Published in final edited form as:

J Allergy Clin Immunol. 2008 May ; 121(5): 1161–1166.e3. doi:10.1016/j.jaci.2008.03.021.

Higher adiposity in infancy associated with recurrent wheeze in a prospective cohort of children

Elsie M. Taveras, MD, MPH^a, Sheryl L. Rifas-Shiman, MPH^a, Carlos A. Camargo Jr, MD, DrPH^b, Diane R. Gold, MD, MPH^b, Augusto A. Litonjua, MD, MPH^b, Emily Oken, MD, MPH^a, Scott T. Weiss, MD^b, and Matthew W. Gillman, MD, SM^{a,c}

^aObesity Prevention Program, Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, Mass

^bChanning Laboratory, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, Mass

^cDepartment of Nutrition, Harvard School of Public Health, Boston, Mass

Abstract

Background—Few prospective data link early childhood adiposity with asthma-related symptoms.

Objective—We sought to examine the associations of weight-for-length (WFL) at age 6 months with incidence of wheezing by age 3 years.

Methods—We studied 932 children in a prospective cohort of children. The main outcome was *recurrent wheezing*, which was defined as parents' report of wheezing between 2 and 3 years of age plus wheezing in either year 1 or 2 of life. Secondary outcomes included any wheezing from 6 months to 3 years and current asthma. We used multiple logistic regression to examine associations of 6-month WFL *z* scores with these outcomes.

Results—At 6 months, the infants' mean WFL *z* score was 0.68 (SD, 0.94; range −2.96 to 3.24). By age 3 years, 14% of children had recurrent wheezing. After adjustment for a variety of potential confounders, we found that each 1-unit increment in 6-month WFL *z* score was associated with greater odds of recurrent wheezing (odds ratio [OR], 1.46; 95% CI, 1.11–1.91) and any wheezing (OR, 1.23; 95% CI, 1.03–1.48). We observed a weaker association between 6-month WFL *z* score and current asthma (OR, 1.22; 95% CI, 0.94–1.59).

Conclusion—Infants with higher WFL *z* scores at 6 months of age had a greater risk of recurrent wheezing by age 3 years. It is unclear whether the relationship of infant adiposity and early-life wheeze extends to allergic asthma or wheeze that can persist into later childhood. Our findings suggest that early interventions to prevent excess infant adiposity might help reduce children's risk of asthma-related symptoms.

Keywords

Asthma; wheeze; adiposity; children; prospective study

© 2008 American Academy of Allergy, Asthma & Immunology

Reprint requests: Elsie M. Taveras, MD, MPH, Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care and Harvard Medical School, 133 Brookline Ave, 6th Floor, Boston, MA 02215. Elsie_Taveras@hphc.org.

Disclosure of potential conflict of interest: S. T. Weiss has consulting arrangements with Genentech and GlaxoSmithKline, has received research support from GlaxoSmith-Kline, and is on the advisory board for Genentech. The rest of the authors have declared that they have no conflict of interest.

Asthma, the most common cause of chronic childhood disease in the United States, is the pediatric diagnosis most frequently resulting in admission to hospitals¹ and school absences.² The diagnosis of asthma is difficult in infants and toddlers given their age and the frequency of isolated wheezing for other reasons (eg, respiratory tract infections). Nevertheless, evidence suggests that half of all cases of childhood asthma are diagnosed by age 3 years, and 80% of all cases of childhood asthma are diagnosed by age 6 years.^{3,4} Thus it is important to investigate possible early-life risk factors for asthma incidence.

The prevalence of obesity in children has increased concurrently with asthma in the last 20 years.^{5–7} Several cross-sectional^{8–18} and longitudinal^{19–23} studies have found direct associations between higher body mass index (BMI) and airway hyperresponsiveness, wheeze, or asthma in children. There is, however, heterogeneity in the literature with regard to the relationship between BMI and asthma among boys and girls. In one longitudinal study of BMI and asthma-related outcomes in children, Gold et al²¹ studied 9828 children aged 6 to 14 years participating in the Six-City Study. Over a median follow-up time of 5 years, obesity was associated with the development of asthma among girls in the study. In boys the authors observed a bimodal relationship, with an increase in asthma incidence observed in both the lowest and highest BMI quintiles. The cause of the heterogeneity in the sex dependence of this relationship is not clear.

All but one of the existing prospective studies assessed asthma outcomes in school-age children or later, whereas the incidence of asthma peaks in younger children. The one exception was a study of 1232 adults born between 1974 and 1978 in Chile.²³ In that study Rona et al²³ found that a rapid rate of growth in length, but not weight, in the first year of life was associated with wheezing in adulthood. The study is likely not generalizable to the United States in the 21st century because it was done in an era when infant malnutrition was prevalent in Chile. In addition, the authors did not study adiposity and were unable to adjust for several prenatal and postnatal factors thought to be associated with asthma, including exposure to cigarette smoke *in utero* and during the first year of life and family history of asthma.

The pathophysiologic basis for an association linking excess adiposity to risk of asthma is a topic of active investigation.^{24,25} Proposed mechanisms include direct effects of obesity on mechanical functioning of the lung,²⁶ changes in the immune or inflammatory responses directly^{27–29} or through genetic mechanisms,³⁰ sex-specific influences relating to hormones,²⁵ and gastric reflux.³¹ In children, other factors, such as infant feeding, might be mutually correlated with obesity and asthma and need to be accounted for in analyses.

