



Published in final edited form as:

J Asthma. 2015 ; 52(10): 1006–1012. doi:10.3109/02770903.2015.1054405.

Birth weight and asthma incidence by asthma phenotype pattern in a racially diverse cohort followed through adolescence

Christine Cole Johnson, Ph.D., M.P.H.¹, Edward L. Peterson, Ph.D., M.S.¹, Christine L.M. Joseph, Ph.D., M.P.H.¹, Dennis R. Ownby, M.D.², and Naomi Breslau, Ph.D.³

¹Department of Public Health Sciences, Henry Ford Health System, Detroit, MI

²Section of Allergy-Immunology, Georgia Regents University, Augusta, GA

³Department of Epidemiology, College of Human Medicine, Michigan State University, East Lansing, MI

Abstract

Objective—Low birth weight (LBW) has been shown to be an independent risk factor for asthma. We hypothesized that LBW would have its greatest impact on early onset disease.

Methods—A racially diverse cohort of children born from 1983–1985 at two hospitals, one urban and one suburban in the same metropolitan area, and oversampled for babies weighing 2500 grams, was identified retrospectively when the children were six years of age and followed periodically. At the age 17 years study visit, cohort members and their parent/guardians were separately interviewed face-to-face regarding the subject’s history of asthma using the standardized ISAAC questionnaire. We measured the cumulative incidence of asthma from birth through adolescence defined by age of diagnosis and persistence/remittance.

Results—680 teens (82.6% of the original cohort) were included in analyses, 387 with LBW and 293 of normal birth weight. The prevalence of physician-diagnosed “Current Asthma” was associated with LBW ($p=0.003$ for trend), with patterns stronger in males and whites. LBW was associated most strongly with Late Onset Persistent asthma (current asthma that was diagnosed after 8yrs); p for trend 0.032. This trend was again most evident in males and whites. None of the asthma categories classified as “remittent” were statistically associated with LBW.

Conclusions—LBW was not associated with diagnosed asthma that remitted before age 17 yrs. LBW was associated with asthma diagnosis in mid-childhood that persisted through adolescence, suggesting that the asthmagenic effects of LBW can become evident post the early years of childhood and persist into adulthood.

Corresponding author and reprint requests to: Christine Cole Johnson, Ph.D., M.P.H., Henry Ford Health System, 1 Ford Place, 3E, Detroit, MI 48202, phone: (313) 874-6672, fax: (313) 874-6656, cjohnso1@hfhs.org.

The authors have no conflict of interest. The authors alone are responsible for the content and writing of this paper.

Declaration of interest statement

Funding sources: US National Institutes of Health (MH44586) (AI24156) (AI50681) (HL068971) (AI089473); Fund for Henry Ford Hospital

Keywords

cumulative incidence; pediatrics; age of onset; life course epidemiology; ISAAC; blacks; whites

Introduction

Low birth weight (less than 2500 grams or 5 lbs., 8 oz.) accounted for 7.99% of all births in the U.S. in 2012.(1) Low birth weight (LBW) has been shown to be a risk factor for asthma in numerous, but not all, studies.(2–6) Twin studies suggest that birth weight has an effect independent of gestation.(7;8)

Few studies of LBW as an exposure have distinguished asthma incidence in terms of specific time course phenotype patterns over the entire span of childhood,(9) which have become a focus of recent attention.(10–13) To our knowledge, such an analysis has not been done in a U.S. study population, or in one that is racially diverse. The latter is especially important when studying LBW since this parameter varies dramatically by race/ancestry in the US, with LBW more common in non-Hispanic blacks.(1) The prevalence of asthma also varies by race.(14) In addition, the majority of those with current asthma at the threshold of adulthood will likely not experience remission through middle age.(15–19) Therefore, considering phenotype patterns over the duration of childhood through late adolescence presents a fuller picture of the potential adult public health burden associated with LBW.

Martinez et al described several mutually exclusive time course phenotypes of pediatric wheeze and asthma: 1) transient wheeze, which appears one or more times before three years of age, is usually associated with respiratory infections and then does not appear again in the child's lifetime; 2) early onset persistent wheeze which is incident before 3 years of age and persists into adulthood; and 3) late onset wheeze that first develops in the middle of a child's first decade and persists into adulthood.(20) Sears et al. defined additional categories from their New Zealand birth cohort, which began being observed at age 9 years, including "wheeze in remission" (remitted asthma), that is, recurring wheeze that had stopped sometime after age 11 and not occurred in their cohort again through an age 26 yr. follow up.(21) Others have investigated similar patterns in their own cohorts and found them to be relatively consistent.(12;13)

Since LBW is hypothesized to be associated with impaired lung development in utero,(22–24) and an increased risk for neonatal respiratory infections,(25) we hypothesized that LBW would be associated with a higher cumulative incidence of early onset transient asthma as well as early onset persistent asthma, but not late onset persistent asthma. Our initial theory was that LBW would result in more immediate consequences such as early transient wheezing/asthma that eventually remits during childhood or is not resolved and persists, while late onset asthma appearing first later in childhood, persistent or remittent, would be more strongly related instead to early childhood environmental exposures. We also thought that these incidence patterns might differ by race and sex. First, African Americans have been consistently shown to have lower mean birth weights than American babies of European descent,(1;26;27) as well as a higher prevalence of asthma.(28;29) Second, boys have a higher prevalence of asthma than girls prior to the teen years and then the male:

female ratio reverses, at least in populations of European ancestry.(30–32) To study these questions, we capitalized on a large birth cohort of U.S. Detroit area children of European and African descent that included a substantial fraction of low birth weight babies and who were evaluated at age 17 years regarding a history of asthma diagnosis.

