnancy), were correlated with other variables in the model (maternal smoking during pregnancy with environmental smoke exposure, child care attendance with bronchiolitis, parental eczema, and hay fever with parental asthma), or both. In a subanalysis we analyzed the age-specific effects of the covariates on wheeze by stratifying the cohort by age (<5 and ≥ 5 years) and sex. If the results suggested an age-specific effect, we further examined the interaction between age and those risk factors on wheeze.

Additionally, we applied latent class mixed modeling to identify distinct phenotypes of wheeze. To increase the validity of the analysis, we included only children who had at least 1 wheeze measure between 1 and 5 years and at least 1 wheeze measure between 6 and 9 years of age. We initially performed latent class mixed modeling stratified by sex to compare wheeze phenotypes

between boys and girls and assessed the goodness of fit for the number of latent classes by using the Bayesian information criterion. Based on previous literature,^{14,24} we specified 3, 4, and 5 latent classes, and 3 latent classes provided the best fit. Because of the similarity of the latent classes in both sexes, subsequently, we performed this analysis in the entire cohort using the same parameters. We examined sex-specific risk factors for individual patterns through multinomial logistic regression stratified by sex. Covariates included in the multinomial logistic regression were the same as those for the GEE analysis.

To optimize power, we imputed missing exposures in the final model. We used Proc MI in SAS software (version 9.3; SAS Institute, Cary, NC) and imputed 50 values for each missing observation to create 50 "completed" data sets. We combined multivariable modeling estimates by using Proc MIANALYZE. Characteristics were similar in the unimputed and imputed data sets (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org). Multiple imputation also did not substantially change the associations resulting from our analyses. P values are 2-sided. We performed analyses with SAS (version 9.3) and R (version 3.2.1; www.r-project.org) software. We performed multiple imputation, GEE analysis, and multinomial logistic regression with proc MI, proc GENMOD and MIANALYZE, and proc LOGISTIC in SAS software, respectively. We performed longitudinal latent class analysis with the package "lcmm"²⁵ in R software.

RESULTS

A total of 1623 children in Project Viva had at least 1 wheeze outcome available for questionnaire years 1 through 9; 1574 (97.0%) had at least 1 wheeze measure between 1 and 5 years, and 1344 (82.8%) had at least 1 wheeze measure between 6 and 9 years (see Table E3 in this article's Online Repository at www.jacionline.org for detailed distribution of data availability by questionnaire year). A total of 1295 children with at least 1 wheeze outcome available at 5 years or less and greater than 5 years were included in the latent class analysis. Baseline characteristics of the children, their family history of atopy, and important environmental exposures for these 2 subgroups are presented in Tables I and II, respectively. These characteristics are similar to those of the entire Project Viva cohort ($n = 2128$, see Table E4 in this article's Online Repository at www.jacionline.org). This is a predominantly white cohort (64.6%), with 13.5% and 11.8% of children having a history of maternal and paternal asthma, respectively. The prevalence of bronchiolitis before age 1 year was statistically significantly higher in boys (12.3% in girls and 17.2% in boys). The prevalence of wheeze was higher in boys at each questionnaire year, although it had a decreasing trend with time for both sexes, with possibly a slight increase in prevalence at questionnaire year 9 (Fig 1).

Sex- and age-specific predictors of wheeze

Risk factors for wheeze among girls included being black (odds ratio [OR], 2.36; 95% CI, 1.84-3.04), being Hispanic (OR, 3.24; 95% CI, 2.13-4.93), maternal asthma (OR, 1.92; 95% CI, 1.54-2.41), paternal asthma (OR, 1.53; 95% CI, 1.19-1.96), bronchiolitis before age 1 year (OR, 3.51; 95% CI, 2.76-4.47), and atopic dermatitis before age 1 year (OR, 1.72; 95% CI, 1.39-2.13; Table III). These were also predictors of wheeze in boys, but the effects of being black (OR, 1.54; 95% CI, 1.23-1.93) and Hispanic (OR, 1.63; 95% CI, 1.15-2.29) were less important, whereas the effect of paternal asthma (OR, 2.15; 95% CI, 1.74-2.66) was more important. There was a significant statistical interaction between sex and being black ($P = .002$), sex and being Hispanic ($P = .01$), and sex and paternal asthma ($P = .03$).

TABLE I. Baseline characteristics of the Project Viva cohort (children with ≥ 1 wheeze outcome from questionnaire years 1-9 [$n = 1623$])

	Total ($n = 1623$)	Girls ($n = 778$)	Boys ($n = 845$)
	No. (%)		
Maternal smoking status			
Never	1119 (69.0)	545 (70.0)	575 (68.0)
Former	321 (19.8)	156 (20.1)	165 (19.5)
Smoked during pregnancy	183 (11.3)	77 (9.9)	105 (12.5)
Maternal asthma	219 (13.5)	110 (14.2)	109 (12.9)
Maternal hay fever	487 (30.0)	232 (29.8)	255 (30.1)
Maternal eczema	210 (12.9)	96 (12.4)	114 (13.4)
Paternal asthma	191 (11.8)	85 (10.9)	106 (12.6)
Paternal hay fever	430 (26.5)	209 (26.8)	221 (26.2)
Paternal eczema	96 (5.9)	42 (5.3)	55 (6.5)
Household income $> \$70,000/y$	966 (59.5)	456 (58.6)	510 (60.3)
Child race/ethnicity			
Black	254 (15.7)	114 (14.7)	140 (16.6)
Hispanic	86 (5.3)	35 (4.5)	51 (6.0)
White	1049 (64.6)	518 (66.5)	532 (62.9)
Other	233 (14.4)	111 (14.3)	122 (14.5)
Season of birth			
Winter	410 (25.3)	199 (25.6)	211 (25.0)
Spring	430 (26.5)	207 (26.6)	223 (26.4)
Summer	426 (26.2)	201 (25.8)	225 (26.6)
Fall	357 (22.0)	171 (22.0)	186 (22.0)
	Mean (SD)		
Gestation length (wk)	39.5 (1.9)	39.5 (1.8)	39.4 (1.9)
Birth weight for gestational age (z score)	0.20 (0.96)	0.18 (0.94)	0.21 (0.98)
Duration of breast-feeding (mo)	6.0 (4.6)	6.1 (4.6)	5.9 (4.6)
	No. (%)		
Environmental smoke exposure before 1 y	149 (9.2)	71 (9.1)	78 (9.2)
Bronchiolitis before age 1 y	241 (14.9)	96 (12.3)	146 (17.2)
Atopic dermatitis before age 1 y	369 (22.8)	162 (20.8)	207 (24.5)

Older age at outcome time point and greater gestational length were associated with lower risk of wheeze in both sexes. Environmental smoke exposure before 1 year was associated with higher risk of wheeze in boys (OR, 1.45; 95% CI, 1.09-1.92), although the effect size was similar in girls. Being born in the summer and fall was associated with a lower risk of wheeze in girls only. Although household income of greater than \$70,000/y was significantly associated with lower risk of wheeze in boys (OR, 0.77; 95% CI, 0.64-0.92), effect sizes were similar, although with CIs that straddled the null in the opposite sex. Longer duration of breast-feeding was associated with lower wheeze risk in girls (OR, 0.96 per month; 95% CI, 0.94-0.97).