The purpose of this study was to examine the longitudinal association of infant weight-for-length (WFL), a proxy of adiposity, with incidence of wheezing by age 3 years. WFL reflects body weight relative to length and is a proxy for adiposity among infants and young children younger than 24 months.³² An increase in WFL over time indicates that a child's weight has increased out of proportion to his or her increase in length and suggests that the child has experienced an increase in adiposity. We hypothesized that higher adiposity and, secondarily, infant growth would be associated with increased risk of incident asthma among both boys and girls.

METHODS

Study design and participants

Study subjects were participants in Project Viva, a prospective observational cohort study of gestational diet, pregnancy outcomes, and offspring health.³³ Details of recruitment, eligibility, and retention procedures are available elsewhere.³³ Fig E1 (available in the

Online Repository of www.jacionline.org) shows a detailed description of our process for including participants in the current analysis. Our sample size for analysis was 932 infants.

After obtaining informed consent, we performed in-person study visits with the mothers during pregnancy and with both the mothers and their infants immediately after delivery and at 6 months and 3 years postpartum. The participating mothers completed mailed questionnaires at 1 and 2 years postpartum, on which they updated the information on their child's wheezing status. Institutional review boards of participating institutions approved the study, and all procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki.

Measurements

Main exposure—We measured the children's weight at 6 months by using a digital scale (Seca model 881; Seca Corp, Hanover, Md) and measured length at birth and 6 months with a calibrated stadiometer (Shorr Productions, Olney, Md). We obtained infant birthweight from the hospital clinical record. We calculated WFL and converted the values into age- and sex-specific WFL z score percentiles by using US national reference data.³⁴ z Scores are typically used for WFL to adjust for child's age and sex through the use of national reference data. z Scores indicate how many SDs someone is above or below the mean. A z score of 0 indicates that a child is of average WFL (50th percentile), a z score of -1.0 indicates a child is 1 SD below the mean, and a z score of 1.0 indicates a child is 1 SD above the mean. We ranked WFL z score percentiles into quartiles for male and female subjects. Research assistants performed all measurements following standardized techniques and participated in biannual in-service training to ensure measurement validity (IJ Shorr, Shorr Productions).³⁵ Interrater and intrarater measurement errors were well within published reference ranges for all measurements (example for length: rater 1, 0.22 cm; rater 2, 0.35 cm; rater 3, 0.19 cm; rater 4, 0.25 cm; between raters, 0.29 cm).³⁶ Our main exposure was WFL z score at 6 months adjusted for birthweight, a measure of attained adiposity. Among a subsample of 569 infants for whom we had measured length at birth, we also examined change in WFL and change in length-for-age in the first 6 months of life as measures of growth.

Outcome measures—We ascertained the wheeze outcomes from questions from the first-year, second-year, and third-year questionnaires: "Since your child was born/Since your child was 12 months old/Since your child was 2 years old, has he/she ever had wheezing (or whistling in the chest)?" The primary outcome was *recurrent wheezing*, which was defined as parents' report of wheezing on the 3-year questionnaire plus wheezing on either the first- or second-year questionnaires. If the child had a positive response at the 3-year questionnaire but a negative response on the other questionnaires, he or she was excluded from the analysis for recurrent wheeze, making the comparison group for the recurrent wheeze outcome the children who never wheezed in the first 3 years of life.

Secondary wheeze outcomes included (1) any wheezing (or whistling in the chest) from 6 months to 3 years of age, which was defined as parents' report of wheezing symptoms anytime from 6 months to age 3 years, and (2) current asthma defined, which was defined as parents' report of a physician's diagnosis of asthma, wheeze, or reactive airway disease at any time between birth and age 3 years plus current wheeze between 2 and 3 years of age.

In a subset from whom we collected blood specimens at age 3 years, we examined a related outcome: wheezing with or without atopy at age 3 years. Based on previously published definitions,^{37,38} we defined *wheezing plus atopy* as recurrent wheezing plus either total IgE levels of the 75th percentile or greater of the distribution (≥ 75.6 IU/mL) or at least 1 detectable allergy-specific IgE level (≥ 0.35 IU/mL). We defined *wheezing without atopy* as

recurrent wheezing plus none of these 2 factors. More details regarding the subsample of participants in this analysis, and the methods for collecting and analyzing IgE are presented in the Methods section of the Online Repository at www.jacionline.org.

Other measures—We also measured maternal age, height, weight, education, household income, smoking during pregnancy, passive smoking exposure in the first year of life, duration of breast-feeding, paternal height and weight, maternal and paternal history of asthma, and the number of children under the age of 12 years living in the household. We calculated gestational age and determined birthweight for gestational age *z* values by use of US national reference data.³⁹ We calculated maternal vitamin D intake from a validated semiquantitative food frequency questionnaire during pregnancy.^{40,41} An expanded section on other measures is presented in the Methods section of the Online Repository.

