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Early Life Weight Status and Risk of Childhood Asthma or Recurrent Wheeze in Preterm and Term Offspring

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Abstract

Background—Excessive weight is associated with the development of childhood asthma. However, trends among preterm and term offspring may differ.

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Objective—To assess whether the association of longitudinal weight for age (WFA) and odds of asthma/recurrent wheeze in early life differ between children born preterm or term.

Methods—This study used prospectively collected data from the Vitamin D Antenatal Asthma Reduction Trial (VDAART). Children (n=804) were followed-up and anthropometric measurements, including WFA, were taken at birth and annually until 6 years of age. The primary outcome was asthma/recurrent wheeze by 3 and 6 years of age.

Results—Among offspring, 71 (8.8%) were premature. In all children, the odds of asthma/recurrent wheeze increased by 15% (aOR=1.15, 95%CI:1.10–1.20; $p<0.001$) by 3 years and 9% (aOR=1.09, 95%CI:1.07–1.11; $p<0.001$) by 6 years of age for each unit increase in WFA z-score. Odds were different among term and preterm offspring ($p_{interaction}<0.001$). In term offspring, the odds of having asthma/recurrent wheeze by 3 and 6 years of age increased by 22% and 15%, respectively (aOR=1.22, 95%CI:1.16–1.27; $p<0.001$ and aOR=1.15, 95%CI:1.11–1.18; $p<0.001$). In preterm offspring, by 3 years of age, odds of asthma/recurrent wheeze decreased by 10% for each unit increase in WFA *z*-score (aOR=0.90, 95%CI:0.81–0.99; $p=0.030$) and decreased by 27% by 6 years of age (aOR=0.73, 95%CI:0.61–0.86; $p<0.001$).

Conclusion—During early life, increasing standardized WFA is associated with higher odds of asthma/recurrent wheeze in term children. Contrary, in preterm children, a higher standardized WFA during catch-up growth may decrease the odds of asthma/recurrent wheeze associated with prematurity.

Keywords

Childhood asthma; Preterm birth; Weight; *Z*-score; Growth

Introduction

Prevalence of childhood asthma has been 8.1% in the United States (U.S.) between 2016–2018, making it the most common chronic childhood disease in the country. [1] Globally, there is an increase in the prevalence of children reporting ever having asthma with some countries reporting a 12-month prevalence of childhood asthma of more than 20% between 2015–2020. [2] Furthermore, the total cost of asthma to the U.S. economy in 2013 was estimated to be nearly $82 billion in medical costs and losses due to missed school and workdays and asthma-related mortality. [3] Global economic costs of asthma are considerable as well with asthma associated medical care costing $50.1 billion in 2007. [4] Early life factors that could influence the development of childhood asthma are of great interest to help alleviate the disease burden, especially for populations at a higher risk of developing asthma.

Origins of childhood asthma may in part lie in fetal and early life growth. Lung development during this critical time can be influenced by changes in growth trajectory both prenatally and postnatally leading to adverse effects on childhood respiratory health. [5] Abnormalities in fetal growth patterns, including decreased late gestation growth and low birth weight, have been implicated in the increased risk of wheeze and asthma in childhood. [6–9] After birth, early life growth trajectories may also impact asthma development. [10] Excessive weight gain in infancy might predispose children to asthma,[11, 12] even in infants with rapid catch-up growth after being born with low birth weight. [13] Asthma studies on early childhood growth

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of children in the U.S. are lacking. A large study of European children showed increased asthma risk with rapidly increasing body mass index (BMI) trajectory in the first 2 years of life [14] and a study of Taiwanese children aged 6–11 years showed that those with persistently overweight growth trajectory had a higher risk of asthma. [15] In both studies, statistical models were adjusted for gestational age. However, growth trajectories differ among those born term versus preterm [16], the latter of which accounts for approximately 9% of births of women of reproductive age (i.e., 18–39yo). [17] Therefore, the effect of growth trajectory on asthma may differ based on gestational age at delivery, and this difference could alter clinical advice to decrease the risk of childhood asthma. Additionally, both prior studies used BMI to assess weight status, which is not recommended for use in children less than 2 years of age and is also not indicative of adiposity in young children. [18–20] Assessing the relationship between standardized metrics of weight status other than BMI and disease outcomes may be more accurate during early life.

In this secondary analysis using the prospectively collected data from the Vitamin D Antenatal Asthma Reduction Trial (VDAART), we investigated the association of longitudinal weight for age (WFA) from birth to 6 years of age with the risk of childhood asthma or recurrent wheeze in preterm and term offspring. We hypothesized that higher weight during early life increases the risk of asthma and recurrent wheeze, however preterm infants with catch-up growth may have a different pattern from infants born at term.

Methods

Study Population

This study is a secondary analysis of VDAART (www.vdaart.com). VDAART was a placebo-controlled, double-blinded trial of pregnant women randomized to receive either the intervention (4,400 IU of vitamin D_3) or placebo (400 IU of vitamin D_3) starting at 10–18 weeks of gestation. Detailed information on the VDAART and study IRB approval have been previously described. [21] In brief, eligible mothers were non-smoking, between the ages of 18 and 39 years at the time of enrolment with personal or partner history of asthma or atopy. Pregnant women with chronic medical conditions, multiple gestations, and major fetal anomalies were excluded from the trial. Offspring was followed by the age of 3 years for the primary outcome of VDAART (“asthma or recurrent wheeze”) and comprised the intent-to-treat (ITT) cohort of VDAART (n=806) (Figure 1). [22] Follow-up was extended to the age of 6 years for asthma or recurrent wheeze, active asthma status, and anthropometric measurements. [23]

