Online Data Supplement

The Environmental Influences on Child Health Outcomes (ECHO) program

The ECHO Program supports multiple longitudinal studies using existing cohorts to investigate how environmental exposures — including physical, chemical, biological, social, behavioral, natural and built environments — influence child health and development. The studies focus on five key pediatric outcomes that have a high public health impact: pre-, peri-, and postnatal outcomes; upper and lower airway; obesity; neurodevelopment; and positive health. See https://www.nih.gov/research-training/environmental-influences-child-health-outcomes-echo-program for greater details.

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The Children's Respiratory and Environmental Workgroup (CREW)

CREW is funded by the ECHO program and consists of 12 individual cohort studies and 3 scientific centers. The overall goal of CREW program is to develop a better understanding of how early life environmental exposures and host factors interact to promote the development of specific asthma endotypes.

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Supplemental Methods

Data Harmonization

Each CREW birth cohort collected information from their study participants differently. To conduct an analysis using data from multiple cohorts first required harmonizing the data to derive the same variables for all subjects. This involved addressing differences in questions asked, differential length of follow-up, differential length of the recall period, and systematic missingness due to study protocols in which participants were not contacted at specific ages.

Harmonization was an iterative process involving the CREW data coordinating team at the University of Wisconsin (UW), together with data managers from each study. For wheeze data, two authors (SH, GW) first reviewed all questions used by the cohorts that included the word "wheeze." The individual cohorts then provided multiple records per child – one for each point of contact where a wheeze question was included. The questions used by the cohorts are shown in **Table E3** along with the time frame asked about (3mo, 12mo, or since last spoke). This time frame varied substantially as shown in **Figure E1**. Notably, four of the cohorts regularly asked about wheeze several times per year, while the timing of questionnaires for other cohorts was more spread out. After reviewing the questions and time distributions, we focused on creating harmonized variables indicating whether a child wheezed during each year from birth to age 11. For cohorts that asked about wheeze more frequently than one year, subject responses were combined, e.g., if there were four wheeze reports three months apart in a year, with 1 'yes' and 3 'no' responses, that would become a single 'yes' for the whole 12mo period.

Even in cohorts that had very regular follow-up visits, there was still a spread in the actual ages of the children when questionnaires were received. In the IIS cohort, for example, the visit around year 1 occurred between 11 and 15mo, but those responses ask about the last year and can all reasonably be combined under 'year 1'. A similar mapping was used for all the cohorts, such that a range of ages was used for each year variable; these intervals are shown in **Table E4**.

In general, the four cohorts that asked questions more frequently than once per year (CCCEH, COAST, URECA, EHAAS) had fairly small spreads around convenient time points such as 3mo, 6mo, 9mo and 12mo. That fact together with the shorter time periods between questionnaires (either 3mo, or 'since we last spoke'), made it reasonably straightforward to map the original wheeze variables to the new harmonized variables. For the other three cohorts (CCAAPS, IIS, TCRS), there were longer gaps between questionnaires and a larger spread in their timing. To map those responses to the new variables, we considered the time period the wheeze question referred to together with the age at which it was asked. For example, if a question asked about wheeze in the past 12mo and the questionnaire was completed when the child was 25mo old, that question would map to the new year 2 wheeze variable. In some cases, we used larger time ranges, for example, in IIS, there is a large spread of questionnaires from about 96-132mo, so we mapped responses in the interval 90-102mo to Year 8, 103-114mo to Year 9, and 115-126mo to Year 10. **Figure E2** shows the number of individuals with records at each age by cohort and year after mapping the questions from each cohort to the new variables. Data inconsistencies were manually reviewed by the data team in consultation with each participating study-specific research team. Data on the harmonized wheeze variable for each subject were then returned to each site for final review and approval before being collated into a

single data set for analysis. All subjects with three or more data points were included in the wheeze latent class analysis. Missing values by cohort are shown in **Table E5**.

By combining answers to multiple questions used by the cohorts, a single race/ancestry variable was created to categorize each study participant into one of seven groups: African American, European American, Caribbean Hispanic, Mexican American, Hispanic-Other, Multiple, Other.

Each included cohort also collected covariate information using a variety of questions related to environmental tobacco smoke (ETS) exposure, dog and cat exposure in infancy, and total serum IgE. Using the same procedures, the following covariates were harmonized: a variable representing maternal smoking during pregnancy (defined as 0=none, 1=1-10 cigarettes/day, and 2= >10 /day), and binary variables for whether a dog or cat was present in the home during infancy. In addition, total serum IgE measurements were collected from many subjects (n=2010), often at multiple time points and at ages which varied across cohorts. In order to include all the IgE data in our analyses, we first excluded records prior to age 3 (due to rapid increase in IgE levels during that period) and then fit a random intercept mixed-effects model to the longitudinal trajectories. That model was then used to predict the IgE value at age 6 for each individual with at least one data point. The standardized IgE values (z-scores) were then used as covariates in subsequent analyses.

Similar procedures were used to create a harmonized asthma variable. This variable was based on parental reports of whether a child had received an asthma diagnosis at any time by a physician, and if so, when that diagnosis occurred. For this analysis, subjects with a reported asthma diagnosis by age 11 were classified as asthmatics, regardless of whether their symptoms remitted. Age 11 was chosen as it covered the same period for which wheeze was assessed.