Methods

Study design

A cohort of low birth weight and normal birth weight children was established retrospectively based on a random selection of births from two major hospitals in southeastern Michigan, one in Detroit and one in a nearby suburb, and followed for a study of neurodevelopment, as described by Breslau et al.(33;34) Enrolled when the subjects were 6 years of age, they were born from 1983 through 1985 and classified as White or Black. In order to enhance the number of LBW (< 2500 grams) babies, more LBW babies were selected, by design, at a ratio of approximately 1.3~1.4. Of 6698 newborns discharged from the urban hospital and 16 136 from the suburban hospital during this time period, a random sample of 1338 newborns was thus identified. Of those sampled, 196 were unavailable at 6 years of age because they had moved out of the area, were living in foster homes or had not survived. Using medical records, an additional 47 children were excluded due to severe neurologic impairment. Of the 1095 remaining children, 75% (n=823) participated in the study at age 6 years, (4% unable to be traced and 21% refusing).

These children were reassessed for neurologic outcomes at age 11 years and again at age 17 years.(35) Personal face-to-face interviews were conducted independently with the children and a parent/guardian, usually the mother. At the age 17 yrs. visit, questions were added to both the parent and child questionnaire regarding asthma from the validated ISAAC questionnaire,(36) including history of a health care provider diagnosis of asthma and age of diagnosis, as well as whether symptoms had occurred or asthma medications were used in the previous 12 months, which were used to define “Current Asthma”. Institutional review boards of the participating institutions approved the study.

Asthma phenotypes were defined based on the classifications suggested by Martinez and Sears (Table 1).(20;21) “Early Onset Transient Asthma” was asthma reported as diagnosed before age 3 years but the child had not experienced symptoms or medication use in the previous year at age 17 years. If the child still had Current Asthma at 17 years, he or she was classified as having “Early Onset Persistent Asthma”. “Childhood Onset Remittent Asthma” was defined as asthma diagnosed from 3–8 years and the child had not experienced symptoms and/or medication use in the previous 12 months (Current Asthma) at age 17 years. If the child had Current Asthma, he or she was classified as “Childhood Onset Persistent Asthma.” We selected this age range of 3–8 years for incidence because it follows Martinez’s age break of 3 years for transient asthma, includes the age period in which asthma can be reliably diagnosed and is before the 9 year category used by Sears. Also, most children will be pre-pubertal at age 8 yrs., thus it is before the time period when the male: female prevalence ratio begins to reverse. Asthma diagnosed after 8 years but not present at age 17 was classified as “Late Onset Remittent Asthma”. “Late Childhood Onset Persistent

Asthma” was defined as asthma diagnosed after 8 years of age with Current Asthma at 17 years. All other cohort members were classified as “Never Asthma”.

We reviewed each subject, blinded to birth weight status, to determine which parent and child responses were discrepant such that the phenotype could not be readily classified. Seven discrepant responses could be resolved, but 14 discrepant teen-parent responses could not and had to be excluded as well as 19 subjects due to a response of “unknown”. The remainder of the child-parent responses (n=673 or 95.4% of those followed up) were concordant to the degree that a history of an asthma diagnosis, the age category of disease incidence and current asthma status could be determined.

Statistical analyses

Birth weight was classified into normal birth weight or NBW (>2500 grams) and low birth weight (< 2500 grams). The latter category was additionally split for the purposes of this paper into two classes, 2000–2500 grams (moderate low birth weight or MLBW) and <2000 grams (lower low birth weight or LLBW). Cumulative incidences and 95% confidence intervals based on observed proportions were calculated. The entire population and two stratified analyses, by sex and by race, are reported. Group comparisons (those with sufficient data versus those lost to follow-up or missing data) on categorical variables such as race, education level and birth weight were done using chi-squared tests or Fisher’s Exact Tests. Each of the various asthma phenotypes were compared across the three birth weight categories using both a chi-squared test and a Cochran-Armitage test for trend. A p-value of less than 0.05 was considered significant. All analyses were performed using SAS for Windows version 9.1; SAS Institute, Cary, NC.

Results

There were 713 children who completed the 17 yr. old interview (86.6% of the original sample). An additional 14 were excluded due to inability to resolve discordant data between the parent and teen, and another 19 because of missing data. Online-Table S1 displays demographic characteristics of the initial sample selected at age 6 yrs., the sample at age 17 years, the children not used in the study due to loss to follow up or missing/non-congruent data, and the analyzed sample at age 17 years (n=680 or 82.6% of the original sample). The participants included in the analyses were less likely to be male (p=0.053) and more likely to be Black (p=0.055), although differences were slight. The two groups were not statistically different with regard to maternal marital status and education, urban residence at enrollment, and low birth weight status. Online-Table S2 provides the distribution of birth weight categories by sex and race of the teens included in the analyses.