Primary Outcome

The main outcome of this secondary analysis is offspring asthma or recurrent wheeze by 3 years and 6 years of age, similar to the primary outcome of the original VDAART and follow-up report.[22, 23] Asthma at any age was defined as caregiver report of physician-diagnosed asthma. Recurrent wheeze by age 3 years was defined as caregiver report of wheeze or any asthma medication use in two separate years before age 2 or two distinct time points after age 2. [22, 24] Recurrent wheeze by age 6 years was defined as caregiver report of wheeze or any asthma medication use in two separate years before age 6. [23]

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Children assessed for asthma or recurrent wheeze by ages of 3 and 6 years were also followed to determine their asthma status at 6 years of age. As such, we also looked at the outcome of active asthma at 6 years of age as an additional outcome in this study. Active asthma at age of 6 years was determined after the child's 5th birthday and was defined as report of physician-diagnosed asthma at any time in the first 6 years of life and the child's use of any asthma medication after the 5th birthday with or without parental report of wheeze. [23]

Main Study Variables: Preterm/Term Birth and Early Life Age-Standardized Weights

Data at birth was collected through the labour and delivery forms, including birth weight and gestational age. Preterm was defined as offspring born alive before 37 weeks of pregnancy were completed as compared with birth at term pregnancy (≥37 weeks). Anthropometric measurements were then taken during in-person visits annually. The WFA *z*-score demonstrating the distance between an individual child's weight and the average weight of comparable offspring in the reference population was calculated at birth and annually thereafter until 6 years of age using the World Health Organization (WHO) 2006 growth standards as reference. *Z*-scores were used for this analysis as they can advantageously be used as a sex-independent variable and can be grouped by combining sex and age groups. [25]

Additional Study Variables

Potential confounders in the relationship between WFA-*z* scores and asthma or recurrent wheeze and active asthma were selected *a priori* and included maternal age, maternal asthma, paternal asthma, household income, trial intervention arm, study site, sex of child, and child race. Weight-for-height (WFH), body mass index (BMI) and height-for-age (HFA) *z*-scores were also calculated using sex of the offspring, weight, height, and age and according to the WHO 2006 growth standards. [25]

Statistical Analysis

All statistical analyses were performed using R Statistical Software (V4.0.2). The demographic data of the main study groups, offspring with preterm and term deliveries, were compared using the Student *t*-test and chi-square test. WFA measurements and BMI, WFH, and HFA *z*-scores were calculated using the offspring's weight and age data and converted to *z*-scores using the *z*-scorer R package and the WHO 2006 growth standards as reference. [26, 27]

Our analyses were conducted in three stages. First, we calculated the strength of the linear association between early life WFA *z*-scores and BMI *z*-scores using the paired Pearson correlation coefficient displayed as a correlation matrix. Second, the means of preterm and term offspring's WFA *z*-scores through 6 years of age were compared using the two-sample Wilcoxon test and the yearly trend of the difference in means of WFA *z*-scores were explored. Third, the association between longitudinal standardized WFA *z*-scores and asthma or recurrent wheeze by the ages of 3 and 6 years old (from birth to 3 and 6 years of life) was evaluated using generalized estimated equations (GEE), as an extension of generalized linear models (GLM) to longitudinal data. [28] GEE is a semiparametric method

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that demonstrates the average response change for every one-unit increase in a covariate, i.e., WFA *z*-scores, across the offspring population. To estimate ß coefficients more accurately, the working subject covariance was assumed with exchangeable correlation while fitting the GEE models using the package "geepack" in R and the fit was examined by the quasi-likelihood under the independence model criterion (QIC). [29, 30]

After analysing all subjects, we conducted an interaction test to examine whether WFA *z*-scores effects were different among subgroups of preterm and term offspring. Confirming the interaction, we conducted stratified analyses of the subgroups using GEE models for the association of WFA *z*-scores with asthma or recurrent wheeze. Adjusted odds ratios (aORs) were calculated and 95% confidence intervals (CI) and the corresponding two-tailed *p*-values were obtained. A *p*-value of <0.05 was considered statistically significant.

Sensitivity Analyses

Owing to a higher difference in WFA z-scores between term and preterm children in the first year of life, we also examined the association between standardized WFA *z*-scores from year 1 through year 6 and asthma or recurrent wheeze by the ages of 3 and 6 years old using GEE models.

To assess the robustness of our findings on offspring asthma or recurrent wheeze by ages of 3 and 6 years, we explored the association between the WFA *z*-score and offspring active asthma status at age of 6 years. For this purpose, we calculated paired-differences of birth WFA *z*-scores and WFA *z*-scores at the age of 6 years as the predictor. We then used logistic regression models to examine the association between persistence of asthma at 6 years of age (active asthma status) and paired-difference of WFA *z*-scores. The models were adjusted for the potential confounders used in the primary analyses.

Results

Study Population

Of the 806 mother-child pairs in the VDAART ITT population, 804 (99.7%) with data available on the main study variables were included in this secondary analysis (Figure 1). Among these offspring, 9% (71/804) were born preterm. Primary outcome data of asthma or recurrent wheeze by the ages of 3 and 6 years was available for all subjects. 707 out of 806 offspring (88%) had active asthma status available at 6 years of age.

The comparisons of baseline characteristics between offspring with preterm birth and those born at term were presented in Table 1. There were significant differences in birth weight and weight for gestational age between preterm and term infants. Preterm infants had a higher incidence of all three of the study outcomes. The distribution of treatment arm, study site, parental asthma status, household income, sex of child, child race, early life breastfeeding, eczema, and hay fever by year 6 were similar between term and preterm offspring.