SNP Selection

The nine SNPs used for this study were chosen based on their previous associations with asthma. Because we did not have genome-wide genotypes for all of the CREW cohorts, we were limited in the number SNPs that we could genotype across this ~150kb region. Our selection approach was, therefore, to start with the 17 SNPs that were the lead SNPs in previous GWAS of asthma that were available at the time or were eQTLs for one or more of the genes across this extended locus. These 17 SNPs were described in detail in a previous review of the 17q locus (Stein et al. 2018). We then selected from among those SNPs those that best captured the LD structure among the 17 SNPs in African Americans, using 1000 Genome reference panels. These 17 SNPs are now shown in **Figure E7**. SNPs outlined in boxes were selected for genotyping in this study. As an example, we selected a SNP in *ZPBP2* (SNP #6) because this SNP has been shown to directly impact the looping and binding of an enhancer in *IKZF3* to the promoter of *ORMDL3*, and is the strongest eQTL for *ORMDL3* and *GSDMB* in blood immune cells. Therefore, we did not select SNP #5 in *IKZF3* because it was in LD with the *ZPBP2* SNP #6 in African Americans ($r^2 = 0.64$). Other SNPs were not selected because they were in LD with a selected SNP (e.g., #4, #9, and #10 were all in LD with SNP #8) or because the evidence for association was limited to populations of European ancestry and only in the context of early life ETS exposure (e.g., #7 and #11). This process was guided by extensive knowledge of and experience with this locus, and eventually resulted in nine SNPs being chosen for the study.

Statistical Analyses

We performed a latent class analysis (LCA) on the harmonized wheeze data to derive longitudinal “wheeze phenotypes” as represented by the different latent classes. The goal of the LCA was to assess wheezing over time. Thus subjects with only one data point do not provide

this information, and subjects with only two data points provide very limited information. Further, almost all subjects with only two data points had data limited to the first three years of the study, limiting inference about their wheeze patterns over time. For these reasons, study participants with fewer than three responses through age 11 were removed from the data set. For each remaining subject (n=3786), we constructed a wheezing "trajectory" from the binary yes/no variables indicating whether or not the child wheezed in each year of life. We used the R package poLCA (1) to discover latent classes. The Bayesian Information Criterion (BIC) was used to select the number of classes and is shown in **Figure E3**, with a minimum at k=4 classes. We used this number of classes in all subsequent association analyses.

To evaluate whether our requirement of three or more data points somehow biased analyses, we reran the LCA with all subjects, and with all subjects with two or more data points. In both cases, k=4 classes had the minimum BIC, and the resulting latent classes were nearly identical, reflecting the limited information in subjects with fewer than three data points.

Missing data

Many children could not be evaluated at one or more time points because data collection was not conducted in those years or the child's response was missing. **Table E5** provides information on total sample sizes and the number of missing values by cohort. To assess the role of missing data, we repeated the latent classes analyses in several ways. We reran the LCA using only complete cases, up to one missing data point, and up to two missing data points. In LCA, there is a general relationship such that the number of classes "chosen" by BIC tends to increase with sample size. As we only had n=601 complete cases (i.e. with data for all 11 years), for that LCA BIC was lowest for k=3 classes. Allowing up to two missing data points again produced a lowest BIC at k=4 classes. When we limited the data to year 10 and chose complete cases, the LCA

similarly produced the lowest BIC at k=4 classes. Finally, we found similar results when we sequentially removed individual cohorts from the analysis. As the genetic analyses only considered EA and AA children, we reran the LCA on those subsets separately. In both cases, BIC was lowest at k=4 classes. Overall, we found that LCA is quite robust to missing data, partially because only available data are used in the likelihood computations. Results from these sensitivity analyses were qualitatively very similar, with results comparable to our main Infrequent, Transient, Late-onset and Persistent classes.

Compositional data analysis (CoDA)

LCA assigns each participant a posterior probability of class membership for each latent class that sum to 1. Because many subjects did not have a high probability (e.g., > 0.80) of belonging to any single class, we did not categorize subjects to a single class based on their highest posterior probability class. Instead, we used a compositional data analysis (CoDA) approach that incorporated the probability of class membership information directly into subsequent analyses.

In this approach, each subject's wheezing "phenotype" consisted of the vector of posterior probabilities. To address the positivity and summation constraints associated with compositional data, we used the additive log ratio (alr) transform on the matrix of posterior probabilities of latent class membership (2). To compute this for *k* latent classes, one class is first chosen as the reference group, and then log[Prob(Class j) / Prob(Reference)] is computed for each of the other *k-1* wheezing classes. These represent the log-odds of being in each of the non-reference latent classes vs. being in the reference class. Each subject is then represented by *k-1* correlated outcomes corresponding to the log-odds of being classified as Class j versus the Reference class (a total of *k-1* log-ratios). For computational stability, we set any posterior probabilities less than

0.01 to be equal to 0.01 and reclosed the compositions. In two cases (total IgE and asthma), we first classified individuals to their posterior mode in order to discuss the percentages of individuals in the different groups

Associations with covariates and genotypes

We tested for associations between latent class membership and our non-genetic covariates using the following multiple regression model for the *k-1* log-ratios defined above:

$$\log[\ \text{Prob(Class j)} / \text{Prob(Reference)}\ ] \sim a + b_1 * \text{Sex} + b_2 * \text{Race} + b_3 * \text{IgE} + b_4 * \text{Smoke} + b_5 * \text{Dogs} + b_6 * \text{Cats},$$

where the IgE variable used the predicted total IgE values at age 6, the Smoke variable encoded maternal smoking during pregnancy, and the Dogs and Cats binary variables encoded whether the subjects were exposed to dogs or cats in the first year of life.

We then sought to quantify associations between our wheezing phenotypes and genotypes at our nine SNPs (**Table E2**) selected *a priori*. Due to ethnicity related differences in linkage disequilibrium (**Figure 3**) structure, we first stratified by our harmonized Race/Ancestry variable. Then, for each SNP, we computed additional multiple regressions with a term for genotype under an additive model:

$$\log[\ \text{Prob(Class j)} / \text{Prob(Reference)}\ ] \sim a + b_1 * \text{Sex} + b_2 * \text{Genotype} + b_3 * \text{IgE} + b_4 * \text{Smoke}.$$

Each SNP was considered separately; full results are presented in **Table E6**. Additional models including interactions between smoking and genotype were also considered. Sample sizes were too small to draw conclusions about such interactions or in subgroups other than African American and European American children.