Table 2 displays, by birth weight classification, the cumulative incidences of the traditionally measured outcomes “Ever Asthma” and “Current Asthma”, by sex and race. Overall, there were significant differences in the cumulative incidence of asthma by birth weight category, as well as statistically significant trends. For Ever Asthma, the LLBW category had a higher cumulative incidence (27.2%) than the MLBW and NBW categories at 19.1% and 17.7%, respectively, with a borderline statistical difference. The p value for trend is significant at p=0.036. These patterns are more strongly reflected for Current Asthma, with an overall p

value of 0.012 and $p=0.003$ for trend. The patterns were stronger in males (p for trend =0.005) and whites (p for trend = 0.008) for Current Asthma, with the latter driven by the high cumulative incidence in the LLBW category.

For the total cohort, the cumulative incidence of Early Onset Transient Asthma was consistent across birth weight classes: 2.2% in the LLBW category, 2.4% in the MLBW category and 2.4% in the NBW category (Table 3). Likewise, the cumulative incidences were similar across birth weight categories for Childhood Onset Remittent and Persistent Asthma, as well as Late Childhood Onset Remittent Asthma. The highest cumulative incidences were found in the LLBW category for Early and Late Childhood Onset Persistent Astmas at 8.8% (95%CI 4.6–14.9) and 8.1% (95%CI 4.1–14.0), respectively. For Early Onset Persistent Asthma, the respective cumulative incidence figures by ascending weight category are 8.8%, 5.2% and 5.2% ($p=0.265$) and the test for trend was also not statistically significant ($p=0.181$). For Late Childhood Onset Persistent Asthma, the corresponding figures are 8.1%, 6.8% and 3.4%, with a borderline significance of $p=0.086$, and a p value for trend that was significant at $p=0.032$.

For males, the most striking pattern was again found in Late Childhood Onset Persistent Asthma with substantially higher cumulative incidences in the LLBW and MLBW categories at 7.1% and 9.5% compared to 2.1% in the NBW group ($P=0.034$) and for trend, $p=0.055$. The cumulative incidences were of similar magnitude across all phenotypes in the NBW category. These patterns were not as striking in the females and none reached statistical significance. By race, there is little association of birth weight with the three non-persistent asthma phenotypes, Early Onset Transient, Childhood Onset Remittent and Late Childhood Onset Remittent. The only statistically significant patterns are found among the Whites, with differences found indicating a much higher cumulative incidence in the LLBW group for Early Onset and Childhood Onset Persistent Asthma. For Late Childhood Onset Persistent Asthma, a steady trend was demonstrated of increased birth weight with lower cumulative incidence, with borderline significance.

Discussion

Contrary to our expectations, we found that birth weight was not associated with early onset transient asthma, but was most consistently related to late onset persistent asthma. Our hypothesis was that effects derived from the prenatal period would be apparent within a few years after birth, and many of these effects would remit after the baby “caught up” with respect to weight. However, there were no associations by birth weight with any of the asthma phenotype categories that were remittent, and the strongest associations were with asthma that was diagnosed after age 8 years and was still present at age 17 years, suggesting that LBW children with no asthma diagnosis before 8 years are still at higher risk. Further, this pattern was most evident in males and Whites. It also appears that nearer normal birth weights (2000 to 2500 g) have a Late Childhood Onset Persistent Asthma risk that is almost as great as infants with lower (<2000 g) birth weights for most subgroups. Thus the effect of low birth weight can be surmised to become evident as late as mid-childhood and persists into adulthood, supporting the hypothesis that the origins of chronic disease can begin in the prenatal period.(24;37)

Symptoms of transient wheezing that would yield an asthma diagnosis may not be associated with LBW as suggested here, or, it is possible transient wheeze may not as often be diagnosed as asthma in a LBW infant but rather ascribed to residual effects of LBW. However, the low and similar cumulative incidences found for early transient asthma across all birthweight categories probably reflects that many physicians are unlikely to diagnosis wheezing as asthma in infants and toddlers regardless of birth weight but choose to wait until a more definitive diagnosis can be made at the age of 4–6 years. This issue should be abrogated in the Childhood Onset and Late Childhood Onset categories as the distance in time from birth increases.

One reason that the cumulative incidence of asthma was more related to birth weight in Whites could be that the usual birth weight categories used herein are not optimally classified for Black children. There is evidence that Black children residing in sub-Saharan Africa have lower birth weight “norms” than African Americans.(38) Since African American birth weights are in general lower on a national scale,(1;39) it is possible that we included more physiologically normal weight African American children in our defined lower birth weight categories, which would tend to attenuate effects. If African Americans have a lower birth weight distribution for physiologically normal births, this would imply exposure misclassification in our study and could account for diminished risk estimates relative to the White babies for all but the very lowest birth weight babies. Additionally, differences by race in access to care or physician predilection for asthma diagnosis could also result in disease misclassification.