The frequency of preterm offspring that had asthma or recurrent wheeze by 3 years was higher than that of term offspring (49.3% vs 24.8%, $p<0.001$). Compared to the offspring

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born at term, preterm offspring continued to have a higher frequency of asthma or recurrent wheeze by 6 years of age (64.8% vs 42.7%, p= 0.001) as well as a higher frequency of active asthma at 6 years of age (32.4% vs 14.9%, p= 0.001, Table 1).

Correlation of Early Life Standardized Weight-for-Age and Body Mass Index Z-Scores

Offspring's WFA z-scores were positively correlated with BMI z-scores throughout early life (Figure 2). The level of correlation increased from moderate to very strong as the offspring grew older with Year 6 WFA z-scores and Year 6 BMI z-scores having the highest level of correlation (r= 0.898, p<0.001; Figure 2).

Early Life Standardized Weight-for-Age Trend by Preterm and Term Birth Status

The difference in means of preterm and term offspring's WFA z-scores was the highest at birth (−2.39 ± 1.03, p<0.001, Figure 3b). The difference in means gradually decreased from birth to year 6 of life such that there was no statistically significant difference in means of WFA z-scores of the two study groups of offspring at age of 6 years old (−0.29 ± 1.40, p= 0.56, Figure 3b). A higher proportion of term infants were overweight or obese compared to the preterm infants (Figure E1).

Longitudinal Weight for Age and Asthma or Recurrent Wheeze

In all study subjects, the odds of having asthma or recurrent wheeze by 3 years of age increased by 15% with each unit increase in WFA z-score (adjusted OR=1.15, 95%CI: 1.10–1.20; p<0.001; Table 2). By 6 years of age, odds of asthma or recurrent wheeze were increased by 9% for each unit increase in WFA z-score (aOR=1.09, 95%CI: 1.07–1.11; p<0.001; Table 2). We observed an interaction between longitudinal WFA and term/preterm status for asthma or recurrent wheeze by 3 and 6 years of age (p<0.001, respectively).

Longitudinal Weight for Age and Asthma or Recurrent Wheeze by Preterm and Term Status

In the stratified analysis, offspring born at term showed an increase in the odds of asthma or recurrent wheeze by 3 years of age and by 6 years of age by 22% and 15%, respectively (aOR=1.22, 95%CI: 1.16–1.27; p<0.001 and aOR=1.15, 95%CI: 1.11–1.18; p<0.001, respectively; Table 2). In offspring with preterm birth, by 3 years of age, the odds of having either asthma or recurrent wheeze decreased by 10% for each unit increase in WFA z-score (aOR=0.90, 95%CI: 0.81–0.99; p=0.030; Table 2) and decreased by 27% by 6 years of age (aOR=0.73, 95%CI: 0.61–0.86; p<0.001; Table 2). There was no interaction between WFA z-scores and study timepoints in association with asthma or recurrent wheeze by the ages of 3 and 6 years among offspring with preterm birth.

Sensitivity Analyses

Examining the longitudinal effect of WFA z-scores from year 1 through year 6 using the GEE model (i.e., excluding WFA in the first year of life), we observed that offspring's early life weight gain assessed by WFA z-scores was still associated with higher odds of asthma or recurrent wheeze by ages of 3 and 6 years (Table E1). Similar to the primary analysis (from birth through year 6), the effect was mainly derived from offspring born at term. As such, higher WFA z-scores in term offspring increased the odds of asthma or recurrent

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wheeze by 3 and 6 years of age (aOR=1.31, 95%CI: 1.24–1.37 and aOR=1.18, 95%CI: 1.14–1.21; respectively, Table E1). In contrast, preterm offspring still showed lower odds of asthma or recurrent wheeze by year 3 and 6 with an increase in WFA z-score (aOR=0.59, 95%CI: 0.41–0.78 and aOR=0.81, 95%CI: 0.55–1.07, respectively; Table E1).

In all study subjects, the odds of having active asthma at 6 years of age increased by 18% for each unit increase in the difference between WFA z-score at birth and at age 6 (aOR=1.18, 95%CI: 1.02–1.37; Table E2). Subgroup analysis of term and preterm children showed no statistical difference in risk of active asthma at 6 years of age with an increasing difference between WFA z-scores at birth and at age 6 (Table E2).

Discussion

Using prospectively collected data from a well-designed trial on pregnant women with follow-up of their children at high risk of offspring asthma and wheezing, we found that offspring's early life weight status assessed by WFA *z*-scores was associated with higher odds of asthma or recurrent wheeze by ages of 3 and 6 years. A greater difference in the offspring's WFA *z*-scores from birth to the age of 6 was also associated with higher odds of active asthma status at the age 6 years. However, the weight status and the associated odds showed a different trend in term and preterm offspring. Higher WFA *z*-scores in term offspring increased the odds of asthma or recurrent wheeze by 3 and 6 years of age. At year 6 of life, preterm offspring's WFA *z*-scores had caught up enough to no longer be different from those of term offspring. However, preterm offspring during catching up weight (by the ages of 3 and 6 years) showed a lower risk of asthma or recurrent wheeze with increasing WFA *z*-scores.