Statistical analysis

We first examined the bivariate relationships of 6-month WFL *z* scores with other covariates and our main outcome, recurrent wheezing. We then used multiple logistic regression models to assess the independent effects of 6-month WFL *z* scores on our main outcome. We initially performed all analyses separately by sex, but because the results were similar, we combined the regression analyses and adjusted for sex. In multivariable models we included only those covariates that were of *a priori* interest or confounded associations of 6-month WFL *z* scores with our wheeze outcomes. We first adjusted for age (at 3-year assessment) and sex only. The multivariable model included child's age, sex, birthweight, race/ethnicity, and passive exposure to smoking during the first year of life; mother's prepregnancy BMI, vitamin D intake during pregnancy, and breast-feeding status at 6 months; father's BMI; household income; number of children younger than 12 years living in the household; and maternal and paternal history of asthma.

In subgroup analyses of the 569 infants for whom we had measured length at birth, we used WFL *z* score at 6 months adjusted for WFL *z* score at birth as a measure of change in WFL in the first 6 months of life. Likewise, we used length-for-age *z* score at 6 months adjusted for length-for-age *z* score at birth as a measure of change in length-for-age in the first 6 months of life. For all results, we report odds ratios (ORs) and 95% CIs for the main predictor.

Finally, we further examined the association of 6-month WFL *z* score with 2 outcomes: (1) atopy alone (ie, total IgE $\geq$ 75th percentile or at least 1 detectable allergy-specific IgE level) and (2) wheezing plus atopy. For the analyses of wheezing plus atopy, we created a 4-level outcome based on the presence or absence of recurrent wheeze and atopy; the comparison group was composed of those who did not have recurrent wheezing and were not atopic. We used multinomial logistic regression and conducted all analyses with SAS, version 9.1 (Cary, NC).

RESULTS

In this study half of the children were male (50%), and 30% were nonwhite. At birth, their mean birthweight was 3.53 kg (SD, 0.51 kg), with a mean gestational age of 39.7 weeks (SD, 1.4 weeks). At 6 months, the infants' mean WFL *z* score was 0.68 (SD, 0.94; range, -2.96 to 3.24). Mean WFL *z* score at birth was 0.47 (SD, 0.76); mean length-for-age *z* score was 0.02 (SD, 0.83) at birth and -0.04 (SD, 0.86) at 6 months of age. The mean change in WFL *z* score from birth to 6 months of age was 0.21 (SD, 1.08). At 6 months, 52% of children were being fed breast milk. Most mothers (74%) had at least a college education, and 67% lived in households with an annual income of more than \$70,000; 15% of mothers and 15% of fathers had a previous history of physician-diagnosed asthma. By age 3 years,

30% of children had any wheezing, 14% of children had recurrent wheezing, and 13% had current asthma.

In bivariate analyses children with higher 6-month WFL z scores were more likely to have higher birthweights and have mothers with higher prepregnancy BMIs and were less likely to be breast-fed (Table I). The home environment of children with higher 6-month WFL z scores was characterized by somewhat more passive smoke exposure, but no difference in exposure to siblings less than age 12 years, pets, or other common allergens.

In age- and sex-adjusted multivariable models we observed a direct association between 6-month WFL z score and risk of any wheezing and recurrent wheezing at age 3 years (Table II). The direct association between WFL z score at 6 months and recurrent wheeze was robust to controlling for a variety of potential confounders (Table II). Compared with children in the lowest quartile of WFL z scores at 6 months (median within quartile, -0.39), those in the highest quartile (median, 1.78) had higher risk of recurrent wheeze at age 3 years (OR, 2.25 ; 95% CI, 1.10 – 4.60).

Table III shows risk of any wheezing, recurrent wheezing, and current asthma with infants' WFL z scores at 6 months, expressed as a 1-unit increment rather than in quartiles and stratified by sex. We found that each 1-unit increment in 6-month WFL z score was associated with greater odds of having had any wheezing (OR, 1.23 ; 95% CI, 1.03 – 1.48) or recurrent wheezing by 3 years of age (OR, 1.46 ; 95% CI, 1.11 – 1.91). We found a weaker association of 6-month WFL z score with current asthma (OR, 1.22 ; 95% CI, 0.94 – 1.59). In fully adjusted multivariable models we did not observe substantial differences in risks between boys and girls (Table III). Furthermore, the association between 6-month WFL z score and risk of wheezing did not vary by birthweight, and adjustment for birthweight did not attenuate the observed estimates. For example, in multivariable models not adjusted for birthweight, the odds of recurrent wheeze was 1.44 (95% CI, 1.10 – 1.88) for each 1-unit increment in 6-month WFL z score. After adjustment for birthweight, the odds of recurrent wheeze was 1.46 (95% CI, 1.11 – 1.91). Independently, birthweight was not associated with any of the outcomes. For example, the odds of recurrent wheeze was 0.81 (95% CI, 0.50 – 1.32) for each 1-kg increment in birthweight.

Subgroup analyses of change in WFL z score in the first 6 months of life (ie, WFL z score at 6 months adjusted for WFL z score at birth) revealed very similar results to those examining attained adiposity. Each 1-unit increment in WFL z score at 6 months (adjusted for WFL z score at birth) was associated with increased odds of any wheezing (OR, 1.17 ; 95% CI, 0.91 – 1.49) and recurrent wheezing (OR, 1.39 ; 95% CI, 0.95 – 2.04). However, with a relatively low sample size ($n = 569$), the CIs were wider than those in the main analyses. Independently, change in length-for-age in the first 6 months of life was not associated with any of the outcomes (data not shown).