Multiple comparisons and Statistical Significance

In **Table E6** we provide both unadjusted p-values, as well as an indication of whether each p-value was smaller than two adjusted thresholds, one given by estimating the "effective" number of SNPs, and the other given by the conservative Bonferroni correction. For the former, the effective number of SNPs, M_{eff}, was determined by the equation

$$M_{eff} = 1 + (M - 1)\left(1 - \frac{\mathrm{Var}(\lambda)}{M}\right),$$

where $\mathrm{Var}(\lambda)$ is the variance of the eigenvalues of the LD correlation matrix, and M=9 SNPs (7).

However, following recent recommendations from the statistical community (4,5), we have de-emphasized p-values and focused on model-based point estimates and 95% confidence intervals together with existing knowledge and LD structure to infer genetic associations. Although we performed multiple comparisons in this study, the SNPs were chosen because they were previously associated with early-onset asthma in children of European ancestry (see Stein et al. 2018 (3) for an extensive review). The idea of this and similar studies is that, by performing the same association analysis in a population with less LD between SNPs, only the "important" (e.g., functional) SNPs will still associate with the outcome. The other SNPs will no longer show an association because the previously observed associations were due to LD. Thus, the "null hypothesis" of no association between any of the SNPs and any wheezing phenotypes is not the correct null hypothesis. Instead, we expected to find multiple SNPs associated with wheeze phenotypes in EA children, and fewer associated in AA children due to the ancestrally-heterogenous LD patterns at the 17q12-21 locus. We find exactly that as shown in **Figure 2**. This type of analysis was also recently done for the early-onset asthma phenotype by comparing

associations in EA and AA children across this same 17q locus with the same resulting lead SNP (6).

Additional Results

For completeness, in this section we present additional results (**Figure E6**) from the latent class analysis and the relationships between wheezing and the included covariates.

Overall, boys were more likely than girls to have wheezed by age 11 years (70% vs 61%, $p = 5.1x10^{-8}$), and had a higher posterior probability of being in the Transient (20% vs 18%, $p = 2.3x10^{-7}$), Late-onset (13% vs 11%, $p = 2.4x10^{-8}$) and Persistent (14% vs 9%, $p = 1.8 x10^{-10}$) classes than girls.

Prenatal maternal smoke exposure was associated with increased odds of wheezing**.** The proportion in the Persistent class was double in children of mothers who smoked >10 cigarettes per day (heavy smokers) compared with children of mothers who never smoked (23% vs 11%, $p=4.8 x10^{-7}$). The proportion in the Transient class was also greater among the heavily smoke exposed (26% vs 19%, $1.4 x10^{-5}$). In contrast, the fraction in the Late-onset class was similar across the three smoke exposure groups (~12%). The proportions of subjects with mothers in the three smoking categories were similar for AA and EA Children. For AA children, 14% of mothers smoked, but only 1% were in the "heavy" (>10 cigarettes per day) category. For EA children, 9% had mothers who smoked, but 3% were in the heavy category. Thus, while AA children had a slightly larger percentage of mothers who smoked during pregnancy, mothers of EA children smoked more during pregnancy.

Total serum IgE, adjusted for age, was also positively associated with wheezing. An increase of one standard deviation in (log) IgE resulted in ORs of 1.34, 1.85, and 2.15 for the Transient,

Late-onset, and Persistent classes respectively vs Infrequent (all three $p < 10^{-5}$). Using only well-classified individuals (i.e., posterior probability > 0.9), the predicted IgE values at age six years were similar for the Persistent and Late-onset classes (98 vs 77 IU/ml, p=0.62), but lower ($p < 0.001$) for the Transient and Infrequent classes, who showed similar IgE levels (35 vs 36 IU/ml, p=0.99).

References:

1. Drew A. Linzer, Jeffrey B. Lewis (2011). poLCA: An R Package for Polytomous Variable Latent Class Analysis. Journal of Statistical Software, 42(10), 1-29.

2. Aitchison, J. (1986). The statistical analysis of compositional data. New York: Chapman and Hall.

3. Stein MM, Thompson EE, Schoettler N, Helling BA, Magnaye KM, Stanhope C, et al. A decade of research on the 17q12-21 asthma locus: Piecing together the puzzle. J Allergy Clin Immunol. 2018;142(3):749-64 e3.

4. Ronald L. Wasserstein & Nicole A. Lazar (2016) The ASA Statement on p-Values: Context, Process, and Purpose, The American Statistician, 70:2, 129-133.

5. Amrhein V, Greenland S, McShane B. (2019) Scientists rise up against statistical significance. Nature. 2019 Mar;567(7748):305-307.

6. Ober C, McKennan CG, Magnaye KM, Altman MC, Washington C, 3rd, Stanhope C, et al. Expression quantitative trait locus fine mapping of the 17q12-21 asthma locus in African American children: a genetic association and gene expression study. Lancet Respir Med. 2020;8(5):482-92.