The prevalence of preterm birth in the VDAART cohort was similar to the national U.S. prevalence, i.e., 9.4%. [17] Prematurity is an independent risk factor for the development of asthma in childhood. [11, 31, 32] As such, most studies exploring weight and risk of asthma will exclude premature infants or adjust for gestational age in the statistical models. These studies have produced inconsistent results. Some studies have shown that high adiposity, overweight status, or obesity is associated with asthma or wheeze during childhood [12, 33, 34], whereas Zhang and colleagues' study implied that being overweight up until the age of 1 year may decrease asthma in later childhood and beyond that might confer a higher risk of asthma. [35] However, the effect of weight gain on asthma may differ based on gestational age at delivery as growth trajectories differ between preterm and term infants. [16] In agreement with prior investigations, [36] we found higher risk of early life asthma among preterm offspring compared to those born at term. Our study adds to existing literature exploring the relationship between weight gain and risk of asthma and recurrent wheeze, distinguishing important trend differences between preterm and term infants at high risk of childhood asthma. These effects were sex-independent as all z-scores were calculated using sex-specific references and our models were corrected for the sex of the child. Preterm infants in VDAART steadily gained weight throughout childhood, with the mean WFA *z*-score in the normal range based on WHO reference standards. [27] However, by age 6 years, term offspring were overweight on average with a mean z-score of 0.74. [37] Our results suggest that weight gain during early life catch-up growth among preterm offspring with low

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birth weight reduces odds of childhood asthma and recurrent wheeze as long as one does not become overweight or obese. This finding would explain the differing odds of asthma and recurrent wheeze by ages of 3 and 6 years between preterm and term offspring.

The optimal anthropometric measurement to use in evaluating adiposity in children has been debated. BMI has commonly been used in assessing adult weight status. However, studies have shown that BMI is not indicative of adiposity in young children. [18–20] Waist circumference can be used as a measurement of adiposity in young children, and high waist circumference has been shown to be associated with asthma diagnosis. [34, 38] However, waist circumference is not routinely assessed at well-child visits and reference ranges have not yet been adopted by the WHO. Tsai and colleagues showed that extremely rapid early life weight gain assessed by WFA trajectory was associated with an increased risk of asthma, but their results were adjusted for preterm status. [12] We instead used WFA, a routinely and easily measured vital sign at paediatric visits, to assess odds of asthma and recurrent wheeze in offspring of all gestational ages. Though WFA is not a measure of adiposity, it may be correlated with adiposity, and could give paediatric physicians a data point other than BMI to assess when considering possible risk factors for asthma. Also, in our study, WFA *z*-scores showed a medium correlation with BMI *z*-scores at birth and the correlation gradually increased to a strong level at the age of 6 years.

Lung development occurs during gestation and continues throughout early childhood. [39] Most premature babies are born after 24 weeks of gestation while the lung is in the saccular period of development. During this period, branching morphogenesis and capillary formation have occurred but alveolar sac formation and maturation, as well as surfactant production, are just beginning. [39] The next stage of lung development, the alveolarization phase, primarily occurs postnatally until the age of 2 years. Alveoli subsequently continue increasing in size and number, while airways increase only in size, until the closing of the long bone growth plates. [40] For premature infants, these postnatal periods of lung development and growth are crucial in completing lung maturation and catch-up alveolarization. [41] This may explain why premature infants with timely increase in standardized WFA to a normal range during catch-up growth might see a lesser increase in the risk of respiratory morbidity such as asthma as their growth may be promoting increased areas for gas exchange and catch-up alveolarization. Term infants also have an increase in the surface area for gas exchange during postnatal lung development as they grow; however, excess weight during this time may lead to airway dysanapsis which may be related to an increased risk of asthma. [42] This notion may contribute to the observed positive relation between WFA and odds of asthma or recurrent wheeze among term offspring in our study.

Our sensitivity analysis showed increased odds of active asthma at the age of 6 years with each unit increase in the difference between the WFA *z*-score at birth and 6 years of age. However, the subgroup analysis did not show any difference in the association of WFA *z*-score with active asthma between term and preterm children. This finding could be due to the fact that the preterm offspring's WFA *z*-scores by the age of 6 years were no longer significantly different from those of term offspring (Figure 3).

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Preterm infants had the greatest increase in weight during the first year of life (Figure 3a). Excluding WFA *z*-scores from birth to year 1 in our sensitivity analysis still showed different trends for term and preterm offspring, similar to our primary analysis from birth to year 6. This observation highlights the importance of preterm offspring's weight gain and catch-up growth from birth up until age 6 years.

There are limitations to this secondary analysis to be noted. The VDAART study design enrolled pregnant women whose offspring would be at high risk for asthma due to a maternal and/or paternal history of asthma and the cohort had a higher proportion of Black participants than the U.S. or European population. These factors limit the generalizability of our results. Furthermore, our study examined the population average effects of WFA on the risk of asthma or recurrent wheeze by ages of 3 and 6 years, as opposed to the individual specific effect in each year of early life. While our study suggests that the effects were similar across study timepoints, further studies representing the general population that explore the effect of WFA on asthma or recurrent wheeze for individuals at specific ages are needed.

In conclusion, we found that increasing WFA *z*-scores increased the odds of asthma or recurrent wheeze as well as active asthma by age of 6 years among offspring at high risk of childhood asthma. The observed odds were mostly driven by children born at term. However, in children with a history of prematurity, increasing WFA decreased the odds of asthma or recurrent wheeze by age of 6 years. Ensuring appropriate weight gain in premature infants as well as those born at term at high risk of asthma may decrease the odds of developing asthma in later childhood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement

Data are available upon reasonable request.