Among the 494 participants with available serum IgE data, 196 (40%) had plasma manifestations of atopy. In multivariable logistic regression analyses 6-month WFL z score was not associated with atopy alone (OR, 1.04 ; 95% CI, 0.83 – 1.29). In addition, higher adiposity in infancy was not associated with the atopic form of recurrent wheezing (see Table E1 in the Online Repository at www.jacionline.org). In a sensitivity analysis, removing sensitization to the one food allergen (egg white) did not materially change the results (data not shown).

DISCUSSION

In this prospective cohort study higher adiposity in infancy was associated with a greater risk of recurrent wheezing by age 3 years. The results were significant, even after adjusting

for a number of potential confounders, including socioeconomic status, breastfeeding, and passive exposure to smoke. Birthweight was not associated with any of the outcomes. Furthermore, infant adiposity was not associated with the atopic form of recurrent wheeze.

Although previous studies have examined the relationship between birthweight and incident asthma,^{42–49} the relationships between postnatal growth, adiposity, and risk of asthma remain understudied. Furthermore, most previous studies are limited by their reliance on weight measures alone. To our knowledge, this is the first study to report associations of infant growth and asthma-related outcomes in childhood. In addition, we were able to use measures of size that included length in addition to weight, which together reflect adiposity better than weight alone.⁵⁰ Our findings are consistent with cross-sectional studies of older children and adolescents that have observed a direct association between higher BMI and airway hyperresponsiveness, wheeze, or asthma in children.^{8–18} Our results also extend to preschool-age children's findings of recent longitudinal studies^{19–23} that have linked obesity with the development of asthma or asthma-like symptoms. Contrary to previous studies in older children, we did not find substantial differences in risks among boys and girls. In addition, we did not find a relationship between rapid rate of growth in length with our asthma-related outcomes.

We observed a weaker association between WFL *z* score at 6 months with current asthma than with our measures of asthma-related symptoms. It is possible that higher adiposity in infancy might be associated with a higher prevalence of conditions that might manifest as wheezing (ie, gastroesophageal reflux) but not with a higher prevalence of asthma. This lack of precision might lead to smaller observed ORs for physician-diagnosed asthma than for asthma-related symptoms. It is also possible that our measure, parental report of a physician's diagnosis of asthma and related symptoms, might lack sensitivity and specificity (ie, pediatric clinicians might be more reluctant to make a diagnosis of asthma or related symptoms in children younger than 3 years), and the diagnosis might be influenced by parental or physician diagnostic bias. The diagnosis of asthma is difficult in infants and toddlers given their age and the frequency of isolated wheezing for other reasons (eg, respiratory tract infections). Although we recognize that not all wheezing illnesses in early childhood equate to asthma, children who experience recurrent wheezing episodes are more likely to have asthma than those with transient wheezing episodes.^{38,51} Thus our findings of an association between WFL *z* score at 6 months with both any wheezing and recurrent wheezing gives us confidence that we captured the clinically important wheezing symptoms. It is still unclear whether the relationship of increased infant adiposity to wheezing extends to asthma itself or alternatively is a risk factor for early-life wheeze, which might or might not persist into later childhood.

Our findings of a null association between birthweight and asthma-related outcomes at age 3 years among this population of term infants are consistent with our earlier published findings of a null relationship with asthma outcomes at 2 years of age⁴² and confirm those of a recent retrospective cohort study by Dik et al,⁵² who examined data from 170,960 children at age 6 years. In multivariate models adjusted for gestational age, the relative risk of asthma was 1.01 (95% CI, 0.97–1.05) for children whose birthweight was 3800 g or greater compared with those whose birthweight was 3500 to 3790 g. However, our results are in contrast to 2 population-based cohort studies that found a direct association between high birthweight and risk of emergency department visits and hospitalizations for asthma among 10- to 12-year-old children.^{46,47} Altogether, our findings of a null association between birthweight and asthma-related outcomes, together with our findings that increasing WFL *z* scores in the first 6 months of life were associated with increased risk of asthma-related outcomes, suggest that growth in infancy has an important influence on children's risk of asthma-related symptoms.

In this study we also found that WFL z score at 6 months was not associated with increased risk of having manifestations of atopy or with recurrent wheeze and atopy combined. Our findings are in contrast to those of previous studies among obese Taiwanese girls¹⁸ and obese Finish^{53,54} and Danish⁵⁵ adults that found an association between higher BMI and increased atopy. Our results were limited by a small sample size of participants with non-missing data on all variables. It is also possible that the null results we observed between adiposity and atopy might be due to the early age of our cohort. Wahn⁵⁶ found that sensitization to indoor and outdoor allergens is still developing between the first and tenth birthdays. The published data on adiposity and atopy, however, have not been consistent,⁵⁷ and further studies are needed to evaluate plausible mechanisms that might explain the relationship between higher adiposity and asthma, including immune-mediated and non-immune-mediated pathways.