7. Nyholt, D. (2004). A Simple Correction for Multiple Testing for Single-Nucleotide Polymorphisms in Linkage Disequilibrium with Each Other. AJHG; 74(4):765-769

Supplemental Figures

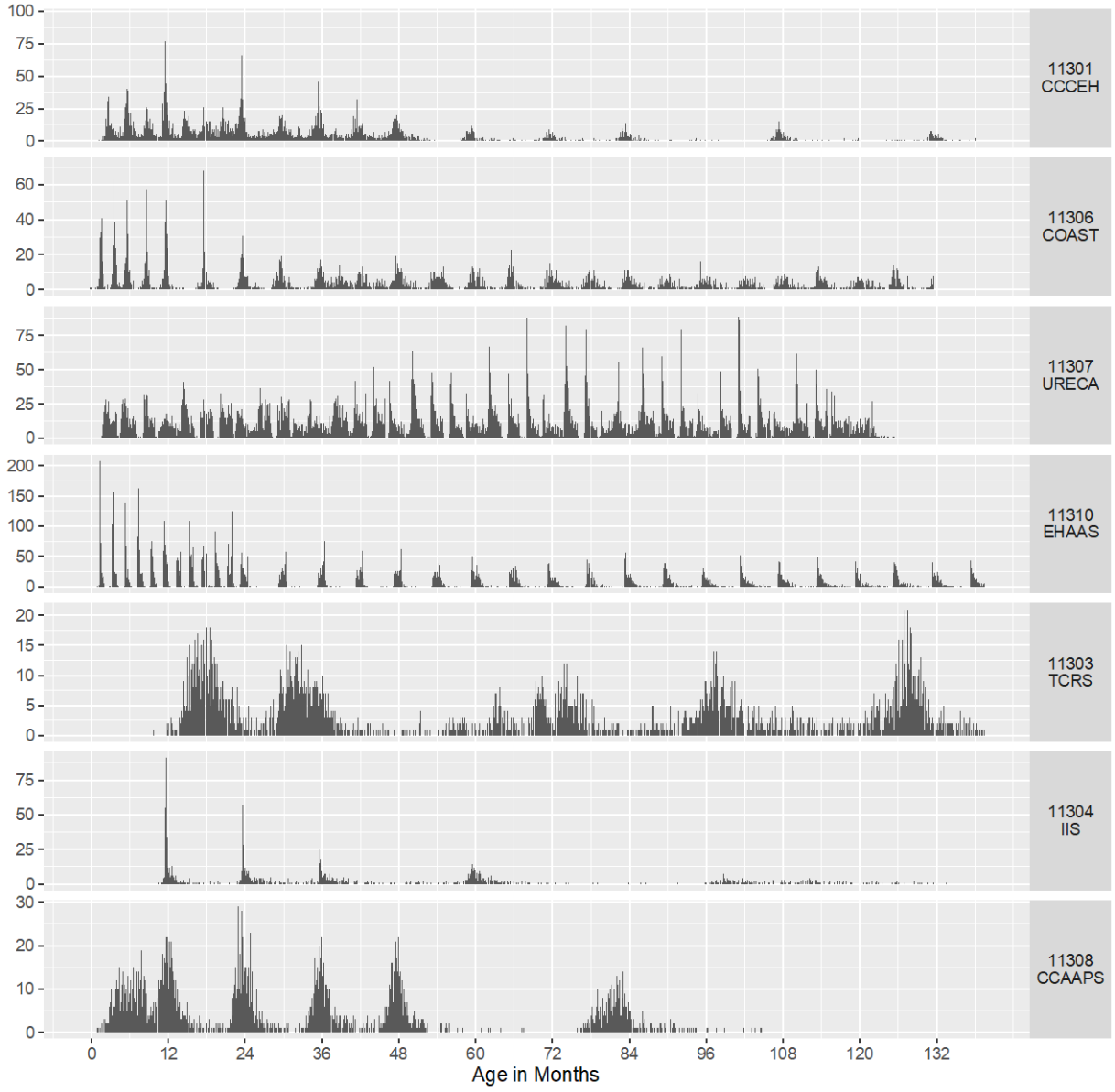

Figure E1. The temporal distribution of wheeze records for the seven cohorts included in this study. Time in months is shown along the x-axis and the number of records at a given time is shown on the y-axis.