Yang et al. examined the question of LBW and asthma in a larger white population in Rochester Minnesota, following children through 7 years and using a propensity score approach to account for variables related to low birth weight.(40) They did not categorize asthma by a time course phenotype pattern as we did. They concluded there was no association between birth weight and asthma. These results are not inconsistent with the phenotypes in our study most similar to theirs in our white population, where we observed no difference by weight category for Early Onset Transient Asthma and a U-shaped pattern for Early Onset Persistent Asthma.

Davidson et al examined perinatal characteristics and asthma hospitalizations using the British Oxford record linkage study of over 248 000 births followed for 10–29 years.(41) They examined these factors related to children hospitalized before age 2 years separately with the same hypothesis as this paper that the possible influences of perinatal factors would be more evident in those with very early diagnoses. Birth weight under 3000 grams was significantly associated in multivariate models with asthma hospitalizations with consistent although modest odds ratios (OR=1.2) for all ages and also for those hospitalized before two years. Interestingly, the authors also considered in a univariate fashion those hospitalized for the first time at over 6 years of age and found no association with LBW, which is not, on the surface, consistent with our findings, although age at diagnosis is obviously a different outcome than age at hospitalization. Additionally, effect modification by race and sex was not considered in their analyses.

In the large Dutch PIAMA birth cohort of 3963 children, Caudri et al. examined perinatal risk factors, including LBW, associated with time course defined wheezing phenotypes, somewhat similar to our approach but only through 8 years of age.(42) Using adjusted models they also found, as we did, no association of birth weight with early transient wheeze. The only significant finding related to LBW was an inverse association with intermediate onset wheeze, defined by the authors as wheeze with a low prevalence up to 18 months, but a rapid rise initiated thereafter through 42 months of age that was sustained through 6–7 years. Decreased birth weight was also associated, but not significantly, with late onset wheeze that was low in prevalence through 42 months but then increased to a peak at around 6 years; however, the numbers were small (n=47) and therefore statistical power was reduced. They did not find that results differed for boys versus girls. In summary this study was relatively consistent with ours, although follow-up was only through childhood. Another study supporting our findings was Project Viva from Boston and their analysis of birth weight with asthma-related outcomes at age 2 years.(43) They found no associations at this age, which equates most closely to our Early Onset Transient Asthma group, with either low or high birth weight, adjusting for length of gestation.

LBW has been shown to be associated with decreased lung function in adults.(44) Barker et al. proposed that LBW is a consequence of slow linear growth *in utero*, which also leads to impaired development of the airways.(24) Interestingly, high birth weight has also been hypothesized to be associated with asthma, but results have been controversial.(6;45;46)

This study's strengths included a large, multi-racial population with both residential and socioeconomic diversity. Follow up at age 17 yrs. was excellent, and standardized questions were administered to both the teen and parent. The time period of follow up brought the study subjects up to young adulthood and past the period of puberty during which asthma becomes more common in females, and allowing for discernment of time course phenotype. The main limitation of the study is that we were constrained by the size of the original birth cohort and despite its relatively large sample size many of the outcome phenotypes were uncommon, resulting in numerators with less than five to ten subjects. Therefore while we found statistical significance in a number of instances, confidence intervals were wide and estimates subject to instability. However, these results should provide important information to those who want to design future studies that consider asthma phenotypes.

A second major limitation was the reliance on survey data that demanded a long term (17 year) recall history. Concern is ameliorated in that the ISAAC survey has been validated in teens (13–14 years) and the comforting fact that all but a small percentage of the teens and parents independently provided responses regarding asthma diagnosis, age at diagnosis and recent symptom information that corresponded. Further, there is no obvious reason why subjects would systematically miss report age at initial diagnosis by birth weight classification. Since the majority of the interview and previous visits were related to cognitive outcomes and the asthma-related questions were unexpected, we believe respondents likely gave us their best estimates of age at diagnosis and symptom experience in the past 12 months. Finally, it has been shown that children older than 10 years of age can validly report respiratory symptoms.(47)

The study was also limited in that there were no biological measures such as pulmonary function, methacholine challenge or exhaled nitric oxide. Moreover, there was no assessment of allergic status by questionnaire, clinical history or allergen-specific IgE testing serologically or by SPT. Disease history was not verified by medical record review. Data were not collected regarding parental history of asthma or allergies so incidence in this subgroup could not be examined. Further, we did not include gestational age or postnatal infant catch up weight gain in our analyses, both of which are related to birth weight, in positive and inverse directions, respectively.(10) However, while preterm birth has been consistently shown to increase the risk for asthma and poor lung function, (48) the effect of birth weight has been shown to be independent of gestational age.(4;5;49;50) We also do not have data on early life upper respiratory infections or exposure to environmental tobacco smoke.