Our study attempted to address limitations of previous studies, which have included small sample sizes and retrospective collection of anthropometric and birthweight data. An additional strength of our study was the ability to adjust for multiple socioenvironmental confounders and other factors, such as infant feeding, which are mutually correlated with obesity and asthma. Our study also has several potential limitations. Although mothers in the study had diverse racial/ethnic backgrounds, their educational and income levels were relatively high. Our results might not be generalizable to more socioeconomically disadvantaged populations. Previous studies have found that racial/ethnic minority children are disproportionately affected by asthma prevalence.⁵⁸ Moreover, racial/ethnic minorities and children of lower socioeconomic position have particularly high rates of obesity in childhood and beyond.⁵⁹ Thus it is possible that there might be residual confounding by shared determinants of asthma and obesity that we were unable to measure. Further longitudinal studies of obesity and asthma are needed among a low-income minority population.

In summary, we found that higher adiposity at 6 months of age was associated with a greater risk of wheezing by age 3 years. As an example of a 1-unit difference in WFL z score, consider two 6-month-old male infants who are of average length (67 cm). The infant with a WFL z score of 0 (ie, 50th percentile) would weigh 7.7 kg, whereas the infant with a WFL z score of 1 would weigh 8.4 kg, a difference of 0.7 kg. Our estimates predict that, after adjusting for birthweight and potential confounders, the heavier of these 2 infants would have a 46% higher risk of recurrent wheezing at age 3 years. Because both obesity and asthma develop in common during the preschool years,^{3,5} clinical and public health efforts to attenuate the increasing prevalence of obesity in the United States and elsewhere could help reduce children's risk of asthma-related symptoms.

Clinical implications: Higher adiposity in infancy was associated with greater risk of recurrent wheezing by age 3 years. Interventions to prevent excess infant adiposity might help reduce children's risk of asthma-related symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported in part by grants from the National Institutes of Health (HD 34568, HL 64925, HL 68041). E. M. Taveras is supported in part by the Physician Faculty Scholars Program of the Robert Wood Johnson Foundation.

We thank the staff and participants of Project Viva.

Abbreviations used

BMI	Body mass index
OR	Odds ratio
WFL	Weight-for-length

REFERENCES

1. Merrill, CT.; Elixhauser, A. Rockville (MD): Agency for Healthcare Research and Quality; 2005. Hospitalization in the United States, 2002: HCUP Fact Book no 6. Available at: <http://www.ahrq.gov/data/hcup/factbk6/>
2. Moonie SA, Sterling DA, Figgs L, Castro M. Asthma status and severity affects missed school days. *J Sch Health*. 2006; 76:18–24. [PubMed: 16457681]
3. Sherman CB, Tosteson TD, Tager IB, Speizer FE, Weiss ST. Early childhood predictors of asthma. *Am J Epidemiol*. 1990; 132:83–95. [PubMed: 2356817]
4. Yunginger JW, Reed CE, O'Connell EJ, Melton LJ III, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma: incidence rates, 1964–1983. *Am Rev Respir Dis*. 1992; 146:888–894. [PubMed: 1416415]
5. Ogden CL, Troiano RP, Briefel RR, Kuczmarski RJ, Flegal KM, Johnson CL. Prevalence of overweight among preschool children in the United States, 1971 through 1994. *Pediatrics*. 1997; 99:e1. [PubMed: 9099776]
6. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA*. 2004; 291:2847–2850. [PubMed: 15199035]
7. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA*. 2006; 295:1549–1555. [PubMed: 16595758]
8. Gold DR, Rotnitzky A, Damokosh AI, Ware JH, Speizer FE, Ferris BG Jr, et al. Race and gender differences in respiratory illness prevalence and their relationship to environmental exposures in children 7 to 14 years of age. *Am Rev Respir Dis*. 1993; 148:10–18. [PubMed: 8317784]
9. 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. Association with social class, perinatal events and race. *Am Rev Respir Dis*. 1990; 142:555–562. [PubMed: 2389907]
10. Luder E, Melnik TA, DiMaio M. Association of being overweight with greater asthma symptoms in inner city black and Hispanic children. *J Pediatr*. 1998; 132:699–703. [PubMed: 9580773]
11. Gennuso J, Epstein LH, Paluch RA, Cerny F. The relationship between asthma and obesity in urban minority children and adolescents. *Arch Pediatr Adolesc Med*. 1998; 152:1197–1200. [PubMed: 9856429]
12. von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax*. 2001; 56:835–838. [PubMed: 11641506]
13. Cassol V, Rizzato TM, Teche SP, Basso DF, Centenaro DF, Maldonado M, et al. Obesity and its relationship with asthma prevalence and severity in adolescents from southern Brazil. *J Asthma*. 2006; 43:57–60. [PubMed: 16448967]
14. Oddy WH, Sherriff JL, de Klerk NH, Kendall GE, Sly PD, Neilin LJ, et al. The relation of breastfeeding and body mass index to asthma and atopy in children: a prospective cohort study to age 6 years. *Am J Public Health*. 2004; 94:1531–1537. [PubMed: 15333310]
15. Somerville S, Rona R, Chinn S. Obesity and respiratory symptoms in primary school. *Arch Dis Child*. 1984; 59:940–944. [PubMed: 6497430]
16. Figueroa-Munoz JI, Chinn S, Rona RJ. Association between obesity and asthma in 4–11 year old children in the UK. *Thorax*. 2001; 56:133–137. [PubMed: 11209102]
17. Xu B, Pekkanen J, Laitinen J, Jarvelin MR. Body build from birth to adulthood and risk of asthma. *Eur J Public Health*. 2002; 12:166–170. [PubMed: 12232953]