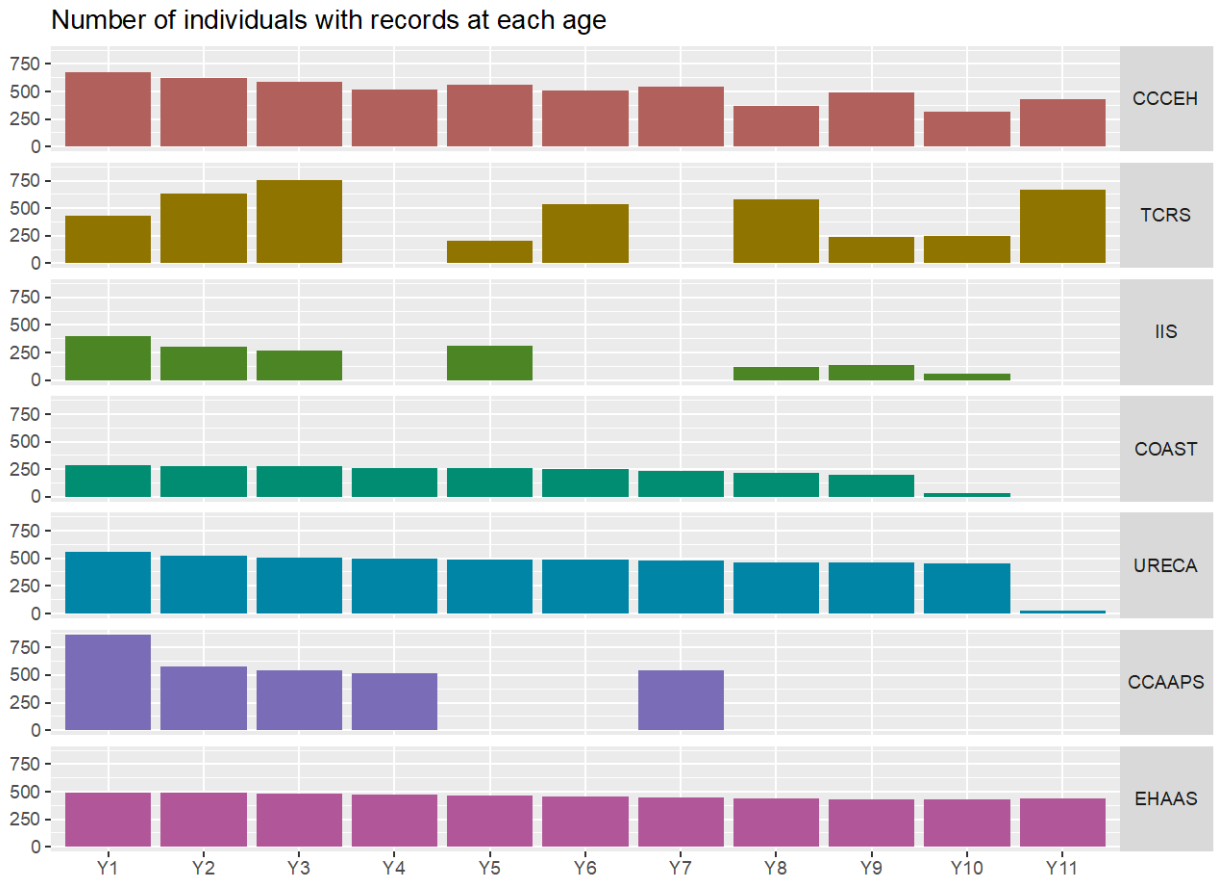

Figure E2. Number of individuals with harmonized wheeze data from each cohort, in each year. The set of records shown in **Figure E1** were harmonized and mapped to this new set of wheeze variables indicating wheeze or not in each year of life.

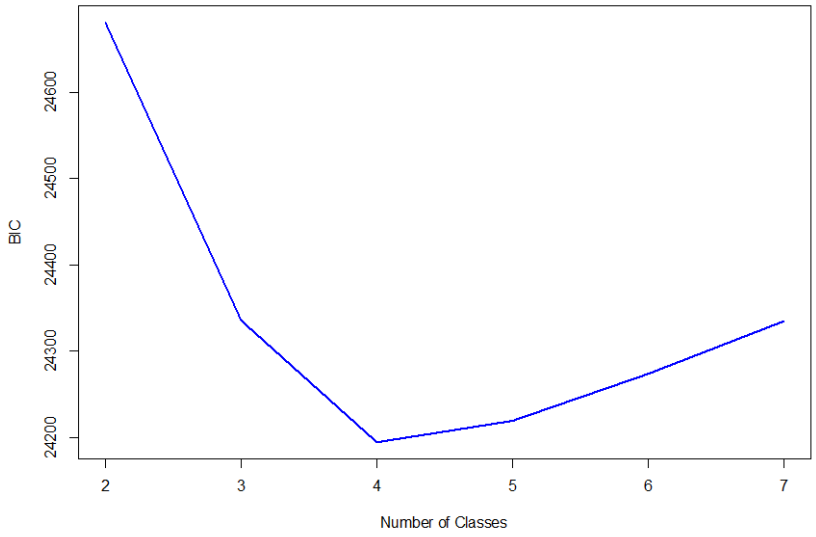

Figure E3. The Bayesian Information Criterion (BIC) was used to select the number of latent classes and achieved its minimum value at k=4 wheeze classes.

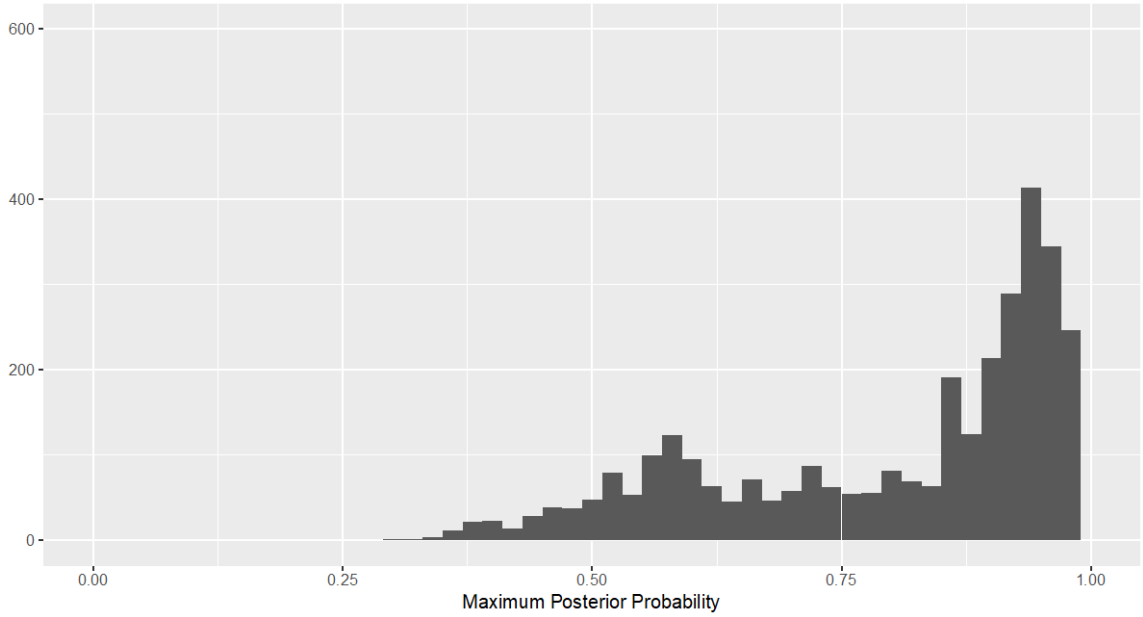

Figure E4. Histogram of the maximum posterior probability for each subject. Only 67% of the subjects had a maximum posterior probability greater than 0.80.