In addition to stratification by sex, we also stratified the cohort by age to examine the age-specific effects of risk factors in a subanalysis (see [Table E5](#) in this article's Online Repository at www.jacionline.org). The effect of infant bronchiolitis on wheeze was greater among subjects aged less than 5 years compared with those 5 years and older for both sexes (age by infant bronchiolitis interaction: $P < .0001$ for both boys and girls), whereas paternal asthma and atopic dermatitis before age 1 year were associated with higher odds of wheeze in those 5 years and older among

TABLE II. Baseline characteristics of children with at least 1 wheeze outcome at less than 5 years and 1 wheeze outcome at 5 years or older ($n = 1295$)

	Total ($n = 1295$)	Girls ($n = 630$)	Boys ($n = 665$)
	No. (%)		
Maternal smoking status			
Never	910 (70.3)	456 (72.4)	454 (68.2)
Former	262 (20.2)	124 (19.6)	138 (20.8)
Smoked during pregnancy	123 (9.5)	50 (7.9)	73 (11.0)
Maternal asthma	166 (12.8)	85 (13.6)	80 (12.1)
Maternal hay fever	392 (30.2)	191 (30.3)	201 (30.2)
Maternal eczema	167 (12.9)	77 (12.3)	89 (13.4)
Paternal asthma	155 (12.0)	76 (12.0)	80 (12.0)
Paternal hay fever	343 (26.5)	171 (27.1)	173 (26.0)
Paternal eczema	79 (6.1)	36 (5.7)	43 (6.5)
Household income $> \$70,000/y$	804 (62.1)	382 (60.7)	422 (63.5)
Child race/ethnicity			
Black	172 (13.3)	82 (13.1)	90 (13.5)
Hispanic	52 (4.0)	21 (3.3)	31 (4.7)
White	881 (68.0)	433 (68.7)	448 (67.4)
Other	190 (14.7)	94 (14.9)	96 (14.4)
Season of birth			
Winter	332 (25.6)	159 (25.2)	173 (26.0)
Spring	328 (25.3)	163 (25.9)	165 (24.8)
Summer	350 (27.0)	168 (26.7)	182 (27.4)
Fall	285 (22.0)	140 (22.2)	145 (21.8)
	Mean (SD)		
Gestation length (wk)	39.5 (1.8)	39.5 (1.8)	39.4 (1.8)
Birth weight for gestational age (z score)	0.19 (0.97)	0.19 (0.93)	0.18 (0.99)
Duration of breast-feeding (mo)	6.4 (4.6)	6.4 (4.6)	6.4 (4.6)
	No. (%)		
Environmental smoke exposure before age 1 y	109 (8.4)	55 (8.7)	54 (8.1)
Bronchiolitis before age 1 y	188 (14.5)	74 (11.7)	114 (17.1)
Atopic dermatitis before age 1 y	297 (22.9)	135 (21.4)	162 (24.3)

boys only (age by paternal asthma interaction: $P < .0001$, age by atopic dermatitis interaction: $P = .01$).

GEE analyses were performed by using an independent correlation structure, which had a high goodness of fit (as measured by using the quasi-Akaike information criterion) that is comparable with the exchangeable structure and higher than that of the unstructured model. Of note, GEE analysis provides robust unbiased estimates even in case of misspecification of the correlation structure.²⁶

Longitudinal wheeze phenotypes and sex-specific predictors of wheeze phenotypes

A total of 1295 subjects had at least 1 wheeze measure at 5 years or less and at least 1 wheeze measure at greater than 5 years and were included in the latent class analysis, with the majority ($n = 1135$ [87.6%]) having 5 or more observations. Three distinct wheeze phenotypes were identified, and patterns were similar in girls and boys: never/infrequent wheeze ($n = 960$, 74.1% overall; $n = 497$, 78.9% in girls; and $n = 665$, 69.6% in boys), early transient wheeze ($n = 165$, 12.7% overall; $n = 64$,

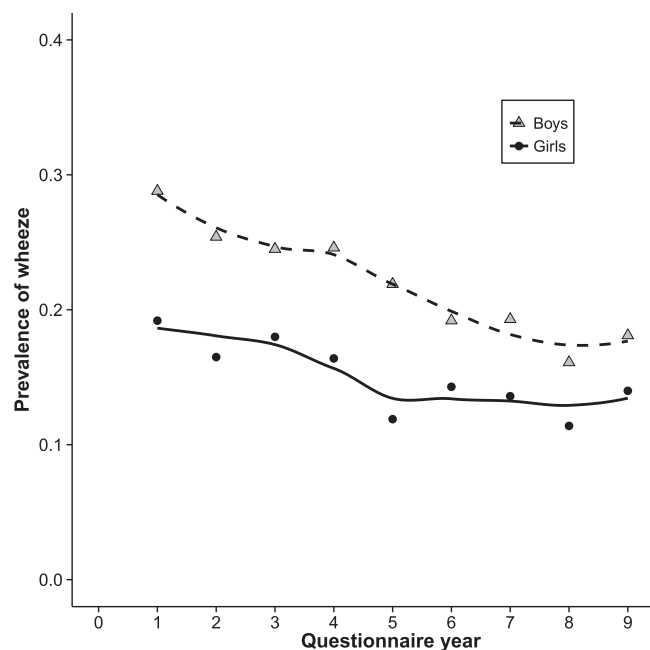


FIG 1. Prevalence of parent-reported wheeze in the past 12 months by age stratified by sex. Curves are calculated by using local regression.

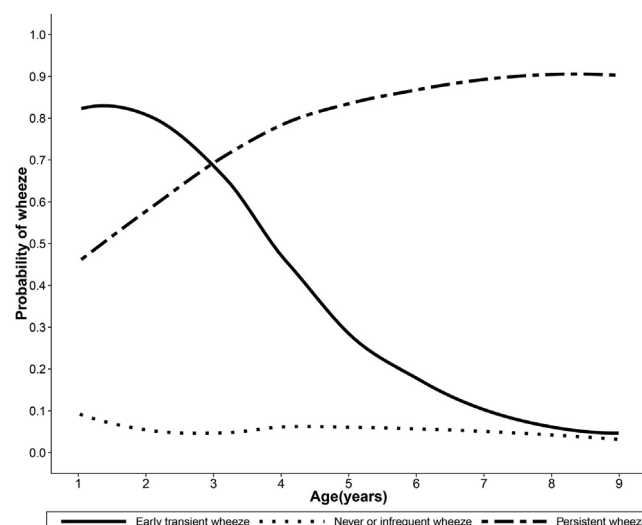


FIG 2. Longitudinal wheeze phenotypes for the entire study cohort. Sex-specific wheeze trajectories were similar in boys and girls. The majority of subjects were in the never or infrequent wheeze group ($n = 960$, 74.1%), with minorities in the early transient wheeze group ($n = 165$, 12.7%) and persistent wheeze group ($n = 170$, 13.1%).