Abbreviations:

VDAART	Vitamin Antenatal Asthma Reduction Trial
WFA	Weight for Age

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WFH	Weight for Height
HFA	Height for Age
BMI	Body Mass Index
ITT	Intention-to-Treat
25(OH)D	25-Hydroxyvitamin D_3
CI	Confidence Interval
aOR	adjusted Odds Ratio

References

1. Pate CA, Zahran HS, Qin X, Johnson C, Hummelman E, Malilay J. Asthma Surveillance - United States, 2006–2018. MMWR Surveill Summ 2021; 70:1–32.
2. Asher MI, Rutter CE, Bissell K, Chiang CY, El Sony A, Ellwood E, et al. Worldwide trends in the burden of asthma symptoms in school-aged children: Global Asthma Network Phase I cross-sectional study. Lancet 2021; 398:1569–80. [PubMed: 34755626]
3. Nurmagambetov T, Kuwahara R, Garbe P. The economic burden of asthma in the United States, 2008–2013. Annals of the American Thoracic Society 2018; 15:348–56. [PubMed: 29323930]
4. Serebrisky D, Wiznia A. Pediatric Asthma: A Global Epidemic. Ann Glob Health 2019; 85. [PubMed: 31225954]
5. Shaheen S, Barker DJ. Early lung growth and chronic airflow obstruction. Thorax 1994; 49:533–6. [PubMed: 8016787]
6. Xu XF, Li YJ, Sheng YJ, Liu JL, Tang LF, Chen ZM. Effect of low birth weight on childhood asthma: a meta-analysis. BMC Pediatr 2014; 14:275. [PubMed: 25339063]
7. 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; 23:511–9. [PubMed: 24582482]
8. Carter JH, Woolcott CG, Liu L, Kuhle S. Birth weight for gestational age and the risk of asthma in childhood and adolescence: a retrospective cohort study. Archives of disease in childhood 2019; 104:179–83. [PubMed: 30026251]
9. 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; 67:670–5. [PubMed: 22381045]
10. Pike KC, Crozier SR, Lucas JS, Inskip HM, Robinson S, Roberts G, et al. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. Thorax 2010; 65:1099–106. [PubMed: 20956394]
11. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, Annesi-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; 133:1317–29. [PubMed: 24529685]
12. Tsai HJ, Wang G, Hong X, Yao TC, Ji Y, Radovick S, et al. Early Life Weight Gain and Development of Childhood Asthma in a Prospective Birth Cohort. Ann Am Thorac Soc 2018; 15:1197–204. [PubMed: 29979628]
13. Van der Gugten A, Koopman M, Evelein A, Verheij T, Uiterwaal C, Van Der Ent C. Rapid early weight gain is associated with wheeze and reduced lung function in childhood. European Respiratory Journal 2012; 39:403–10. [PubMed: 21852338]
14. Rzehak P, Wijga AH, Keil T, Eller E, Bindslev-Jensen C, Smit HA, et al. Body mass index trajectory classes and incident asthma in childhood: results from 8 European Birth Cohorts--a Global Allergy and Asthma European Network initiative. J Allergy Clin Immunol 2013; 131:1528–36. [PubMed: 23403049]
15. Chen YC, Liou TH, Chen PC, Chiang BL, Yang YH, Fan HY, et al. Growth trajectories and asthma/rhinitis in children: a longitudinal study in Taiwan. Eur Respir J 2017; 49.

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16. Sullivan MC, McGrath MM, Hawes K, Lester BM. Growth trajectories of preterm infants: birth to 12 years. J Pediatr Health Care 2008; 22:83–93. [PubMed: 18294577]
17. Martin JA, Hamilton BE, Osterman MJ, Driscoll AK. Births: final data for 2018. 2019.
18. Javed A, Jumean M, Murad MH, Okorodudu D, Kumar S, Somers V, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity in children and adolescents: a systematic review and meta-analysis. Pediatric obesity 2015; 10:234–44. [PubMed: 24961794]
19. Farbo DJ, Rhea DJ. A pilot study examining body composition classification differences between body mass index and bioelectrical impedance analysis in children with high levels of physical activity. Frontiers in Pediatrics 2021:1304.
20. Vanderwall C, Eickhoff J, Randall Clark R, Carrel AL. BMI z-score in obese children is a poor predictor of adiposity changes over time. BMC pediatrics 2018; 18:1–6. [PubMed: 29301539]
21. Litonjua AA, Lange NE, Carey VJ, Brown S, Laranjo N, Harshfield BJ, et al. The Vitamin D Antenatal Asthma Reduction Trial (VDAART): rationale, design, and methods of a randomized, controlled trial of vitamin D supplementation in pregnancy for the primary prevention of asthma and allergies in children. Contemp Clin Trials 2014; 38:37–50. [PubMed: 24614387]
22. Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, et al. Effect of Prenatal Supplementation With Vitamin D on Asthma or Recurrent Wheezing in Offspring by Age 3 Years: The VDAART Randomized Clinical Trial. JAMA 2016; 315:362–70. [PubMed: 26813209]
23. Litonjua AA, Carey VJ, Laranjo N, Stubbs BJ, Mirzakhani H, O'Connor GT, et al. Six-Year Follow-up of a Trial of Antenatal Vitamin D for Asthma Reduction. N Engl J Med 2020; 382:525–33. [PubMed: 32023372]
24. Mirzakhani H, Carey VJ, McElrath TF, Qiu W, Hollis BW, O'Connor GT, et al. Impact of preeclampsia on the relationship between maternal asthma and offspring asthma. An observation from the VDAART clinical trial. American journal of respiratory and critical care medicine 2019; 199:32–42. [PubMed: 30153046]
25. Wang Y, Chen H-J. Use of percentiles and z-scores in anthropometry. In: Handbook of anthropometry: Springer; 2012. p. 29–48.
26. Myatt M, Guervarra E. Package 'zscorer'. Available at: https://cran.rproject.org/web/packages/zscorer/zscorer.pdf. Accessed 3 Oct 2020 2019.
27. Organization WH. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development: World Health Organization; 2006.
28. Ballinger GA. Using generalized estimating equations for longitudinal data analysis. Organizational research methods 2004; 7:127–50.
29. Pan W Akaike's information criterion in generalized estimating equations. Biometrics 2001; 57:120–5. [PubMed: 11252586]
30. Højsgaard S, Halekoh U, Yan J. The R package geepack for generalized estimating equations. Journal of statistical software 2006; 15:1–11.
31. Fierro JL, Passarella M, Lorch SA. Prematurity as an independent risk factor for the development of pulmonary disease. The Journal of Pediatrics 2019; 213:110–4. [PubMed: 31262531]
32. Morata-Alba J, Romero-Rubio MT, Castillo-Corullón S, Escribano-Montaner A. Respiratory morbidity, atopy and asthma at school age in preterm infants aged 32–35 weeks. European Journal of Pediatrics 2019; 178:973–82. [PubMed: 31001655]
33. Flaherman V, Rutherford GW. A meta-analysis of the effect of high weight on asthma. Arch Dis Child 2006; 91:334–9. [PubMed: 16428358]
34. Forno E, Han Y-Y, Libman IM, Muzumdar RH, Celedón JC. Adiposity and asthma in a nationwide study of children and adults in the United States. Annals of the American Thoracic Society 2018; 15:322–30. [PubMed: 29144884]
35. Zhang Z, Lai HJ, Roberg KA, Gangnon RE, Evans MD, Anderson EL, et al. Early childhood weight status in relation to asthma development in high-risk children. J Allergy Clin Immunol 2010; 126:1157–62. [PubMed: 21051081]