Conclusions/Key findings

We have shown data that suggest that low birth weight is not as strongly associated with an early diagnosis of asthma that does not persist, but is most strongly associated with an asthma diagnosis in later childhood and disease that is still present at age 17 years. The effect of LBW appears to be more evident in males and Whites. These findings support the concept of “DOHaD” (the developmental origins of health and disease), that is, the paradigm that the origins of adult chronic disease are initiated at the earliest stages of life. (51–53)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and acronyms

OR	odds ratio
aOR	adjusted odds ratio
CI	95% confidence interval

Reference List

1. Martin, JA.; Hamilton, BE.; Osterman, MJK.; Curtin, SC.; Mathews, TJ. National Vital Statistics Reports. Vol. 62. Hyattsville, MD: National Center for Health Statistics; 2013. Births: Final data for 2012.
2. Joseph CLM, Ownby DR, Peterson EL, Johnson CC. Does low birth weight help to explain the increased prevalence of asthma among African-Americans? *Ann Allergy Asthma Immunol.* 2002; 88(5):507–512. [PubMed: 12027073]
3. Kindlund K, Thomsen SF, Stensballe LG, Skytthe A, Kyvik KO, Backer V, et al. Birth weight and risk of asthma in 3–9-year-old twins: exploring the fetal origins hypothesis. *Thorax.* 2010; 65(2): 146–149. [PubMed: 19996338]
4. Liu X, Olsen J, Agerbo E, Yuan W, Cnattingius S, Gissler M, et al. Birth weight, gestational age, fetal growth and childhood asthma hospitalization. *Allergy Asthma Clin Immunol.* 2014; 10(1):13. [PubMed: 24602245]

5. Metsala J, Kilkkinen A, Kaila M, Tapanainen H, Klaukka T, Gissler M, et al. Perinatal factors and the risk of asthma in childhood--a population-based register study in Finland. *Am J Epidemiol*. 2008; 168(2):170–178. [PubMed: 18511427]
6. Mu M, Ye S, Bai MJ, Liu GL, Tong Y, Wang SF, et al. Birth Weight and Subsequent Risk of Asthma: A Systematic Review and Meta-Analysis. *Heart Lung Circ*. 2014; 23:511–519. [PubMed: 24582482]
7. Ortqvist AK, Lundholm C, Carlstrom E, Lichtenstein P, Cnattingius S, Almqvist C. Familial factors do not confound the association between birth weight and childhood asthma. *Pediatr*. 2009; 124(4):e737–e743.
8. Villamor E, Iliadou A, Cnattingius S. Is the association between low birth weight and asthma independent of genetic and shared environmental factors? *Am J Epidemiol*. 2009; 169(11):1337–1343. [PubMed: 19357326]
9. Agache I, Akdis C, Jutel M, Virchow JC. Untangling asthma phenotypes and endotypes. *Allergy*. 2012; 67(7):835–846. [PubMed: 22594878]
10. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, nnesi-Maesano I, Arshad SH, Barros H, et al. Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 European children. *J Allergy Clin Immunol*. 2014; 133(5):1317–1329. [PubMed: 24529685]
11. 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(6):1505–1512. [PubMed: 21411131]
12. 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(5):311–315. [PubMed: 22541400]
13. Collins SA, Pike KC, Inskip HM, Godfrey KM, Roberts G, Holloway JW, et al. Validation of novel wheeze phenotypes using longitudinal airway function and atopic sensitization data in the first 6 years of life: evidence from the Southampton Women's survey. *Pediatr Pulmonol*. 2013; 48(7):683–692. [PubMed: 23401430]
14. Akinbami LJ, Moonman JE, Simon AE, Schoendorf KC. Trends in racial disparities for asthma outcomes among children 0 to 17 years, 2001–2010. *J Allergy Clin Immunol*. 2014; 134:547–553. [PubMed: 25091437]
15. Panhuysen CIM, Vonk JM, Koëter GH, Schouten JP, vanAltena R, Bleecker ER, et al. Adult patients may outgrow their asthma. A 25-year follow-up study. *Am J Respir Crit Care Med*. 1997; 155:1267–1272. [PubMed: 9105065]
16. Ronmark E, Jonsson E, Lundback B. Remission of asthma in the middle aged and elderly: report from the Obstructive Lung Disease in Northern Sweden study. *Thorax*. 1999; 54(7):611–613. [PubMed: 10377206]
17. Bronnimann S, Burrows B. A prospective study of the natural history of asthma. Remission and relapse rates. *Chest*. 1986; 90(4):480–484. [PubMed: 3757559]
18. Settipane GA, Greisner WA III, Settipane RJ. Natural history of asthma: a 23-year followup of college students. *Ann Allergy Asthma Immunol*. 2000; 84(5):499–503. [PubMed: 10831002]
19. de Marco R, Pattaro C, Locatelli F, Svanes C. Influence of early life exposures on incidence and remission of asthma throughout life. *J Allergy Clin Immunol*. 2004; 113(5):845–852. [PubMed: 15131565]
20. Martinez FD, Wright AL, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *New Engl J Med*. 1995; 332:133–138. [PubMed: 7800004]
21. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med*. 2003; 349(15):1414–1422. [PubMed: 14534334]
22. Chan KN, Noble-Jamieson CM, Elliman A, Bryan EM, Silverman M. Lung function in children of low birth weight. *Arch Dis Child*. 1989; 64(9):1284–1293. [PubMed: 2817949]
23. Canoy D, Pekkanen J, Elliott P, Pouta A, Laitinen J, Hartikainen AL, et al. Early growth and adult respiratory function in men and women followed from the fetal period to adulthood. *Thorax*. 2007; 62(5):396–402. [PubMed: 17105780]