TABLE III. Predictors of wheeze stratified by sex*

	Girls ($n = 778$), OR (95% CI)	Boys ($n = 845$), OR (95% CI)
Maternal asthma	1.92 (1.54-2.41)	1.80 (1.46-2.22)
Paternal asthma†	1.53 (1.19-1.96)	2.15 (1.74-2.66)‡
Household income >\$70,000/y	0.84 (0.68-1.02)	0.77 (0.64-0.92)
Child race/ethnicity (vs white)		
Black†	2.36 (1.84-3.04)	1.54 (1.23-1.93)
Hispanic†	3.24 (2.13-4.93)	1.63 (1.15-2.29)
Other	1.22 (0.96-1.56)	1.03 (0.83-1.28)
Season of birth (vs winter)		
Spring	0.93 (0.74-1.16)	1.05 (0.86-1.29)
Summer	0.65 (0.51-0.83)	0.85 (0.69-1.04)
Fall	0.72 (0.56-0.92)	1.09 (0.88-1.34)
Gestation length (wk)	0.94 (0.90-0.98)	0.95 (0.91-0.98)
Birth weight for gestational age (z score)†	0.91 (0.82-1.00)	1.07 (0.98-1.15)
Duration of breast-feeding (mo)†	0.96 (0.94-0.97)	1.01 (0.99-1.02)
Environmental smoke exposure before age 1 y	1.36 (0.97-1.90)	1.45 (1.09-1.92)
Bronchiolitis before age 1 y	3.51 (2.76-4.47)‡	4.23 (3.40-5.25)‡
Atopic dermatitis before age 1 y	1.72 (1.39-2.13)	1.54 (1.28-1.85)‡
Child age at outcome (y)	0.94 (0.91-0.97)	0.92 (0.90-0.94)

*Multivariable model adjusted for all variables presented in the table.

†Statistically significant interaction with sex on wheeze.

‡Statistically significant interaction with age on wheeze.

10.2% in girls; and $n = 101$, 15.2% in boys), and persistent wheeze ($n = 170$, 13.1% overall; $n = 69$, 11.0% in girls; and $n = 101$, 15.2% in boys). Consistent with the prevalence of wheeze throughout the age categories, there were more boys in the early transient wheeze and persistent wheeze groups. These phenotypes were labelled based on their temporal pattern (Fig 2) and based on patterns reported in the literature.

In the multinomial analysis infant bronchiolitis (OR of 4.84 [95% CI, 2.34-9.98] in girls and 10.17 [95% CI, 5.47-18.93 in

boys]) was associated with higher odds of early transient wheeze in boys and girls compared with never/infrequent wheeze (Table IV). Maternal asthma was also associated with early transient wheeze in boys (OR, 3.59; 95% CI, 1.90-6.75) and showed a borderline significance in girls (OR, 2.03; 95% CI, 0.97-4.25). Interestingly, the association of infant bronchiolitis with early transient wheeze appeared greater in boys, although the sex by infant bronchiolitis interaction was not statistically significant ($P = .15$). The sex by maternal asthma and atopic dermatitis interactions were also not significant ($P = .41$ and $.32$, respectively). In girls only duration of breast-feeding (OR, 0.92; 95% CI, 0.86-0.98) and atopic dermatitis (OR, 2.06; 95% CI, 1.04-4.09) were associated with a lower and higher odds of early transient wheeze, respectively.

Although maternal asthma, infant bronchiolitis, and atopic dermatitis were associated with increased odds of persistent wheeze in both girls and boys (sex by maternal asthma interaction: $P = .76$, sex by infant bronchiolitis interaction: $P = .25$, and sex by atopic dermatitis interaction: $P = .33$), paternal asthma was a predictor of persistent wheeze in boys only (OR, 4.27; 95% CI, 2.33-7.83; P for sex by paternal asthma interaction = .02). Being black (OR of 3.23 [95% CI, 1.55-6.75] in girls vs 1.50 [95% CI, 0.73-3.09] in boys) or Hispanic (OR of 3.60 [95% CI, 1.06-12.17] in girls vs 1.38 [95% CI, 0.47-4.08] in boys) was a risk factor for persistent wheeze in girls but not boys, with a statistically significant interaction between sex and being black on wheeze ($P = .02$).

To further characterize the atopic phenotype within the longitudinal wheeze phenotypes, we documented that the presence of a positive specific IgE level to one of 5 inhalant allergens (dust, cat, dog, cockroach, and mold) at age 3 years was more than twice as high for those with persistent wheeze (45%) compared with those with never/infrequent wheeze and early wheeze (20% and 16%, respectively; see Table E6 in this article's Online Repository at www.jacionline.org). Similarly, the prevalence of midchildhood (year 7) inhalant sensitization

TABLE IV. Multinomial logistic regression for wheeze phenotypes stratified by sex (vs never/infrequent wheeze)*

	Early transient wheeze		Persistent wheeze	
	Girls (n = 64)	Boys (n = 101)	Girls (n = 69)	Boys (n = 101)
Maternal asthma	2.03 (0.97-4.25)	3.59 (1.90-6.75)	2.13 (1.04-4.35)	2.21 (1.11-4.40)
Paternal asthma*	1.29 (0.59-2.83)	0.85 (0.35-2.09)	1.46 (0.68-3.15)	4.27 (2.33-7.83)
Household income >\$70,000/y	0.78 (0.42-1.46)	0.85 (0.48-1.50)	0.72 (0.38-1.36)	0.72 (0.41-1.26)
Child race/ethnicity (vs white)				
Black*	0.56 (0.21-1.53)	1.25 (0.57-2.76)	3.23 (1.55-6.75)	1.50 (0.73-3.09)
Hispanic	0.69 (0.13-3.59)	1.11 (0.35-3.53)	3.60 (1.06-12.17)	1.38 (0.47-4.08)
Other	0.83 (0.38-1.82)	1.27 (0.64-2.51)	1.39 (0.63-3.11)	0.96 (0.46-2.01)
Season of birth (vs winter)				
Spring	0.93 (0.46-1.88)	1.74 (0.88-3.43)	0.98 (0.46-2.09)	0.87 (0.45-1.69)
Summer	0.54 (0.25-1.19)	1.36 (0.69-2.70)	0.85 (0.40-1.84)	0.82 (0.43-1.57)
Fall	0.52 (0.23-1.19)	1.30 (0.63-2.70)	0.67 (0.30-1.52)	0.86 (0.44-1.70)
Gestation length (wk)	0.93 (0.81-1.07)	1.05 (0.91-1.21)	0.97 (0.84-1.12)	0.92 (0.81-1.04)
Birth weight for gestational age (z score)*	0.76 (0.55-1.03)	1.13 (0.87-1.47)	0.83 (0.61-1.13)	1.11 (0.86-1.42)
Duration of breast-feeding (mo)	0.92 (0.86-0.98)	0.98 (0.92-1.03)	0.97 (0.91-1.03)	1.02 (0.97-1.08)
Environmental smoke exposure before age 1 y	1.73 (0.67-4.44)	1.02 (0.39-2.64)	1.96 (0.81-4.73)	2.16 (0.96-4.89)
Bronchiolitis before age 1 y	4.84 (2.34-9.98)	10.17 (5.47-18.93)	4.38 (2.03-9.45)	6.49 (3.29-12.79)
Atopic dermatitis before age 1 y	2.06 (1.04-4.09)	1.24 (0.69-2.23)	2.88 (1.54-5.38)	2.01 (1.16-3.49)

*Statistically significant interaction with sex on persistent wheeze.

prevalence was 62%, 33%, and 40% among children with persistent, early transient, and never/infrequent wheeze, respectively. For both of these periods, inhalant sensitization prevalence is up to 1.9 times in children with persistent wheeze compared with the other wheeze phenotypes, whereas the prevalence of sensitization is more similar among those with early transient and never/infrequent wheeze. If food allergen sensitization and any atopy (total IgE, ≥ 100 IU/mL) are included in midchildhood, the prevalence of sensitization is similar between the wheeze phenotypes (see Table E6). For those with wheezing and current asthma at year 7, the prevalence of any sensitization was similar (approximately 65%).