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36. Shan L-S, Zhou Q-L, Shang Y-X. Bidirectional association between asthma and obesity during childhood and adolescence: A systematic review and meta-analysis. Frontiers in pediatrics 2020; 8:576858. [PubMed: 33194908]

37. Gamliel A, Ziv-Baran T, Siegel RM, Fogelman Y, Dubnov-Raz G. Using weight-for-age percentiles to screen for overweight and obese children and adolescents. Preventive medicine 2015; 81:174–9. [PubMed: 26348454]

38. Papoutsakis C, Chondronikola M, Antonogeorgos G, Papadakou E, Matziou V, Drakouli M, et al. Associations between central obesity and asthma in children and adolescents: a case–control study. Journal of Asthma 2015; 52:128–34.

39. Smith LJ, McKay KO, van Asperen PP, Selvadurai H, Fitzgerald DA. Normal development of the lung and premature birth. Paediatric respiratory reviews 2010; 11:135–42. [PubMed: 20692626]

40. Arigliani M, Spinelli AM, Liguoro I, Cogo P. Nutrition and lung growth. Nutrients 2018; 10:919. [PubMed: 30021997]

41. Narayanan M, Beardsmore CS, Owers-Bradley J, Dogaru CM, Mada M, Ball I, et al. Catch-up alveolarization in ex-preterm children. Evidence from 3He magnetic resonance. American journal of respiratory and critical care medicine 2013; 187:1104–9. [PubMed: 23491406]

42. Forno E, Weiner DJ, Mullen J, Sawicki G, Kurland G, Han YY, et al. Obesity and airway dysanapsis in children with and without asthma. American journal of respiratory and critical care medicine 2017; 195:314–23. [PubMed: 27552676]

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Highlights

What is already known about this topic:

Weight gain has been explored as a risk factor for childhood asthma, the most common chronic disease in childhood. However, trends among preterm and term offspring may differ and are crucial to investigate.

What does this article add to our knowledge:

We found that above average weight gain is associated with increased odds of childhood asthma, and this was mainly driven by children at term. However, we observed lower odds of childhood asthma in preterm children during catch-up growth.

How does this study impact current management guidelines:

Tailored weight gain strategies in early life may mitigate risk of childhood asthma.

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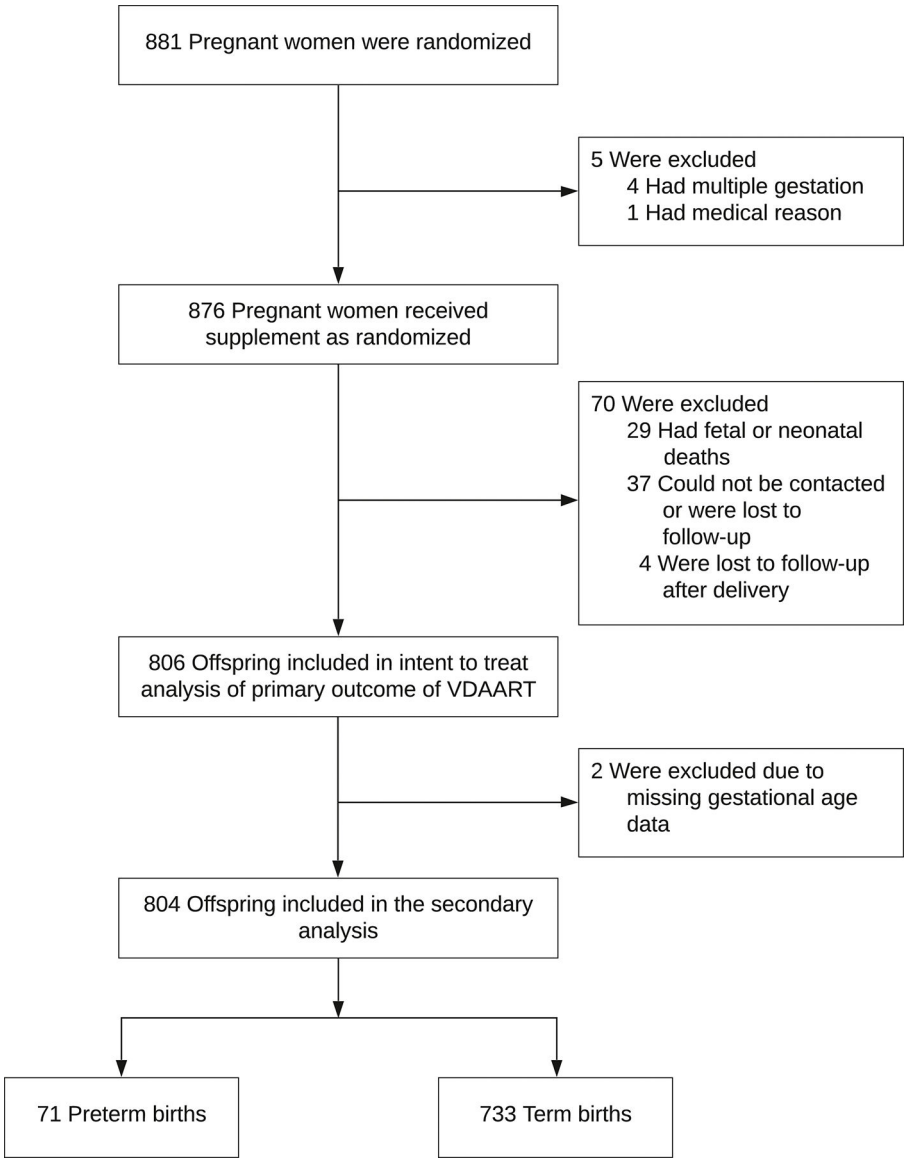