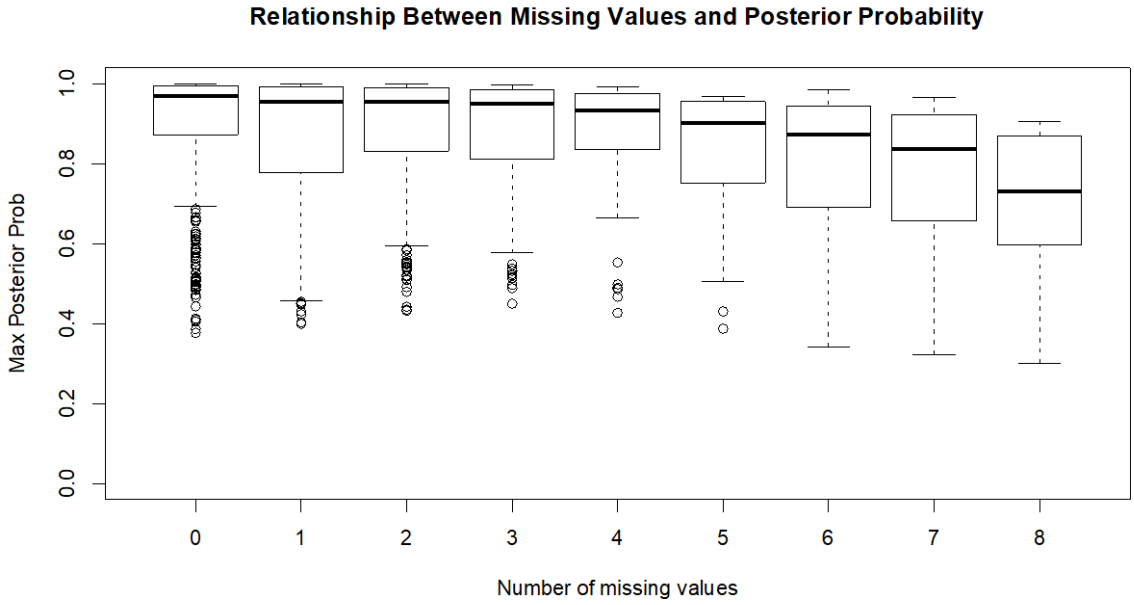

Figure E5. The maximum posterior probability for each individual plotted as a function of the number of missing values. Although subjects with a lot of missing data tended to have lower maximum posterior probabilities, some subjects with complete or nearly complete data were also classified this way.

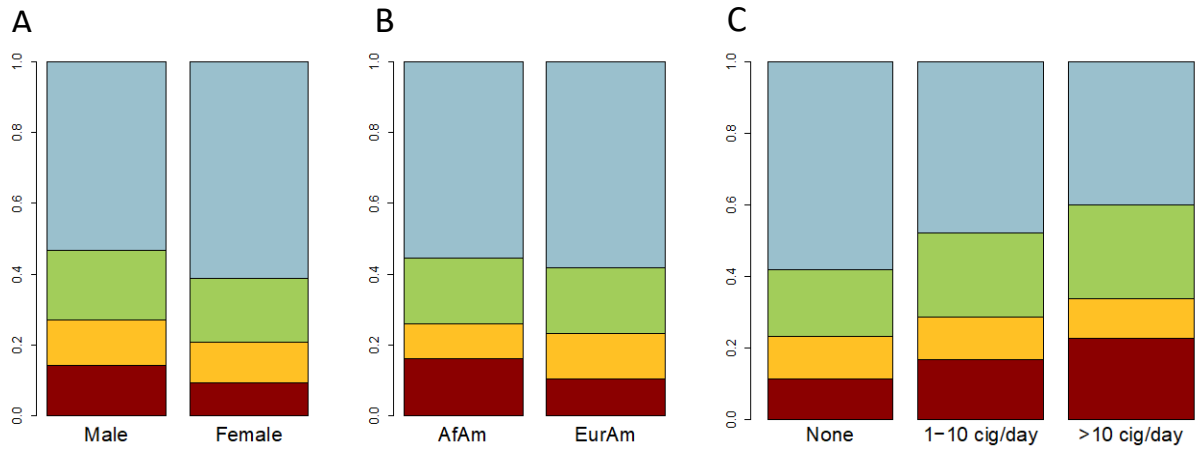

Figure E6. Proportions of each latent class by gender (A), race/ancestry (B), and maternal smoking during pregnancy (C). The colors correspond to those used in **Figure 1**: Red=Persistent, Yellow=Late-onset, Green=Transient, and Blue=Infrequent.