24. Barker DJ, Osmond C, Forsen TJ, Thornburg KL, Kajantie E, Eriksson JG. Foetal and childhood growth and asthma in adult life. *Acta Paediatr.* 2013; 102(7):732–738. [PubMed: 23560734]
25. Flaherman VJ, Ragins AI, Li SX, Kipnis P, Masaquel A, Escobar GJ. Frequency, duration and predictors of bronchiolitis episodes of care among infants ≥ 32 weeks gestation in a large integrated healthcare system: a retrospective cohort study. *BMC Health Serv Res.* 2012; 12:144. [PubMed: 22682080]
26. Fuller KE. Low birth-weight infants: the continuing ethnic disparity and the interaction of biology and environment. *Ethn Dis.* 2000; 10(3):432–445. [PubMed: 11110360]
27. Kramer MR, Hogue CR. Place matters: variation in the black/white very preterm birth rate across U.S. metropolitan areas, 2002–2004. *Public Health Rep.* 2008; 123(5):576–585. [PubMed: 18828412]
28. Schwartz J, Gold D, Dockery DW, Weiss ST, Speizer FE. Predictors of asthma and persistent wheeze in a national sample of children in the United States. *Am Rev Respir Dis.* 1990; 142:555–582. [PubMed: 2389907]
29. Bloom B, Jones LI, Freeman G. Summary health statistics for u.s. Children: national health interview survey, 2012. *Vital Health Stat.* 2013; 10(258):1–81.
30. 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. [PubMed: 1412098]
31. Nicolai T, Pereszlenyiova-Bliznakova L, Illi S, Reinhardt D, von ME. Longitudinal follow-up of the changing gender ratio in asthma from childhood to adulthood: role of delayed manifestation in girls. *Pediatr Allergy Immunol.* 2003; 14(4):280–283. [PubMed: 12911505]
32. Hedman L, Andersson M, Bjerg A, Forsberg B, Lundback B, Ronmark E. Environmental risk factors related to the incidence of wheeze and asthma in adolescence. *Clin Exp Allergy.* 2014
33. Breslau N, DeDotto JE, Brown GG, Kumar S, Ezhuthachan S, Hufnagle KG, et al. A gradient relationship between low birth weight and IQ at age 6 years. *Arch Pediatr Adolesc Med.* 1994; 148(4):377–383. [PubMed: 8148937]
34. Breslau N, Chilcoat HD, Susser ES, Matte T, Liang KY, Peterson EL. Stability and change in children's intelligence quotient scores: a comparison of two socioeconomically disparate communities. *Am J Epidemiol.* 2001; 154(8):711–717. [PubMed: 11590083]
35. Breslau J, Miller E, Breslau N, Bohnert K, Lucia V, Schweitzer J. The impact of early behavior disturbances on academic achievement in high school. *Pediatr.* 2009; 123(6):1472–1476.
36. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J.* 1995; 8(3): 483–491. [PubMed: 7789502]
37. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ.* 1991; 303(6804):671–675. [PubMed: 1912913]
38. Matthews LT, Ribaldo HJ, Parekh NK, Chen JY, Binda K, Ogwu A, et al. Birth weight for gestational age norms for a large cohort of infants born to HIV-negative women in Botswana compared with norms for U.S. -born black infants. *BMC Pediatr.* 2011; 11:115. [PubMed: 22176889]
39. Broussard CS, Gilboa SM, Lee KA, Oster M, Petrini JR, Honein MA. Racial/ethnic differences in infant mortality attributable to birth defects by gestational age. *Pediatr.* 2012; 130(3):e518–e527.
40. Yang HJ, Qin R, Katusic S, Juhn YJ. Population-based study on association between birth weight and risk of asthma: a propensity score approach. *Ann Allergy Asthma Immunol.* 2013; 110(1):18–23. [PubMed: 23244653]
41. Davidson R, Roberts SE, Wotton CJ, Goldacre MJ. Influence of maternal and perinatal factors on subsequent hospitalisation for asthma in children: evidence from the Oxford record linkage study. *BMC Pulm Med.* 2010; 10:14. [PubMed: 20233433]
42. 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(12):1395–1405. [PubMed: 24261948]