DISCUSSION

In this large prebirth cohort study, we identified sex-specific predictors of wheeze over the first 9 years of life, described distinct longitudinal phenotypes of wheeze using latent class analysis, and explored the sex-specific predictors of these wheeze phenotypes. There were 3 key findings. First, although some risk factors were associated with longitudinal reporting of wheeze in both boys and girls in patterns consistent with previous studies, paternal asthma had a greater association with wheeze in boys, whereas black or Hispanic race/ethnicity had a greater association in girls. Second, 3 longitudinal phenotypes of wheeze were identified by using latent class analysis: never/infrequent wheeze, early transient wheeze, and persistent wheeze. Finally, as well as finding sexual dimorphism in longitudinal predictors of annual reports of wheeze, we identified the same sex-specific risk factors for the phenotype of persistent wheeze, namely paternal asthma for boys and being black or Hispanic for girls.

Sexual dimorphism in asthma prevalence and asthma-related morbidities is well documented.¹⁻⁷ However, few longitudinal cohorts have examined sex-specific risk factors for wheeze and asthma. Furthermore, sex-specific risk factors for longitudinal wheeze phenotypes have not been examined. In a smaller recent study (n = 499) of a birth cohort of children with a parental history of atopy,¹³ we found that although maternal asthma was a risk factor for wheeze in girls and boys, paternal asthma and

infant bronchiolitis were risk factors for boys only. In the current study, by using a similar analysis but a cohort of children not selected for risk of atopy and using multiple imputation to account for missing covariates, paternal asthma, but not infant bronchiolitis, showed a statistically significant sex-specific effect on wheeze, although the effect sizes were higher in boys for bronchiolitis. The differences between the 2 studies might be due in part to analytic technique (no imputation vs imputation of covariates), characteristics of the birth cohort (high risk for atopy vs general population), and differences in sample sizes (larger cohort in Project Viva, the current study).

Paternal history of asthma as a predictor of child wheeze: Sexual dimorphism

Interestingly, paternal asthma was not only a predictor of any wheeze in boys, it was also a predictor of persistent wheeze in boys but not girls. Consistent with the findings of our current and previous studies,¹³ another birth cohort documented that paternal asthma was associated with asthma in boys.²⁷ However, although both our studies found that maternal asthma was associated with wheeze in both sexes, they documented this association with asthma among girls only, although the statistical interaction between sex and maternal asthma was not significant. These differences might reflect differences in the cohort composition or methodological differences, including the use of parental report of asthma as the outcome (vs wheeze in our studies) and a longer follow-up to 18 years in their study.²⁷ A recent study demonstrated that paternal imprinting of a disintegrin and metalloprotease 33 (*ADAM33*), a gene that has been associated with asthma, was associated with the severity of airway hyperreactivity in children with asthma,²⁸ suggesting a parent-of-origin-specific effect. However, this effect was not examined in the context of the child's sex. On the other hand, Naumova et al²⁹ recently documented that sex-specific DNA methylation patterns in the promoter region of zona pellucida binding protein 2 (*ZPBP2*), a gene in the 17q12-21 region, were associated with childhood asthma development. Taken together, these studies suggest that the sex-specific effect of paternal asthma can result

from complex interactions between genetic and epigenetic factors. Our age-specific analysis demonstrated that the association between paternal asthma and wheeze was greater for children 5 years and older, further reinforcing the notion of this risk factor for the persistent wheeze phenotype. The notion that paternal asthma has a longer-lasting effect on wheeze has been reported recently, although sex-specific effects were not examined.³⁰ Further studies are needed to elucidate the mechanisms underlying this observation.

Infant bronchiolitis as a predictor of child wheeze

Our findings indicated that infant bronchiolitis was associated with wheeze in both boys and girls and that this association was strongest in the early ages for both sexes. Although the interaction between sex and bronchiolitis was not statistically significant, the effect of infant bronchiolitis on wheeze in boys was consistently higher than for girls. This is true of infant bronchiolitis as a predictor of wheeze and of the wheeze phenotypes (specifically for early transient wheeze and persistent wheeze). This finding is consistent with our previous study, in which we reported an association between infant bronchiolitis and wheeze in boys only. Although studies document a higher incidence of bronchiolitis in male infants worldwide^{31,32} and a higher prevalence of wheeze among infants who had bronchiolitis,^{33,34} few studies examined the sex-specific effects of infant bronchiolitis on future wheeze. Consistent with our findings, Valkonen et al³⁵ documented a higher risk of asthma development at 3-year follow-up in boys with a history of bronchiolitis compared with girls. Another study reported increased airway hyperresponsiveness in boys 11 years after infant bronchiolitis.³⁶ Further studies are needed to elucidate the mechanisms underlying this association.

Black and Hispanic race/ethnicity as predictors of wheeze: Sexual dimorphism

We found that that being black or Hispanic had a greater effect on wheeze among girls than boys. It was also a predictor of persistent wheeze in girls only, although further studies are needed to confirm this finding given the relatively small numbers of racial/ethnic minorities in each wheeze phenotype group after stratification by sex. The higher prevalence of wheeze and asthma is well documented among black compared with white children.³⁷⁻⁴⁰ Among Hispanic groups, a wide range in asthma prevalence has been documented, with Puerto Ricans and Mexicans having higher and lower prevalence, respectively.³⁹ Interestingly, among Puerto Rican children with asthma, a higher percentage of African ancestry has been associated with decreased lung function.⁴¹ Of note, Borrell et al⁴² showed that the effect of obesity on asthma control differed by race/ethnicity in girls, with obese African American girls having better controlled asthma compared with their normal-weight counterparts, whereas Mexican American girls had worse asthma control. This interaction between obesity and race/ethnicity was not seen in boys. Another study in children with asthma showed larger lung function deficits in Hispanic girls compared with non-Hispanic white girls, whereas this was not statistically significant in boys.⁴³ Taken together, these studies support our findings by suggesting that race/ethnicity can have a sex-specific effect on wheeze and asthma, likely interacting with other environmental and genetic factors.

Immune phenotypes play an important role in the overall asthma phenotype of the patient, with atopy being a well-documented risk factor of persistent wheeze. In this study we used infant atopic dermatitis as a measure of the immune phenotype of the child. Atopic dermatitis was associated with any wheeze and persistent wheeze in both sexes. Interestingly, although atopic dermatitis was associated with wheeze across age categories in girls, it was more strongly associated with wheeze in later ages in boys, suggesting that other factors, such as bronchiolitis, might be more important in early life. Furthermore, although we did not have data on cord blood IgE levels, as consistent with the existing literature,⁴⁴ we documented a doubled prevalence of inhalant sensitization in early childhood and midchildhood among children with persistent wheeze compared with never/infrequent or early wheeze. Specifically, inhalant allergen sensitization might be more indicative of the wheeze phenotype because the prevalence of sensitization was similar between the wheeze phenotypes when food allergen sensitization was also considered.

