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Gestational Weight Gain, Offspring Asthma and Wheeze Phenotypes in Project Viva

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GESTATIONAL WEIGHT GAIN, OFFSPRING ASTHMA AND WHEEZE PHENOTYPES IN PROJECT VIVA

A Thesis Presented

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ABSTRACT

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In the US, 8.4% of children are diagnosed with asthma by age 18, making asthma one of the most common chronic conditions among children. Additionally, 25% of children experience persistent wheezing by age 6, an indicator of childhood asthma. Both childhood asthma and persistent wheezing may be linked to inflammatory and immune mechanisms, which are associated with inadequate and excessive gestational weight gain. Studies investigating the relationship between gestational weight gain and offspring asthma and wheeze phenotypes are limited by self-reported gestational weight gain, early age at asthma and wheeze assessments, limited adjustment for potential confounders and no trimester-specific evaluations. Therefore, we investigated the association between total and trimester-specific gestational weight gain, offspring asthma and wheeze phenotypes among 2128 mother-child pairs in Project Viva, a prospective cohort study in eastern Massachusetts. Gestational weight gain was abstracted from medical records and

self-reported prepregnancy weight, and defined both continuously and using Institute of Medicine guidelines. Offspring asthma was obtained via maternal report at approximately 7 years, while wheeze trajectories were derived via latent class mixed models based on presence of wheeze between 1 and 9 years, inclusively, via maternal report. We investigated the relationship between gestational weight gain, offspring asthma and wheeze phenotypes using multivariable regressions and predicted probabilities, adjusting for important covariates. Most women had excessive gestational weight gain (56%), while 31% had adequate gestational weight gain and 13% had inadequate gestational weight gain. Approximately 18% of children had current mid-childhood asthma, 13% had early transient wheeze and 13% had persistent wheeze. We found a non-linear association between total gestational weight gain and offspring current mid-childhood asthma. Additionally, there was a 36% decreased odds of early transient wheeze among children of mothers with excessive third trimester gestational weight gain (aOR= 0.64; 95% CI: 0.42-0.98). This study adds to the body of literature by incorporating adequate inclusion of confounders and risk factors for adjustment, as well as being the first study to evaluate the association between trimester-specific gestational weight gain, offspring asthma and wheeze phenotypes.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

BACKGROUND AND SIGNIFICANCE

A. Introduction

Asthma is a chronic lung disease that causes inflammation and narrowing of the airways.[1] This causes recurrent wheezing, chest tightness and discomfort, coughing, shortness of breath, reduced energy and feelings of weakness or tiredness.[1,2] Asthma is usually diagnosed in childhood (<18 years) and is one of the most common chronic conditions among children.[3,4] In the United States, approximately 6.2 million children under the age of 18, or 8.4%, have been diagnosed with asthma, with boys having higher prevalence of childhood asthma than girls.[5,28,29,30] Overall rates have been fairly consistent over the past two decades;[4,5] therefore assessing potential modifiable risk factors for childhood asthma remains critical.

Childhood asthma has serious, long-term health consequences that can last a lifetime. The mucus that accumulates in the lungs due to asthmatic symptoms increases the likelihood of developing bronchitis and pneumonia.[6] These conditions can further affect the lungs by causing permanent lung scarring or damage and, in the case of pneumonia, can lead to antibiotic resistance if repeat infections occur.[6] Additionally, if asthma symptoms are not well controlled, chronic inflammation of the airways can lead to lung scarring and have health effects similar to chronic obstructive pulmonary disease, or COPD.[6] Uncontrolled and untreated asthma is particularly harmful and can be fatal; in 2015, 3,615 people in the United States, or 10 people per day, died from asthma.[6,7]

In addition to lung health consequences, childhood asthma can cause lifestyle changes that affect long-term health. Children who have asthma are more likely to miss school than those who do not have asthma, and later in life this could also lead to missed work.[8] Additionally, asthma is the third leading cause of hospitalization in children.[8] Asthma also causes changes to an individual's daily lifestyle and personal choices, which can have repercussions on personal health. Asthma, particularly exercise-induced asthma, can cause children to develop a decreased exercise tolerance, which can lead to a sedentary lifestyle and associated negative health effects including obesity, diabetes, and high blood pressure.[3,6] Sleep can also be affected by asthma since coughing, wheezing and shortness of breath can all make it difficult to fall asleep and/or stay asleep.[3,9]

Established risk factors for developing childhood asthma include allergies, eczema, family history of allergies, eczema and/or asthma, frequent respiratory infections, low birth weight, second-hand smoke before and/or after birth and growing up in a low-income, urban environment.[1,2,4,5] African-Americans and Puerto Ricans are at an increased risk for asthma than those of other racial and ethnic groups.[1,4,5] Additionally, boys have childhood asthma at a higher prevalence than girls, though this pattern switches after puberty.[28,29,30] It is important to continue to explore potential modifiable risk factors for childhood asthma due to its large, continued prevalence in children and its serious health and personal consequences.