Figure 1. The VDAART participant flow diagram and study subjects.

CONSORT diagram of VDAART.

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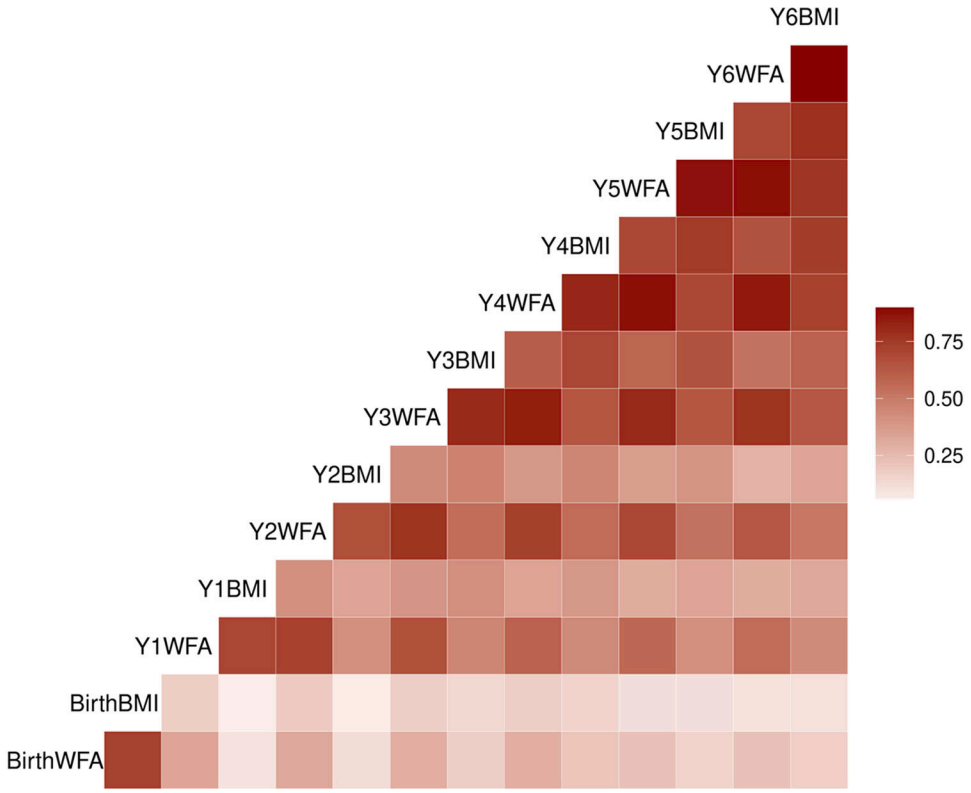
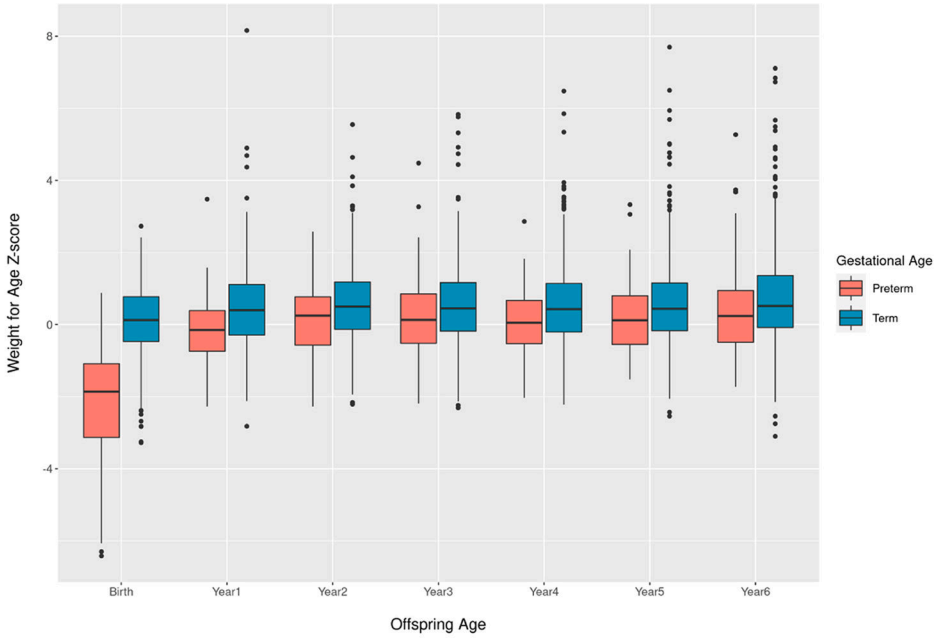


Figure 2. Estimated Pearson correlation between weight for age (WFA) z-scores and body mass index (BMI) z-scores in the first 6 years of life.