43. Taveras EM, Camargo CA Jr, Rifas-Shiman SL, Oken E, Gold DR, Weiss ST, et al. Association of birth weight with asthma-related outcomes at age 2 years. *Pediatr Pulmonol*. 2006; 41(7):643–648. [PubMed: 16703577]
44. Lawlor DA, Ebrahim S, Davey SG. Association of birth weight with adult lung function: findings from the British Women’s Heart and Health Study and a meta-analysis. *Thorax*. 2005; 60(10):851–858. [PubMed: 16055617]
45. Flaherman V, Rutherford GW. A meta-analysis of the effect of high weight on asthma. *Arch Dis Child*. 2006; 91(4):334–339. [PubMed: 16428358]
46. Sevelsted A, Bisgaard H. Neonatal size in term children is associated with asthma at age 7, but not with atopic dermatitis or allergic sensitization. *Allergy*. 2012; 67(5):670–675. [PubMed: 22381045]
47. Yu TS, Wong TW. Can schoolchildren provide valid answers about their respiratory health experiences in questionnaires? Implications for epidemiological studies. *Pediatr Pulmonol*. 2004; 37(1):37–42. [PubMed: 14679487]
48. Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Med*. 2014; 11(1):e1001596. [PubMed: 24492409]
49. Hancox RJ, Poulton R, Greene JM, McLachlan CR, Pearce MS, Sears MR. Associations between birth weight, early childhood weight gain and adult lung function. *Thorax*. 2009; 64(3):228–232. [PubMed: 19052051]
50. Tennant PW, Gibson GJ, Pearce MS. Lifecourse predictors of adult respiratory function: results from the Newcastle Thousand Families Study. *Thorax*. 2008; 63(9):823–830. [PubMed: 18408051]
51. Gluckman, P.; Hanson, M. *The Developmental Origins of Health and Disease: An Overview*. Cambridge: Cambridge University Press; 2006. p. 1-5.
52. Prescott SL. Disease prevention in the age of convergence—the need for a wider, long ranging and collaborative vision. *Allergol Int*. 2014; 63(1):11–20. [PubMed: 24457816]
53. Geronimus AT. Deep integration: letting the epigenome out of the bottle without losing sight of the structural origins of population health. *Am J Public Health*. 2013; 103(Suppl 1):S56–S63. [PubMed: 23927509]

Definitions of asthma phenotypes

Table 1

Phenotype Label	Definition
Ever Asthma	Ever diagnosed with asthma
Current Asthma	Ever diagnosed & symptoms or asthma medication use in last 12 months
Early Onset Transient	Diagnosed before 3 yrs; not current at age 17 yrs
Early Onset Persistent	Diagnosed before 3 yrs; current at age 17 yrs
Child Onset Remittent	Diagnosed from 3–8 yrs; not current at age 17 yrs
Child Onset Persistent	Diagnosed from 3–8 yrs; current at age 17 yrs
Late Child Onset Remittent	Diagnosed after 8 yrs; not current at age 17 yrs
Late Child Onset Persistent	Diagnosed after 8 yrs; current at age 17 yrs

Table 2
Cumulative incidence of doctor diagnosed Ever Asthma and Current Asthma by birth weight, sex and race

	NBW (n=293) Birth Weight >2500 grams % (CI), n*	MLBW (n=251) Birth Weight 2000–2500 grams % (CI), n*	LLBW (n=136) Birth Weight <2000 grams % (CI), n*	Overall P value by Weight	P value for trend
Total (n=680)					
Ever Asthma	17.7 (13.5, 22.6), 52	19.1 (14.4, 24.9), 48	27.2 (19.9, 35.5), 37	0.066	0.036
Current Asthma	10.6 (7.3, 14.7), 31	14.7 (10.6, 19.8), 37	21.3 (14.8, 29.2), 29	0.012	0.003
Males (n=320)					
Ever Asthma	17.9 (12.1, 25.2), 26	21.9 (14.4, 31.0), 23	30.0 (19.6, 42.1), 21	0.134	0.050
Current Asthma	9.0 (4.9, 14.8), 13	17.1 (10.5, 25.7), 18	22.9 (13.7, 34.5), 16	0.018	0.005
Females (n=360)					
Ever Asthma	17.6 (11.8, 24.7), 26	17.1 (11.4, 24.2), 25	24.2 (14.5, 36.4), 16	0.427	0.333
Current Asthma	12.2 (7.4, 18.5), 18	13.0 (8.0, 19.6), 19	19.7 (10.9, 31.3), 13	0.313	0.186
Black (n=302)					
Ever Asthma	18.3 (11.7, 26.6), 21	25.2 (17.6, 34.2), 29	20.8 (13.2, 32.0), 15	0.433	0.556
Current Asthma	8.7 (4.2, 15.4), 10	19.1 (12.4, 27.5), 22	15.3 (7.9, 25.7), 11	0.074	0.130
White (n=378)					
Ever Asthma	17.4 (12.1, 23.8), 31	14.0 (8.6, 21.0), 19	34.4 (22.9, 47.3), 22	0.002	0.025
Current Asthma	11.8 (7.4, 17.5), 21	11.0 (6.3, 17.5), 15	28.1 (17.6, 40.8), 18	0.002	0.008

* n= number of asthma cases

Table 3

Cumulative incidence of doctor diagnosed asthma by phenotype and birth weight, by sex and race