18. Huang S, Shiao G, Chou P. Association between body mass index and allergy in teenage girls in Taiwan. *Clin Exp Allergy*. 1999; 29:323–329. [PubMed: 10202338]
19. Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med*. 2001; 163:1344–1349. [PubMed: 11371399]
20. Mannino DM, Mott J, Ferdinands JM, Camargo CA, Friedman M, Greves HM, et al. Boys with high body masses have an increased risk of developing asthma: findings from the National Longitudinal Survey of Youth (NLSY). *Int J Obes (Lond)*. 2006; 30:6–13. [PubMed: 16344843]
21. Gold DR, Damokosh AI, Dockery DW, Berkey CS. Body-mass index as a predictor of incident asthma in a prospective cohort of children. *Pediatr Pulmonol*. 2003; 36:514–521. [PubMed: 14618644]
22. Gilliland FD, Berhane K, Islam T, McConnell R, Gauderman WJ, Gilliland SS, et al. Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol*. 2003; 158:406–415. [PubMed: 12936895]
23. Rona RJ, Smeeton NC, Bustos P, Amigo H, Diaz PV. The early origins hypothesis with an emphasis on growth rate in the first year of life and asthma: a prospective study in Chile. *Thorax*. 2005; 60:549–554. [PubMed: 15994261]
24. Tantisira KG, Weiss ST. Complex interactions in complex traits: obesity and asthma. *Thorax*. 2001; 56(suppl):ii64–ii74. [PubMed: 11514709]
25. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med*. 2006; 174:112–119. [PubMed: 16627866]
26. Zerah F, Harf A, Perlemuter L, Lorino H, Lorino AM, Atlan G. Effects of obesity on respiratory resistance. *Chest*. 1993; 103:1470–1476. [PubMed: 8486029]
27. Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol*. 2005; 115:911–920. [PubMed: 15867843]
28. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*. 2003; 112:1796–1808. [PubMed: 14679176]
29. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. *J Clin Invest*. 2003; 112:1785–1788. [PubMed: 14679172]
30. Hallstrand TS, Fischer ME, Wurfel MM, Afari N, Buchwald D, Goldberg J. Genetic pleiotropy between asthma and obesity in a community-based sample of twins. *J Allergy Clin Immunol*. 2005; 116:1235–1241. [PubMed: 16337451]
31. Gunnbjornsdottir MI, Omenaas E, Gislason T, Norrman E, Olin AC, Jögi R, et al. Obesity and nocturnal gastro-oesophageal reflux are related to onset of asthma and respiratory symptoms. *Eur Respir J*. 2004; 24:116–121. [PubMed: 15293613]
32. Mei Z, Grummer-Strawn LM, Pietrobelli A, Goulding A, Goran MI, Dietz WH. Validity of body mass index compared with other body-composition screening indexes for the assessment of body fatness in children and adolescents. *Am J Clin Nutr*. 2002; 75:978–985. [PubMed: 12036802]
33. Gillman MW, Rich-Edwards JW, Rifas-Shiman SL, Lieberman ES, Kleinman KP, Lipshultz SE. Maternal age and other predictors of newborn blood pressure. *J Pediatr*. 2004; 144:240–245. [PubMed: 14760269]
34. Centers for Disease Control and Prevention, National Center for Health Statistics. [Accessed April 7, 2008] CDC Growth Charts: United States. Available at: <http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm>
35. Shorr, IJ. How to weigh and measure children. New York: UN; 1986.
36. Lohman, TG.; Roche, AF.; Martorell, R. Anthropometric standardization reference manual. In: Mueller, WH.; Martorell, R., editors. Reliability and accuracy of measurement. Champaign (IL): Human Kinetic Books; 1988.
37. Platts-Mills TAE, Erwin EA, Allison AB, Blumenthal K, Barr M, Sredl D, et al. The relevance of maternal immune responses to inhalant allergens to antibodies in the first two years of life. *J Allergy Clin Immunol*. 2003; 111:123–130. [PubMed: 12532107]

38. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000; 162:1403–1406. [PubMed: 11029352]
39. Oken E, Kleinman KP, Rich-Edwards JW, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr*. 2003; 3:6. [PubMed: 12848901]
40. Fawzi WW, Rifas-Shiman SL, Rich-Edwards JW, Willett WC, Gillman MW. Calibration of a semi-quantitative food frequency questionnaire in early pregnancy. *Ann Epidemiol*. 2004; 14:754–762. [PubMed: 15519898]
41. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr*. 2007; 85:788–795. [PubMed: 17344501]
42. 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; 41:643–648. [PubMed: 16703577]
43. Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills TA, Weiss ST. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. *Am J Respir Crit Care Med*. 1999; 160:227–236. [PubMed: 10390405]
44. Bjorksten B, Kjellman NIM. Perinatal factors influencing the development of allergy. *Clin Rev Allergy*. 1987; 5:339–347. [PubMed: 3319125]
45. Seidman DS, Laor A, Gale R, Stevenson DK, Danon YL. Is low birth weight a risk factor for asthma during adolescence. *Arch Dis Child*. 1991; 66:584–587. [PubMed: 2039246]
46. Sin DD, Spier S, Svenson LW, Schopflocher DP, Senthilselvan A, Cowie RL, et al. The relationship between birth weight and childhood asthma: a population-based cohort study. *Arch Pediatr Adolesc Med*. 2004; 158:60–64. [PubMed: 14706960]
47. Yuan W, Basso O, Sorensen HT, Olsen J. Fetal growth and hospitalization with asthma during early childhood: a follow-up study in Denmark. *Int J Epidemiol*. 2002; 31:1240–1245. [PubMed: 12540729]
48. Katz KA, Pocock SJ, Strachan DP. Neonatal head circumference, neonatal weight, and risk of hayfever, asthma and eczema in a large cohort of adolescents from Sheffield, England. *Clin Exp Allergy*. 2003; 33:737–745. [PubMed: 12801306]
49. Bolte G, Schmidt M, Maziak W, Keil U, Nasca P, von Mutius P, et al. The relation of markers of fetal growth with asthma, allergies and serum immunoglobulin E levels in children at age 5–7 years. *Clin Exp Allergy*. 2004; 34:381–388. [PubMed: 15005731]
50. Benn RT. Some mathematical properties of weight-for-height indices used as measures of adiposity. *Br J Prev Soc Med*. 1971; 25:42–50. [PubMed: 5551233]
51. Ly NP, Gold DR, Weiss ST, Celedon JC. Recurrent wheeze in early childhood and asthma among children at risk for atopy. *Pediatrics*. 2006; 117:e1132–e1138. [PubMed: 16740815]
52. Dik N, Tate RB, Manfreda J, Anthonisen NR. Risk of physician-diagnosed asthma in the first 6 years of life. *Chest*. 2004; 126:1147–1153. [PubMed: 15486376]
53. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Body mass index and physical activity in relation to asthma and atopic diseases in young adults. *Respir Med*. 2006; 100:1518–1525. [PubMed: 16503404]
54. Xu B, Jarvelin MR, Pekkanen J. Body build and atopy. *J Allergy Clin Immunol*. 2000; 105:393–394. [PubMed: 10669865]
55. Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Factors related to allergic sensitization to aeroallergens in a cross-sectional study in adults: the Copenhagen Allergy Study. *Clin Exp Allergy*. 2001; 31:1409–1417. [PubMed: 11591191]
56. Wahn U. What drives the allergic march? *Allergy*. 2000; 55:591–599. [PubMed: 10921457]
57. Hersoug LG, Linneberg A. The link between the epidemics of obesity and allergic diseases: does obesity induce decreased immune tolerance? *Allergy*. 2007; 62:1205–1213. [PubMed: 17845592]
58. Rodriguez MA, Winkleby MA, Ahn D, Sundquist J, Kraemer HC. Identification of population subgroups of children and adolescents with high asthma prevalence: findings from the Third

- National Health and Nutrition Examination Survey. Arch Pediatr Adolesc Med. 2002; 156:269–275. [PubMed: 11876672]
59. Strauss RS, Pollack HA. Epidemic increase in childhood overweight, 1986–1998. JAMA. 2001; 286:2845–2848. [PubMed: 11735760]

TABLE I

Characteristics of 932 infants in Project Viva according to quartiles of the infants' 6-month WFL z scores

	Overall	Quartile of 6-mo WFL z score				P value for trend
		1	2	3	4	
N	932	232	233	234	233	
Mean	0.68	-0.39	0.37	0.99	1.78	
Mother and family						
Maternal age at enrollment (y)	32.6 (4.8)	33.0 (4.7)	32.4 (4.8)	32.4 (5.0)	32.5 (5.0)	.25
Prepregnancy BMI (kg/m ²)	24.3 (4.9)	23.6 (4.5)	24.3 (5.0)	24.4 (4.6)	25.0 (5.5)	.003
Gestational weight gain (kg)	15.7 (5.3)	15.6 (5.7)	15.6 (4.9)	15.6 (5.0)	16.1 (5.5)	.33
Paternal BMI (kg/m ²)	26.3 (3.8)	26.0 (3.9)	26.4 (3.8)	25.9 (3.2)	26.8 (4.0)	.10
College graduate or more (%)	74	81	69	76	71	.08
Household income >\$70,000/y (%)	67	71	69	65	64	.10
Mother smoked during index pregnancy (%)	9	10	9	7	10	.91
Maternal history of asthma (%)	15	15	17	17	12	.38
Paternal history of asthma (%)	15	16	15	15	14	.69
Maternal Vitamin D intake during pregnancy (IU)	550 (161)	569 (149)	542 (164)	549 (175)	541 (155)	.11
Child and home environment						
Boy (%)	50	50	50	50	50	.98
White (%)	70	69	66	78	69	.40
Birthweight	3.53 (0.51)	3.51 (0.54)	3.44 (0.48)	3.53 (0.48)	3.64 (0.51)	.002
Gestational age at birth (wk)	39.7 (1.4)	39.8 (1.4)	39.6 (1.5)	39.7 (1.5)	39.7 (1.4)	.89
Birthweight for gestational age z score (fetal growth)	0.23 (0.94)	0.18 (1.00)	0.07 (0.85)	0.23 (0.92)	0.45 (0.95)	.0004
Breast-milk feeding at 6 mo (%)	52	64	51	50	45	<.0001
Passive smoke exposure at home (%)	7	4	6	9	7	.08
Recurrent wheezing (%)	14	10	13	18	17	.01
Any wheezing (%)	30	23	27	37	31	.01
Current asthma (%)	13	10	11	16	13	.23
No. of children <12 y living in home	1.66 (0.76)	1.65 (0.83)	1.66 (0.74)	1.66 (0.74)	1.65 (0.75)	.95
Furry pet at home (%)	42	41	42	43	42	.76