Timepoints shown are at birth (Birth), year 1 (Y1), year 2 (Y2), year 3 (Y3), year 4 (Y4) and year 5 (Y5), in conjunction with the measure of interest WFA or BMI.

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A

	Preterm (N=71)	Term (n=733)	Mean Difference	P-value
Birth Weight for Age Z-score, mean (SD)	-2.28 (1.77)	0.11 (0.96)	-2.39 (1.03)	<0.001
Year 1 Weight for Age Z-score, mean (SD)	-0.10 (0.99)	0.45 (1.08)	-0.55 (1.07)	<0.001
Year 2 Weight for Age Z-score, mean (SD)	0.18 (0.92)	0.55 (1.02)	-0.37 (1.01)	0.006
Year 3 Weight for Age Z-score, mean (SD)	0.25 (1.11)	0.54 (1.07)	-0.28 (1.07)	0.015
Year 4 Weight for Age Z-score, mean (SD)	0.12 (0.93)	0.54 (1.12)	-0.42 (1.10)	0.008
Year 5 Weight for Age Z-score, mean (SD)	0.21 (1.03)	0.61 (1.27)	-0.39 (1.25)	0.027
Year 6 Weight for Age Z-score, mean (SD)	0.44 (1.43)	0.74 (1.40)	-0.29 (1.40)	0.056

B

Figure 3. The trend of weight for age z-scores among preterm and term offspring during the first 6 years of life.

a) WFA z-scores vs. offspring age in years among preterm and term offspring. b) Comparison between annual WFA z-scores among preterm and term offspring through 6 years of age.

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Table 1:

Baseline characteristics in this VDAART secondary analysis by preterm/term status

Characteristic	Preterm (N=71)	Term (n=733)	P Value
Site, no. (%)			0.051
Boston, MA	15 (21.1)	223 (30.4)	
San Diego, CA	21 (29.6)	253 (34.5)	
St. Louis, MO	35 (49.3)	257 (35.1)	
Treatment Arm, Placebo (400IU Vitamin D/d), no. (%)	31 (43.7)	370 (50.5)	0.331
Maternal Age >35years, no. (%)	6 (8.5)	54 (7.4)	0.924
Maternal Asthma, no. (%)	27 (38.0)	295 (40.2)	0.812
Maternal Education, no. (%)			0.740
Less than high school diploma	10 (14.1)	90 (12.3)	
Less than college	35 (49.3)	396 (54.0)	
College or more	26 (36.6)	247 (33.7)	
Paternal Asthma, no. (%)	18 (25.4)	169 (23.1)	0.868
Household Income, no. (%)			0.866
Greater than $50K	22 (31.0)	247 (33.7)	
Less than $50K	32 (45.1)	308 (42.0)	
Refused or Unknown	17 (23.9)	178 (24.3)	
Mode of delivery, C-section, no. (%)	25 (35.2)	214 (29.4)	0.372
Male Sex of Child, no. (%)	39 (54.9)	381 (52.0)	0.726
Child Race, no. (%)			0.464
Black	38 (53.5)	351 (47.9)	
White	24 (33.8)	241 (32.9)	
Other	8 (11.3)	135 (18.4)	
Unknown	1 (1.4)	6 (0.8)	
Breastfed during first 6 months of life, no. (%)	34 (47.9)	374 (51.0)	0.602
Birth weight (g), mean (SD)	2351 (688.0)	3365 (461.8)	<0.001
Weight for Gestational Age (%)			0.047
Average for Gestational Age	55 (77.5)	597 (81.4)	
Large for Gestational Age	3 (4.2)	64 (8.7)	
Small for Gestational Age	13 (18.3)	72 (9.8)	
Eczema by age 6, no. (%)	7 (10.9)	67 (11.0)	1.00
Hay fever by age 6, no. (%)	9 (14.1)	51 (8.4)	0.199

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Characteristic	Preterm (N=71)	Term (n=733)	P Value
Asthma or recurrent wheeze by 3yrs, no. (%)	35 (49.3)	182 (24.8)	<0.001
Asthma or recurrent wheeze by 6yrs, no. (%)	46 (64.8)	313 (42.7)	0.001
Active asthma at 6yrs, no. (%)	23 (32.4)	109 (14.9)	0.001

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Table 2:

Generalized Estimated Equation Models for Effect of Longitudinal Weight for Age on Asthma/Recurrent Wheeze by Year 3 and Year 6

	Year 3			Year 6		
	β	**aOR (95% CI)**	**P value**	**β**	**aOR (95% CI)**	**P value**
All Study Subjects	0.140	1.15 (1.10–1.20)	<0.001	0.091	1.09 (1.07–1.11)	<0.001
Term	0.196	1.22 (1.16–1.27)	<0.001	0.138	1.15 (1.11–1.18)	<0.001
Preterm	−0.10	0.90 (0.81–0.99)	0.030	−0.312	0.73 (0.61–0.86)	<0.001

All models are adjusted for maternal age, maternal asthma, paternal asthma, household income, intervention arm, site, sex of child and race