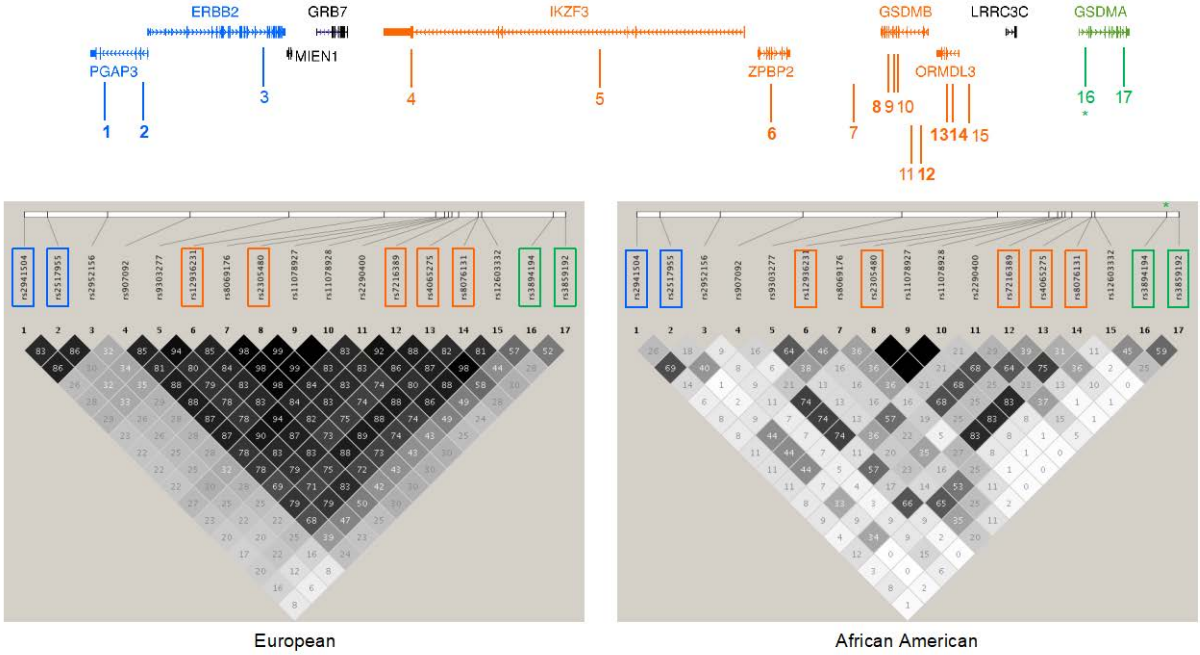

Figure E7. SNPs and LD patterns across the 17q12-21 locus in European and African American samples. The numbered SNPs were lead SNPs in previous GWASs of childhood asthma. The nine SNPs in this study were chosen to cover the locus based on LD patterns.

Table E1. Overview of included cohorts

Cohort	Location	Year began	High risk cohort?	Latent Class Analysis Demographics (n=3786)	Genetic Association Analysis Sample Sizes (n=1928)	
				Sample Size	AA	EA
CCAAPS	Cincinnati, OH	2001	Yes	626	85	320
CCCEH	New York, NY	1997	No	604	132	0
COAST	Madison, WI	1998	Yes	281	10	210
EHAAS	Boston, MA	1994	Yes	489	24	266
IIS	Tucson, AZ	1997	No	334	0	175
TCRS	Tucson, AZ	1980	No	937	8	332
URECA	United States	2004	Yes	515	361	5
Total				3786	620	1308

CCAAPS= Cincinnati Childhood Allergy and Air Pollution Study; CCCEH=Columbia Center for Children's Environmental Health Cohort; COAST=Childhood Origins of Asthma; EHAAS=Epidemiology of Home Allergens and Asthma Study; IIS=Infant Immune Study; TCRS=Tucson Children's Respiratory Study; URECA=Urban Environment and Childhood Asthma

Table E2. Information about the nine SNPs genotyped in this study. See Stein et al. (2018) and Ober et al. (2020) for additional details regarding each SNP.

rs	Chr	Pos	Gene	Alleles	Risk Allele
rs2941504	17	39674647	*PGAP3*	A/G	A
rs2517955	17	39687428	*PGAP3*	C/T	C
rs12936231	17	39872867	*ZPBP2*	C/G	C
rs2305480	17	39905943	*GSDMB*	A/G	G
rs7216389	17	39913696	*GSDMB*	C/T	T
rs4065275	17	39924612	*ORMDL3*	A/G	G
rs8076131	17	39924659	*ORMDL3*	A/G	A
rs8069202	17	39965947	*GSDMA*	A/G	A
rs3859192	17	39972395	*GSDMA*	C/T	T

PGAP3, post-GPI attachment to proteins 3; *ZPBP2*, zona pellucida binding protein 2; *GSDMB*, gasdermin B; *ORMDL3*, ORM1-like 3; *GSDMA*, gasdermin A.

Table E3. Questions used by the cohorts to assess wheeze.

Cohort	Questions	3mo	12mo	Last spoke
CCCEH	Has your child had wheeze in the past 3mo?	X		
	Has your child had wheeze/whistle in chest in the past 12mo?		X	
TCRS	How often has this child had wheezing or whistling in past year?		X	
	During the past year, has chest sounded wheezy or whistling?		X	
IIS	Yr 1,2: How often has this child had wheezing or whistling? Ordinal Scale		X	
	Yr 3,5,9: During the past year, how many wheezing episodes?		X	
COAST	Has your child wheezed in the past year?		X	
	Has your child had wheezing or whistling in the chest at any time in the last year?		X	
	Since the last visit, has your child's chest ever sounded wheezy or whistling? Without a cold?			X
	Since the last visit, has your child's chest ever sounded wheezy or whistling? When (he/she) had a cold?			X
	Has your child had wheezing, shortness of breath, or chest tightness since the last contact with the study coordinator?			X
URECA	Child's chest has made wheezing sound since birth/since last spoken to mother?			X
CCAAPS	In the past 12 months, have you ever noticed your child wheezing?		X	
EHAAS	Wheezing/whistling since last spoke?			X

Table E4. Intervals used for each cohort to map the original wheeze questions to the new harmonized wheeze variables for each year. For example, in IIS, questions asked between 21 and 27 months were mapped to the Year 2 variable.