Three wheeze phenotypes were identified in Project Viva. Although this is consistent with other birth cohorts, some have identified intermediate- and late-onset wheeze as additional phenotypes, such as the Avon Longitudinal Study of Parents and Children and Prevention and Incidence of Asthma and Mite Allergy cohorts.¹⁴ Although the probability of wheeze in the persistent wheeze group remains relatively high (50% to 90%, Fig 2), we noted that this probability also increased with age. Thus it is possible that we were unable to differentiate children with intermediate- and late-onset wheeze from those identified as having persistent wheeze in our cohort. This might be due to the relatively smaller sample size compared with the reported cohorts. Furthermore, differences in identification of subgroups can stem from the composition of the birth cohort and methodological differences. Although latent class mixed models analysis allows the use of exact ages at the time of outcome assessment, other similar analyses, such as longitudinal latent class analysis, do not. Furthermore, because latent class analysis relies on the availability of longitudinal data, differences in the completeness of the data and the length of follow-up of the cohort might partly explain these discrepancies.

Although we focused on the outcome of wheeze in this study, it would be interesting to examine sex-specific risk factors of physician-diagnosed asthma and wheeze without an asthma diagnosis. In the Project Viva cohort, at questionnaire year 7, the prevalence of wheeze in the past 12 months and current asthma were concordant (16.4% and 19.2%, respectively). That is to say, by age 7 years, very few children with wheeze did not have an asthma diagnosis. Thus we expect that an analysis with physician-diagnosed asthma would yield similar results, but further studies are needed to confirm this hypothesis. Because the prevalence of potentially undiagnosed asthma is likely low overall, an analysis with this outcome might not be adequately powered in this cohort.

Our study has several strengths. First, we analyzed data from a large prebirth cohort with regular assessment of respiratory symptoms. Compared with our previous study using the Home Allergens cohort,¹³ children in Project Viva are not selected for high risk of atopy, making the results of this study more generalizable to a general population. The use of longitudinal data has several advantages, including regular data collection with short intervals minimizing recall bias and the possibility of

following an individual's symptoms over time. In addition, although predictors of wheeze are of epidemiologic importance, this study also identified distinct phenotypes of wheeze based on each subject's reports and examined the sex-specific predictors of these phenotypes. Being able to predict the trajectory of a child's symptoms using sociodemographic factors, family history, and early-life events is of clinical and prognostic value. Finally, we used multiple imputation for predictors and covariates in this study to deal with missing data, which maximizes statistical power and improves generalizability of the results to the population sampled by this study. Additionally, the results of the study, including the effect sizes of the risk factors, were similar with and without imputation, further validating the appropriate use of the multiple imputation technique. We chose not to impute the outcome of wheeze because it is difficult to be certain that missing outcomes are not missing completely at random in a longitudinal study, in which case multiple imputations would not be valid. To further validate the absence of obvious bias, we found no correlation between missing data at year 9 and previous reports of wheeze at years 1, 3, 5, and 7 and found that the baseline characteristics of the subjects with at least 1 wheeze outcome ($n = 1623$) and those with 1 or more wheeze outcomes at 5 years or less and 1 or more wheeze outcomes at greater than 5 years ($n = 1295$) were similar to those of the Project Viva cohort ($n = 2128$).

One limitation of this study is that the cohort was mostly white and relatively well-off (almost 60% had a yearly household income $> \$70,000$ at enrollment during pregnancy), which might limit the generalizability of the findings to other populations with a different composition. The assessment of the outcome was based on parental reports but not validated with clinical records. In this cohort more boys wheezed than girls, with a total of 64 and 69 girls identified as having early transient and persistent wheeze, respectively. Thus it is possible that there was limited power to examine predictors of distinct wheeze phenotypes, and future larger studies are needed to confirm the current findings. Finally, given that infant bronchiolitis was associated with wheeze, having data on the viruses associated with bronchiolitis might further provide insight on the mechanism leading to wheeze in children. In particular, respiratory syncytial virus and, more recently, rhinovirus C have been associated with recurrent wheezing illness^{45,46} and an increased prevalence of subsequent asthma.^{34,47} However, we did not have data on the specific viruses that caused bronchiolitis in infancy.

In conclusion, using a large birth cohort of children followed through preadolescence, we identified sex-specific risk factors for wheeze and for distinct phenotypes of wheeze. These predictors can have clinical and prognostic significance. Future studies are needed to examine the mechanisms underlying these sex-specific effects.

Clinical implications: This study found sex-specific predictors of wheeze and longitudinal wheeze patterns, including paternal asthma and race/ethnicity. These findings can have prognostic value in the care of children with asthma.

REFERENCES

- Venn A, Lewis S, Cooper M, Hill J, Britton J. Questionnaire study of effect of sex and age on the prevalence of wheeze and asthma in adolescence. *BMJ* 1998;316:1945-6.
- Skobeloff EM, Spivey WH, St Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA* 1992;268:3437-40.
- Fu L, Freishtat RJ, Gordish-Dressman H, Teach SJ, Resca L, Hoffman EP, et al. Natural progression of childhood asthma symptoms and strong influence of sex and puberty. *Ann Am Thorac Soc* 2014;11:939-44.
- Schatz M, Camargo CA Jr. The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Ann Allergy Asthma Immunol* 2003;91:553-8.
- Almqvist C, Worm M, Leynaert B. Impact of gender on asthma in childhood and adolescence: a GAZLEN review. *Allergy* 2008;63:47-57.
- Debley JS, Redding GJ, Crichtlow CW. Impact of adolescence and gender on asthma hospitalization: a population-based birth cohort study. *Pediatr Pulmonol* 2004;38:443-50.
- Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. *Thorax* 1992;47:537-42.
- Hibbert M, Lannigan A, Raven J, Landau L, Phelan P. Gender differences in lung growth. *Pediatr Pulmonol* 1995;19:129-34.
- Dratva J, Schindler C, Curjuric I, Stolz D, Macsali F, Gomez FR, et al. Perimenstrual increase in bronchial hyperreactivity in premenopausal women: results from the population-based SAPALDIA 2 cohort. *J Allergy Clin Immunol* 2010;125:823-9.
- Kharitonov SA, Logan-Sinclair RB, Busset CM, Shinebourne EA. Peak expiratory nitric oxide differences in men and women: relation to the menstrual cycle. *Br Heart J* 1994;72:243-5.
- Yu CK, Liu YH, Chen CL. Dehydroepiandrosterone attenuates allergic airway inflammation in *Dermatophagoides farinae*-sensitized mice. *J Microbiol Immunol Infect* 2002;35:199-202.
- Wright AL, Stern DA, Kauffmann F, Martinez FD. Factors influencing gender differences in the diagnosis and treatment of asthma in childhood: the Tucson Children's Respiratory Study. *Pediatr Pulmonol* 2006;41:318-25.
- Tse SM, Coull BA, Sordillo JE, Datta S, Gold DR. Gender- and age-specific risk factors for wheeze from birth through adolescence. *Pediatr Pulmonol* 2015;50:955-62.
- Savenije OE, Granell R, Caudri D, Koppelman GH, Smit HA, Wijga A, et al. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J Allergy Clin Immunol* 2011;127:1505-12.e14.
- Stein RT, Holberg CJ, Morgan WJ, Wright AL, Lombardi E, Taussig L, et al. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. *Thorax* 1997;52:946-52.
- Caudri D, Savenije OE, Smit HA, Postma DS, Koppelman GH, Wijga AH, et al. Perinatal risk factors for wheezing phenotypes in the first 8 years of life. *Clin Exp Allergy* 2013;43:1395-405.
- Lodge CJ, Zaloumis S, Lowe AJ, Gurrin LC, Matheson MC, Axelrad C, et al. Early-life risk factors for childhood wheeze phenotypes in a high-risk birth cohort. *J Pediatr* 2014;164:289-94, e1-2.
- Midodzi WK, Rowe BH, Majaesic CM, Saunders LD, Senthilselvan A. Predictors for wheezing phenotypes in the first decade of life. *Respirology* 2008;13:537-45.
- Oken E, Baccarelli AA, Gold DR, Kleinman KP, Litonjua AA, De Meo D, et al. Cohort profile: project viva. *Int J Epidemiol* 2015;44:37-48.
- Chippes BE. Determinants of asthma and its clinical course. *Ann Allergy Asthma Immunol* 2004;93:309-18, 80.
- Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics* 2012;129:735-44.
- Turner S. Perinatal programming of childhood asthma: early fetal size, growth trajectory during infancy, and childhood asthma outcomes. *Clin Dev Immunol* 2012;2012:962923.
- Sonnenschein-van der Voort AM, Jaddoe VW, van der Valk RJ, Willemsen SP, Hofman A, Moll HA, et al. Duration and exclusiveness of breastfeeding and childhood asthma-related symptoms. *Eur Respir J* 2012;39:81-9.
- Chen Q, Just AC, Miller RL, Perzanowski MS, Goldstein IF, Perera FP, et al. Using latent class growth analysis to identify childhood wheeze phenotypes in an urban birth cohort. *Ann Allergy Asthma Immunol* 2012;108:311-5.e1.
- Proust-Lima C, Philipps V, Diakite A, Liqueur B. lcmr: estimation of latent class mixed models, joint latent class mixed models and mixed models for curvilinear outcomes. R package version 163. Available at: <https://cran.r-project.org/web/packages/lcmr/>. 2013. Accessed July 17, 2013.
- Pan W, Connett J. Selecting the working correlation structure in generalized estimating equations with application to the lung health study. *Stat Sin* 2002;12:475-90.
- Arshad SH, Karmaus W, Raza A, Kurukulaaratchy RJ, Matthews SM, Holloway JW, et al. The effect of parental allergy on childhood allergic diseases depends on the sex of the child. *J Allergy Clin Immunol* 2012;130:427-34.e6.