	Quartile of 6-mo WFL z score					P value for trend
	Overall	1	2	3	4	
Home cockroach exposure (%)	5	6	5	3	4	.20
Moisture or mildew in home (%)	24	27	21	27	21	.30

Values are presented as n (%) or mean (SD) where shown.

TABLE II
Associations of quartile of 6-month WFL z scores with risk of clinical outcomes during the first 3 years of life

Clinical outcomes at age 3 y ^a	Quartile of 6-mo WFL z score: OR (95% CIs)				P value for trend
	1	2	3	4	
Range of WFL z score					
Boys	−2.29 to 0.10	0.11 to 0.74	0.74 to 1.42	1.42 to 3.24	
Girls	−2.96 to 0.02	0.04 to 0.66	0.66 to 1.26	1.26 to 2.84	
Recurrent wheezing (n = 100)					
Age and sex adjusted	1.00 (reference)	1.33 (0.68–2.59)	2.15 (1.14–4.05)	1.93 (1.03–3.63)	.02
Multivariable model	1.00 (reference)	1.23 (0.58–2.61)	2.38 (1.16–4.88)	2.25 (1.10–4.60)	.008
Any wheezing (n = 253)					
Age and sex adjusted	1.00 (reference)	1.25 (0.81–1.93)	2.00 (1.31–3.05)	1.52 (0.99–2.34)	.01
Multivariable model ^b	1.00 (reference)	1.08 (0.66–1.75)	2.00 (1.26–3.19)	1.50 (0.93–2.41)	.02
Current asthma (n = 107)					
Age and sex adjusted	1.00 (reference)	1.12 (0.61–2.06)	1.66 (0.94–2.96)	1.28 (0.70–2.34)	.23
Multivariable model	1.00 (reference)	0.80 (0.40–1.62)	1.64 (0.86–3.14)	1.29 (0.65–2.56)	.16

Data are from multivariable analyses of infants participating in Project Viva.

* The exposure was 6-month WFL z score in quartiles; the first quartile was designated as the reference group. We examined 3 separate outcomes: recurrent wheezing, any wheezing, and current asthma. After excluding missing data, the sample size for recurrent wheezing is 701, that for any wheezing is 854, and that for current asthma is 842.

† The multivariable model adjusts for child's birthweight, sex, age, race/ethnicity, and passive exposure to smoking during the first year of life; mother's prepregnancy BMI, vitamin D intake during pregnancy, and breast-feeding status at 6 months; father's BMI; household income; number of children younger than 12 years living in the household; and maternal and paternal history of asthma.

TABLE III

Associations of 6-month WFL *z* score with risk of clinical outcomes during the first 3 years of life stratified by sex

Clinical outcomes at age 3 y [*]	OR (95% CIs) per 1-unit increment in 6-mo WFL <i>z</i> score		
	Overall	Boys	Girls
Recurrent wheezing (n = 100)			
Age and sex adjusted	1.31 (1.04–1.64), c statistic = 0.64	1.25 (0.95–1.64)	1.44 (0.97–2.15)
Multivariable Model	1.46 (1.11–1.91), c statistic = 0.78	1.40 (1.01–1.95)	1.70 (0.99–2.91)
Any wheezing (n = 253)			
Age and sex adjusted	1.23 (1.05–1.44), c statistic = 0.58	1.15 (0.93–1.41)	1.37 (1.07–1.75)
Multivariable model [†]	1.23 (1.03–1.48), c statistic = 0.68	1.18 (0.93–1.50)	1.33 (0.99–1.80)
Current asthma (n = 107)			
Age and sex adjusted	1.15 (0.92–1.43), c statistic = 0.56	1.10 (0.83–1.46)	1.23 (0.87–1.74)
Multivariable model	1.22 (0.94–1.59), c statistic = 0.73	1.20 (0.86–1.67)	1.26 (0.80–1.99)

Data are from multivariate analyses of infants participating in Project Viva.

* The exposure was 6-month WFL *z* score as a continuous variable. We examined 3 separate outcomes: recurrent wheezing, any wheezing, and current asthma. After excluding missing data, the sample size for recurrent wheezing is 701, that for any wheezing is 854, and that for current asthma is 842.

[†] The multivariable model adjusts for child's birthweight, sex, age, race/ethnicity, and passive exposure to smoking during the first year of life; mother's prepregnancy BMI, vitamin D intake during pregnancy, and breast-feeding status at 6 months; father's BMI; household income; number of children younger than 12 years living in the household; and maternal and paternal history of asthma.