Study	Year 1		Year 2		Year 3		Year 4		Year 5		Year 6		Year 7		Year 8		Year 9		Year 10		Year 11	
CCCEH	0	13.5	13.5	25.5	25.5	39	39	51	51	63	63	75	75	87			105	111			129	135
TCRS	0	18	18	30	30	39			54	66	66	78			90	102	102	114	114	126	126	138
IIS	0	15	21	27	33	39			57	66					90	102	102	114	114	126		
COAST	0	15	15	27	27	39	39	51	51	63	63	75	75	87	87	99	99	111	111	123	123	132
URECA	0	15	15	27	27	39	39	51	51	63	63	75	75	87	87	99	99	111	111	123	123	135
CCAAPS	0	15	21	27	33	39	45	51					78	90								
EHAAS	0	13	13	27	27	39	39	51	51	63	63	75	75	87	87	99	99	111	111	123	123	135

Table E5. Total sample sizes and missing values by cohort. The top row shows the number of complete cases (n=601). The cumulative total column shows the number of subjects with up to that many missing values. For example, there were n=307 subjects with 2 missing values, and n=1511 subjects with <=2 missing values. Individuals with 9 or 10 missing values were excluded from the final LCA, representing n=283 and n=354 subjects, respectively. The final total LCA sample size was n=3786. Some cohorts had structural missingness, i.e., questionnaires not given in some years.

nMissing	CCCEH	TCRS	IIS	COAST	URECA	CCAAPS	EHAAS	Sum	Cumulative Total
0	195	0	0	0	27	0	379	601	601
1	140	0	0	8	404	0	51	603	1204
2	91	0	0	177	26	0	13	307	1511
3	71	0	0	47	9	0	8	135	1646
4	41	0	0	10	13	0	5	69	1715
5	20	0	0	11	8	0	5	44	1759
6	11	483	167	8	1	318	6	994	2753
7	12	293	96	5	14	204	9	633	3386
8	23	161	71	15	13	104	13	400	3786
9	37	87	47	3	19	85	5	283	
10	42	57	54	1	34	166	0	354	
Sum	683	1081	435	285	568	877	494	4423	

Table E6. Results of the genetic association analysis. Odds ratios (OR) use the Infrequent class as the comparison. The p-value column is unadjusted. The last two columns show whether the unadjusted p-value was below the multiple comparison p-value threshold (in green) given by either using the effective number of SNPs (< p_M_{eff}) based on LD (<0.00679 for AA and <0.0126 for EA) or the conservative Bonferroni threshold (< p_Bonf = 0.0018 in both cases). For example, for rs2941504, no SNPs were significant with Bonferroni, while the Persistent class was significant using the M_{eff} cutoff.

SNP	Race	Comparison (vs Infrequent)	OR	lower CI	upper CI	p-value	< p_M_{eff}	< p_Bonf
rs2941504	AA	Persistent	0.80	0.54	1.19	0.269		
		Late-onset	0.96	0.71	1.31	0.817		
		Transient	0.88	0.64	1.23	0.458		
	EA	Persistent	1.41	1.10	1.80	0.006		
		Late-onset	1.22	1.00	1.48	0.051		
		Transient	1.16	0.93	1.44	0.181		
rs2517955	AA	Persistent	1.73	1.08	2.77	0.024		
		Late-onset	1.42	0.99	2.04	0.058		
		Transient	1.27	0.86	1.87	0.235		
	EA	Persistent	1.37	1.07	1.74	0.011		
		Late-onset	1.17	0.97	1.42	0.109		
		Transient	1.12	0.90	1.39	0.297		
rs12936231	AA	Persistent	0.73	0.50	1.08	0.116		
		Late-onset	1.01	0.75	1.37	0.937		
		Transient	0.85	0.62	1.17	0.310		
	EA	Persistent	1.42	1.13	1.78	0.002		
		Late-onset	1.23	1.03	1.48	0.024		
		Transient	1.25	1.02	1.53	0.028		
rs2305480	AA	Persistent	1.82	1.00	3.32	0.049		
		Late-onset	1.95	1.24	3.09	0.004		
		Transient	1.45	0.88	2.37	0.144		
	EA	Persistent	1.45	1.16	1.82	0.001		
		Late-onset	1.27	1.06	1.52	0.011		
		Transient	1.26	1.03	1.54	0.026		
rs7216389	AA	Persistent	1.19	0.72	1.96	0.504		
		Late-onset	1.15	0.78	1.69	0.473		
		Transient	0.82	0.54	1.23	0.336		
	EA	Persistent	1.51	1.21	1.90	0.000		
		Late-onset	1.29	1.08	1.55	0.006		
		Transient	1.31	1.07	1.60	0.008		
rs4065275	AA	Persistent	0.79	0.53	1.17	0.246		
		Late-onset	0.95	0.70	1.29	0.737		
		Transient	0.73	0.53	1.01	0.058		
	EA	Persistent	1.49	1.19	1.86	0.001		
		Late-onset	1.30	1.08	1.55	0.005		
		Transient	1.27	1.04	1.56	0.019		
rs8076131	AA	Persistent	1.44	0.85	2.45	0.174		
		Late-onset	1.34	0.89	2.01	0.156		
		Transient	0.94	0.61	1.45	0.772		
	EA	Persistent	1.48	1.18	1.86	0.001		
		Late-onset	1.31	1.09	1.57	0.003		
		Transient	1.30	1.06	1.59	0.011		
rs8069202	AA	Persistent	0.88	0.57	1.34	0.549		
		Late-onset	0.92	0.66	1.27	0.616		
		Transient	0.89	0.63	1.27	0.528		
	EA	Persistent	1.36	1.08	1.70	0.008		
		Late-onset	1.26	1.05	1.51	0.011		
		Transient	1.25	1.02	1.53	0.029		
rs3859192	AA	Persistent	0.85	0.57	1.27	0.423		
		Late-onset	0.92	0.67	1.25	0.590		
		Transient	1.05	0.75	1.46	0.792		
	EA	Persistent	1.17	0.93	1.47	0.173		
		Late-onset	1.19	0.99	1.43	0.058		
		Transient	1.17	0.96	1.44	0.122		