28. Kopriva F, Godava M, Markova M, Vodicka R, Dusek L, Muzik J, et al. Possible control of paternal imprinting of polymorphisms of the ADAM33 gene by epigenetic mechanisms and association with level of airway hyperresponsiveness in asthmatic children. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2013;157:367-73.
29. Naumova AK, Al Tuwaijri A, Morin A, Vaillancout VT, Madore AM, Berlivet S, et al. Sex- and age-dependent DNA methylation at the 17q12-q21 locus associated with childhood asthma. *Hum Genet* 2013;132:811-22.
30. Paaso EM, Jaakkola MS, Rantala AK, Hugg TT, Jaakkola JJ. Allergic diseases and asthma in the family predict the persistence and onset-age of asthma: a prospective cohort study. *Respir Res* 2014;15:152.
31. Green CA, Yeates D, Goldacre A, Sande C, Parslow RC, McShane P, et al. Admission to hospital for bronchiolitis in England: trends over five decades, geographical variation and association with perinatal characteristics and subsequent asthma. *Arch Dis Child* 2016;101:140-6.
32. Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA Jr. Temporal trends in emergency department visits for bronchiolitis in the United States, 2006 to 2010. *Pediatr Infect Dis J* 2014;33:11-8.
33. Midulla F, Pierangeli A, Cangiano G, Bonci E, Salvadei S, Scagnolari C, et al. Rhinovirus bronchiolitis and recurrent wheezing: 1-year follow-up. *Eur Respir J* 2012;39:396-402.
34. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax* 2010;65:1045-52.
35. Valkonen H, Waris M, Ruohola A, Ruuskanen O, Heikkinen T. Recurrent wheezing after respiratory syncytial virus or non-respiratory syncytial virus bronchiolitis in infancy: a 3-year follow-up. *Allergy* 2009;64:1359-65.
36. Mikalsen IB, Halvorsen T, Oymar K. The outcome after severe bronchiolitis is related to gender and virus. *Pediatr Allergy Immunol* 2012;23:391-8.
37. Wegienka G, Havstad S, Joseph CL, Zoratti E, Ownby D, Woodcroft K, et al. Racial disparities in allergic outcomes in African Americans emerge as early as age 2 years. *Clin Exp Allergy* 2012;42:909-17.
38. Kumar R, Tsai HJ, Hong X, Gignoux C, Pearson C, Ortiz K, et al. African ancestry, early life exposures, and respiratory morbidity in early childhood. *Clin Exp Allergy* 2012;42:265-74.
39. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. *NCHS Data Brief* 2012;(94):1-8.
40. Gold DR, Wypij D, Wang X, Speizer FE, Pugh M, Ware JH, et al. Gender- and race-specific effects of asthma and wheeze on level and growth of lung function in children in six U.S. cities. *Am J Respir Crit Care Med* 1994; 149:1198-208.
41. Brehm JM, Acosta-Perez E, Klei L, Roeder K, Barmada MM, Boutaoui N, et al. African ancestry and lung function in Puerto Rican children. *J Allergy Clin Immunol* 2012;129:1484-90.e6.
42. Borrell LN, Nguyen EA, Roth LA, Oh SS, Tcheurekdjian H, Sen S, et al. Childhood obesity and asthma control in the GALA II and SAGE II studies. *Am J Respir Crit Care Med* 2013;187:697-702.
43. Zhang Y, McConnell R, Gilliland F, Berhane K. Ethnic differences in the effect of asthma on pulmonary function in children. *Am J Respir Crit Care Med* 2011;183: 596-603.
44. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332:133-8.
45. Cox DW, Bizzintino J, Ferrari G, Khoo SK, Zhang G, Whelan S, et al. Human rhinovirus species C infection in young children with acute wheeze is associated with increased acute respiratory hospital admissions. *Am J Respir Crit Care Med* 2013;188:1358-64.
46. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541-5.
47. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000;161:1501-7.

TABLE E1. Baseline characteristics of subjects with and without MI (n = 1623)