	NBW (n=293) Birth Weight >2500 grams % (CI), n [*]	MLBW (n=251) Birth Weight 2000–2500 grams % (CI), n [*]	LLBW (n=136) Birth Weight <2000 grams % (CI), n [*]	Overall P value For Weight	P value for trend
TOTAL					
Early Onset Transient	2.4 (1.0, 4.9), 7	2.4 (0.9, 5.1), 6	2.2 (0.5, 6.3), 3	0.992	0.919
Early Onset Persistent	5.2 (2.9, 8.3), 15	5.2 (2.8, 8.7), 13	8.8 (4.6, 14.9), 12	0.265	0.181
Child Onset Remittent	3.1 (1.4, 5.8), 9	1.6 (0.4, 4.0), 4	1.5 (0.2, 5.2), 2	0.408	0.224
Child Onset Persistent	2.0 (0.7, 4.4), 6	2.8 (1.1, 5.7), 7	4.4 (1.6, 9.4), 6	0.385	0.179
Late Child Onset Remittent	1.7 (0.5, 3.9), 5	0.4 (0.0, 2.2), 1	2.2 (0.5, 6.3), 3	0.249	0.973
Late Child Onset Persistent	3.4 (1.6, 6.2), 10	6.8 (4.0, 10.6), 17	8.1 (4.1, 14.0), 11	0.086	0.032
MALES (n=320)					
Early Onset Transient	2.8 (0.7, 6.9), 4	2.9 (0.6, 8.1), 3	4.3 (0.9, 12.0), 3	0.818	0.583
Early Onset Persistent	3.4 (1.1, 7.9), 5	5.7 (2.1, 12.0), 6	8.6 (3.2, 17.7), 6	0.285	0.114
Child Onset Remittent	3.4 (1.1, 7.9), 5	1.9 (0.2, 6.7), 2	1.4 (0.0, 7.7), 1	0.601	0.333
Child Onset Persistent	3.4 (1.1, 7.9), 5	1.9 (0.2, 6.7), 2	7.1 (2.4, 15.9), 5	0.196	0.292
Late Child Onset Remittent	2.8 (0.7, 6.9), 4	0.0 (0.0, 3.5), 0	1.4 (0.0, 7.7), 1	0.221	0.294
Late Child Onset Persistent	2.1 (0.4, 5.9), 3	9.5 (4.7, 16.8), 10	7.1 (2.4, 15.9), 5	0.034	0.055
FEMALES (n=360)					
Early Onset Transient	2.0 (0.4, 5.8), 3	2.1 (0.4, 5.9), 3	0.0 (0.0, 5.4), 0	0.504	0.361
Early Onset Persistent	6.8 (3.3, 12.1), 10	4.8 (1.9, 9.6), 7	9.1 (3.4, 18.6), 6	0.482	0.717
Child Onset Remittent	2.7 (0.7, 6.8), 4	1.4 (0.2, 4.9), 2	1.5 (0.0, 8.2), 1	0.683	0.466
Child Onset Persistent	0.7 (0.0, 3.7), 1	3.4 (1.1, 7.8), 5	1.5 (0.0, 8.2), 1	0.224	0.409
Late Child Onset Remittent	0.7 (0.0, 3.7), 1	0.7 (0.0, 3.8), 1	3.0 (0.4, 10.5), 2	0.258	0.196
Late Child Onset Persistent	4.7 (1.9, 9.5), 7	4.8 (1.9, 9.6), 7	9.1 (3.4, 18.8), 6	0.382	0.267
BLACKS (n=302)					
Early Onset Transient	3.5 (0.9, 8.7), 4	3.5 (0.9, 8.7), 4	1.4 (0.0, 7.5), 1	0.661	0.452
Early Onset Persistent	4.3 (1.4, 9.9), 5	9.6 (4.9, 11.5), 11	8.3 (3.1, 17.3), 6	0.291	0.237
Child Onset Remittent	4.3 (1.4, 9.9), 5	2.6 (0.5, 7.4), 3	1.4 (0.0, 7.5), 1	0.489	0.235

	NBW (n=293) Birth Weight >2500 grams % (CI), n *	MLBW (n=251) Birth Weight 2000–2500 grams % (CI), n *	LLBW (n=136) Birth Weight <2000 grams % (CI), n *	Overall P value For Weight	P value for trend
Child Onset Persistent	2.6 (0.5, 7.4), 3	5.2 (1.9, 11.0), 6	1.4 (0.0, 7.5), 1	0.315	0.811
Late Child Onset Remittent	1.7 (0.2, 6.1), 2	0.0 (0.0, 3.2), 0	2.8 (0.3, 9.7), 2	0.240	0.711
Late Child Onset Persistent	1.7 (0.2, 6.1), 2	4.3 (1.4, 9.9), 5	5.6 (1.5, 13.6), 4	0.350	0.157
WHITES (n=378)					
Early Onset Transient	1.7 (0.3, 4.9), 3	1.5 (0.2, 5.2), 2	3.1 (0.4, 10.8), 2	0.702	0.567
Early Onset Persistent	5.6 (2.7, 10.1), 10	1.5 (0.2, 5.2), 2	9.4 (3.5, 19.3), 6	0.038	0.642
Child Onset Remittent	2.2 (0.6, 5.7), 4	0.7 (0.0, 4.0), 1	1.6 (0.0, 8.4), 1	0.569	0.509
Child Onset Persistent	1.7 (0.3, 4.9), 3	0.7 (0.0, 4.0), 1	7.8 (2.6, 17.3), 5	0.007	0.032
Late Child Onset Remittent	1.7 (0.3, 4.9), 3	0.7 (0.0, 4.0), 1	1.6 (0.0, 8.4), 1	0.753	0.765
Late Child Onset Persistent	4.5 (2.0, 8.7), 8	8.8 (4.6, 14.9), 12	10.9 (4.5, 21.2), 7	0.146	0.054

* n= number of asthma cases