Characteristic	With MI data				Girls vs boys (<i>P</i> value)	Missing values	Without MI data		
	Total (n = 1623)	Girls (n = 778)	Boys (n = 845)	Total (n = 1623)			Girls (n = 778)	Boys (n = 845)	
	No. (%)			No. (%)					
Maternal smoking status				.27	12				
Never	1119 (69.0)	544 (70.0)	575 (68.0)			1111 (69.0)	540 (69.9)	571 (68.1)	
Former	321 (19.8)	156 (20.1)	165 (19.5)			319 (19.8)	155 (20.1)	164 (19.5)	
Smoked during pregnancy	182 (11.2)	77 (9.9)	105 (12.5)			181 (11.2)	77 (10.0)	104 (12.4)	
Maternal asthma	219 (13.5)	110 (14.2)	109 (12.9)	.45	8	218 (13.5)	110 (14.2)	108 (12.9)	
Maternal hay fever	487 (30.0)	232 (29.8)	255 (30.1)	.88	8	484 (30.0)	231 (29.8)	253 (30.1)	
Maternal eczema	210 (12.9)	96 (12.4)	114 (13.4)	.52	7	209 (12.9)	96 (12.4)	113 (13.5)	
Paternal asthma	191 (11.8)	85 (10.9)	106 (12.6)	.31	48	185 (11.7)	82 (10.8)	103 (12.6)	
Paternal hay fever	430 (26.5)	208 (26.8)	222 (26.2)	.77	79	411 (26.6)	199 (27.0)	212 (26.3)	
Paternal eczema	96 (5.9)	41 (5.3)	55 (6.5)	.34	51	93 (5.9)	40 (5.3)	53 (6.5)	
Household income >\$70,000/y	966 (59.5)	456 (58.6)	510 (60.3)	.50	159	917 (62.6)	437 (60.9)	480 (64.3)	
Child race/ethnicity				.31	2				
Black	254 (15.7)	114 (14.7)	140 (16.6)			254 (15.7)	114 (14.7)	140 (16.6)	
Hispanic	86 (5.3)	35 (4.5)	51 (6.0)			86 (5.3)	35 (4.5)	51 (6.0)	
White	1049 (64.6)	518 (66.5)	532 (62.9)			1048 (64.7)	517 (66.5)	531 (62.9)	
Other	233 (14.4)	111 (14.3)	122 (14.5)			233 (14.4)	111 (14.3)	122 (14.5)	
Season of birth				.98	0				
Winter	410 (25.3)	199 (25.6)	211 (25.0)			410 (25.3)	199 (25.6)	211 (25.0)	
Spring	430 (26.5)	207 (26.6)	223 (26.4)			430 (26.5)	207 (26.6)	223 (26.4)	
Summer	426 (26.2)	201 (25.8)	225 (26.6)			426 (26.2)	201 (25.8)	225 (26.6)	
Fall	357 (22.0)	171 (22.0)	186 (22.0)			357 (22.0)	171 (22.0)	186 (22.0)	
Mean (SD)									
Gestation length (wk)	39.5 (1.9)	39.5 (1.8)	39.4 (1.9)	.47	0	39.5 (1.9)	39.5 (1.8)	39.4 (1.9)	
Birth weight for gestational age, (z score)	0.20 (0.96)	0.18 (0.94)	0.21 (0.98)	.60	1	0.20 (0.96)	0.18 (0.94)	0.21 (0.98)	
Duration of breast-feeding (mo)	6.0 (4.6)	6.1 (4.6)	5.9 (4.6)	.42	127	6.2 (4.6)	6.2 (4.6)	6.1 (4.6)	
No. (%)									
Environmental smoke exposure before age 1 y	149 (9.2)	71 (9.1)	78 (9.3)	.92	208	109 (7.7)	54 (7.8)	55 (7.6)	
Bronchiolitis before age 1 y	243 (15.0)	96 (12.3)	147 (17.4)	.01	324	171 (13.2)	64 (10.0)	107 (16.2)	
Atopic dermatitis before age 1 y	369 (22.8)	162 (20.8)	207 (24.5)	.10	325	290 (22.3)	132 (20.8)	158 (23.9)	

Note: We did not use imputed outcome data for this article.

MI, Multiple imputation.

TABLE E2. Baseline characteristics of subjects assigned to a wheeze phenotype with and without MI (n = 1295)

Characteristic	With MI data			Girls vs boys (<i>P</i> value)	Missing values	Without MI data		
	Total	Girls	Boys			Total	Girls	Boys
	(n = 1295)	(n = 630)	(n = 665)			(n = 1295)	(n = 630)	(n = 665)
	No. (%)					No. (%)		
Maternal smoking status				.12	6			
Never	910 (70.3)	456 (72.4)	454 (68.2)			906 (70.3)	454 (72.4)	452 (68.3)
Former	262 (20.2)	124 (19.6)	138 (20.8)			261 (20.2)	123 (19.6)	138 (20.8)
Smoked during pregnancy	123 (9.5)	50 (7.9)	73 (11.0)			122 (9.5)	50 (8.0)	72 (10.9)
Maternal asthma	166 (12.8)	85 (13.6)	80 (12.1)	.43	5	165 (12.8)	85 (13.5)	80 (12.1)
Maternal hay fever	392 (30.2)	191 (30.3)	201 (30.2)	.96	5	390 (30.2)	190 (30.3)	200 (30.2)
Maternal eczema	167 (12.9)	77 (12.3)	89 (13.4)	.53	4	166 (12.9)	77 (12.3)	89 (13.4)
Paternal asthma	155 (12.0)	76 (12.0)	80 (12.0)	.99	35	151 (12.0)	73 (11.9)	78 (12.0)
Paternal hay fever	343 (26.5)	171 (27.1)	173 (26.0)	.64	59	329 (26.6)	163 (27.2)	166 (26.1)
Paternal eczema	79 (6.1)	36 (5.7)	43 (6.5)	.58	35	77 (6.1)	35 (5.7)	42 (6.5)
Household income >\$70,000/y	804 (62.1)	382 (60.7)	422 (63.5)	.32	97	772 (64.4)	369 (62.4)	403 (66.4)
Child race/ethnicity				.65	1			
Black	172 (13.3)	82 (13.1)	90 (13.5)			172 (13.3)	82 (13.0)	90 (13.5)
Hispanic	52 (4.0)	21 (3.3)	31 (4.7)			52 (4.0)	21 (3.3)	31 (4.7)
White	881 (68.0)	433 (68.7)	448 (67.4)			880 (68.0)	432 (68.7)	448 (67.4)
Other	190 (14.7)	94 (14.9)	96 (14.4)			190 (14.7)	94 (14.9)	96 (14.4)
Season of birth				.96	0			
Winter	332 (25.6)	159 (25.2)	173 (26.0)			332 (25.6)	159 (25.2)	173 (26.0)
Spring	328 (25.3)	163 (25.9)	165 (24.8)			328 (25.3)	163 (25.9)	165 (24.8)
Summer	350 (27.0)	168 (26.7)	182 (27.4)			350 (27.0)	168 (26.7)	182 (27.4)
Fall	285 (22.0)	140 (22.2)	145 (21.8)			285 (22.0)	140 (22.2)	145 (21.8)
	Mean (SD)					Mean (SD)		
Gestation length (wk)	39.5 (1.8)	39.5 (1.8)	39.4 (1.8)	.41	0	39.5 (1.8)	39.5 (1.8)	39.4 (1.8)
Birth weight for gestational age (<i>z</i> score)	0.19 (0.97)	0.19 (0.93)	0.18 (0.99)	.87	1	0.19 (0.97)	0.19 (0.93)	0.18 (1.00)
Duration of breast-feeding (mo)	6.4 (4.6)	6.4 (4.6)	6.4 (4.6)	.82	53	6.5 (4.6)	6.4 (4.6)	6.5 (4.6)
	No. (%)					No. (%)		
Environmental smoke exposure before age 1 y	109 (8.4)	55 (8.7)	54 (8.1)	.69	91	88 (7.3)	46 (7.8)	42 (6.9)
Bronchiolitis before age 1 y	188 (14.5)	74 (11.7)	114 (17.1)	.01	168	147 (13.0)	56 (10.1)	91 (15.9)
Atopic dermatitis before age 1 y	297 (22.9)	135 (21.4)	162 (24.3)	.23	168	252 (22.4)	117 (21.1)	135 (23.6)

Note: We did not use imputed outcome data for this article.

MI, Multiple imputation.

TABLE E3. Number of subjects with 1 to 9 wheeze outcomes available (n = 1623)

No. of wheeze outcomes	Total	Girls	Boys
1	116	54	62
2	128	56	72
3	112	48	64
4	112	54	58
5	150	67	83
6	174	87	87
7	180	82	98
8	250	126	124
9	401	204	197
Total	1623	778	845

TABLE E4. Baseline characteristics of the Project Viva cohort (n = 2128), those with at least 1 parental report of wheeze outcome on questionnaire years 1 to 9 (n = 1623, imputed data), and those included with at least 1 wheeze outcome at 5 years or less and at least 1 wheeze outcome at greater than 5 years (n = 1295, imputed data)

	Project Viva cohort (n = 2128)	Subset with >1 wheeze outcome (n = 1623)	Subset with >1 wheeze outcome ≤5 y and >1 wheeze outcome at >5 y (n = 1295)
		No. (%)	
Maternal smoking status			
Never	1458 (68.5)	1119 (69.0)	910 (70.3)
Former	401 (18.9)	321 (19.8)	262 (20.2)
Smoked during pregnancy	269 (12.6)	182 (11.2)	123 (9.5)
Maternal asthma	286 (13.4)	219 (13.5)	166 (12.8)
Maternal hay fever	605 (28.4)	487 (30.0)	392 (30.2)
Maternal eczema	273 (12.9)	210 (12.9)	166 (12.9)
Paternal asthma	244 (11.5)	191 (11.8)	155 (12.0)
Paternal hay fever	545 (25.6)	430 (26.5)	343 (26.5)
Paternal eczema	121 (5.7)	96 (5.9)	79 (6.1)
Household income >\$70,000/y	1229 (57.8)	966 (59.5)	804 (62.1)
Child race/ethnicity			
Black	357 (16.8)	254 (15.7)	172 (13.3)
Hispanic	129 (6.1)	86 (5.3)	52 (4.0)
White	1355 (63.7)	1049 (64.6)	881 (68.0)
Other	288 (13.5)	233 (14.4)	190 (14.7)
Season of birth			
Winter	521 (24.5)	410 (25.3)	332 (25.6)
Spring	557 (26.2)	430 (26.5)	328 (25.3)
Summer	579 (27.2)	426 (26.2)	350 (27.0)
Fall	471 (22.1)	357 (22.0)	285 (22.0)
Mean (SD)			
Gestation length (wk)	39.4 (2.0)	39.5 (1.9)	39.5 (1.8)
Birth weight for gestational age (z score)	0.17 (0.97)	0.20 (0.96)	0.19 (0.97)
Duration of breast-feeding (mo)	5.6 (4.5)	6.0 (4.6)	6.4 (4.6)
No. (%)			
Environmental smoke exposure before age 1 y	200 (9.4)	149 (9.2)	108 (8.4)
Bronchiolitis before age 1 y	317 (14.9)	243 (15.0)	189 (14.6)
Atopic dermatitis before age 1 y	482 (22.7)	369 (22.8)	297 (22.9)

TABLE E5. Age- and sex-specific predictors of any wheeze

	<5 y		≥5 y	
	Girls (n = 754), OR (95% CI)	Boys (n = 819), OR (95% CI)	Girls (n = 669), OR (95% CI)	Boys (n = 712), OR (95% CI)
Maternal asthma	2.09 (1.56-2.81)	2.14 (1.62-2.83)	1.73 (1.22-2.44)	1.40 (1.01-1.94)
Paternal asthma*	1.68 (1.21-2.34)	1.60 (1.20-2.15)	1.35 (0.92-1.98)	3.12 (2.31-4.21)
Household income >\$70,000/y	0.70 (0.54-0.92)	0.80 (0.63-1.00)	1.05 (0.78-1.42)	0.74 (0.56-0.96)
Child race/ethnicity (vs white)				
Black	1.94 (1.39-2.71)	1.42 (1.05-1.93)	3.05 (2.11-4.41)	1.79 (1.28-2.51)
Hispanic	2.75 (1.56-4.88)	1.42 (0.90-2.23)	4.19 (2.29-7.70)	1.95 (1.15-3.30)
Other	1.21 (0.88-1.67)	1.13 (0.85-1.51)	1.26 (0.87-1.82)	0.94 (0.67-1.30)
Season of birth (vs winter)				
Spring	0.95 (0.70-1.29)	1.28 (0.98-1.66)	0.92 (0.65-1.30)	0.86 (0.63-1.16)
Summer	0.67 (0.48-0.92)	0.92 (0.70-1.21)	0.62 (0.43-0.90)	0.75 (0.55-1.03)
Fall	0.66 (0.48-0.92)	1.20 (0.90-1.59)	0.76 (0.53-1.10)	0.98 (0.72-1.35)
Gestation length (wk)	0.93 (0.88-0.99)	0.95 (0.90-1.00)	0.95 (0.88-1.01)	0.94 (0.88-0.99)
Birth weight for gestational age (z score)	0.86 (0.76-0.98)	1.11 (1.00-1.24)	0.96 (0.83-1.11)	1.00 (0.89-1.13)
Duration of breast-feeding (mo)	0.94 (0.92-0.97)	0.99 (0.97-1.02)	0.97 (0.94-1.00)	1.02 (1.00-1.05)
Environmental smoke exposure before age 1 y	1.40 (0.93-2.12)	1.38 (0.96-2.00)	1.28 (0.76-2.15)	1.59 (1.04-2.42)
Bronchiolitis before age 1 y†	5.11 (3.75-6.96)	5.98 (4.58-7.81)	2.20 (1.50-3.24)	2.73 (1.99-3.74)
Atopic dermatitis before age 1 y*	1.70 (1.28-2.26)	1.29 (1.02-1.64)	1.77 (1.29-2.43)	1.93 (1.49-2.51)
Child age at outcome (y)	0.96 (0.87-1.06)	0.93 (0.86-1.01)	0.99 (0.91-1.07)	0.92 (0.85-0.99)

*Significant interaction with child's age in boys.

†Significant interaction with child's age in girls and boys.

TABLE E6. Allergen sensitization in early childhood and midchildhood and wheeze phenotypes*

	Never/infrequent wheeze, no. (%)	Early transient wheeze, no. (%)	Persistent wheeze, no. (%)
Sensitization to any inhalant allergen in early childhood (year 3) [†]	99 (20)	14 (16)	40 (45)
Sensitization to any inhalant allergen in midchildhood (year 7) [‡]	178 (40)	23 (33)	50 (62)
Sensitization to any allergen (inhalant and food) in midchildhood (year 7) [§]	230 (52)	36 (51)	54 (67)

*A total of 655 subjects had sensitization data in early childhood (year 3) and a wheeze phenotype (489 with never/infrequent wheeze, 87 with early transient wheeze, and 89 with persistent wheeze). A total of 595 subjects had sensitization data in midchildhood (year 7) and a wheeze phenotype (444 with never/infrequent wheeze, 70 with early transient wheeze, and 81 with persistent wheeze).

[†]Inhalant allergens in early childhood include dust, cat, dog, cockroach, and mold. A subject is considered sensitized if the specific IgE level is greater than 0.35 IU/mL.

[‡]Inhalant allergens in midchildhood include *Dermatophagoides farinae*, cat, dog, rye grass, cockroach, *Aspergillus* species, *Alternaria* species, and ragweed. A subject is considered sensitized if the specific IgE level is greater than 0.35 IU/mL.

[§]Food allergens in midchildhood include egg white, milk, soybean, wheat, and peanut. A subject is considered sensitized if the specific IgE level is greater than 0.35 IU/mL or the total IgE level is 100 IU/mL or greater.