Wheezing during childhood is a common ailment, characterized by a high-pitched whistling sound made while breathing, particularly exhaling, caused by narrowed airways or inflammation.[31] While wheezing is commonly associated with asthma, it is also a symptom of multiple other respiratory and immunologic conditions, such as respiratory

infections, allergies and cystic fibrosis.[31, 32,33] Wheezing is most often diagnosed within the first six years of life.[31] The Global Initiative for Asthma (GINA) has produced guidelines, proposing a number of tools, including frequency, gravity and duration of wheezing symptoms, to guide clinicians in determining whether a child's wheezing patterns are indicative of asthma.[31] One system for wheeze classification is the time-trend, or temporal, classification which categorizes wheezing into early transient (ending before 3 years), recurrent or persistent (starting before 3 years and persisting beyond 6 years) and late onset wheeze (starting after 3 years).[35] It is estimated that by age 6, 20-30% of children have recurrent or persistent wheezing and half experience at least one episode of wheezing of any kind.[31,33] Children with recurrent and persistent episodes of wheeze have been determined by the GINA guidelines to have a higher probability of having asthma, while early transient wheeze is more indicative of having early respiratory infections.[31,43] Properly identifying when wheezing symptoms represent asthma is imperative for clinicians since early identification of asthma may predict long-term outcomes and improved treatment responses.[31, 35]

Childhood wheezing, though a symptom of multiple respiratory and immunologic conditions, has been associated with negative health consequences in and of itself. Childhood wheezing has been shown to decrease adulthood lung function as compared to children with no wheezing in a recent meta-analysis.[34] Additionally, childhood atopic wheezing was found to be significantly associated with chronic obstructive pulmonary disease (COPD) prevalence in adults in the same meta-analysis.[34]

In addition to health consequences, wheezing of any phenotype can be severe and result in reduced quality of life stemming from frequent use of health care systems,

leading to increased economic costs.[31,36] Many of the health and social consequences associated with asthma, such as sleep disturbances, limited activities, and missed school are also applicable to childhood wheezing due to the frequent relationship between the two.

Established risk factors associated with childhood wheezing include exposure to environmental tobacco smoke, maternal smoking during pregnancy, breast feeding for less than or equal to six months, having siblings, attending a day care center, personal history of eczema or allergic rhinitis, having acid reflux, low socioeconomic status, crowding, and allergen exposure. [37, 32, 38] Males are also more likely to experience wheezing in childhood as compared to females.[37,38,41] It is important to continue to explore potential modifiable risk factors for childhood wheeze, particularly recurrent or persistent wheeze, due to its association with childhood asthma and to aid clinicians in properly identifying childhood asthma as early as possible to promote positive outcomes and treatment responses.

B. Physiology of Exposure-Outcome Relationship

It is generally accepted that childhood asthma and persistent wheezing have roots in in-utero and early life development, but the mechanisms behind this are not well understood. Since asthma is the inflammation and subsequent narrowing of the lungs' airways, the proposed biological mechanism between gestational weight gain and childhood asthma and the persistent wheeze phenotype largely focus on two inflammatory and immune mechanisms: 1) leptin (Figure 1) and 2) tumor necrosis factor α, (TNF- α) (Figure 2). These inflammation and immune responses occur during both

inadequate and excessive gestational weight gain, though studies have largely focused on excessive gestational weight gain due to the current obesity epidemic in the United States.[10, 20]

In terms of the first mechanism, leptin is a pro-inflammatory adipokine, a type of cell-signaling protein known as a cytokine, that is secreted from adipose tissue.[10,11] Abnormal cytokine production has been observed in obese individuals; high gestational weight gain creates an increased adiposity in the mother's body that may cause abnormal cytokine production to occur. [12,13, 14, 15,39] Excessive gestational weight gain, particularly in the second and third trimester, has been associated with higher levels of cord blood leptin. [16,17] It has been suggested that leptin has a pro-inflammatory effect on a child's airways as it increases airway responsiveness and exacerbates asthma and asthma symptoms, such as wheeze.[10,11,18]

In terms of the second mechanism, tumor necrosis factor α (TNF-α) is another cytokine that is involved with systemic inflammation.[19] It has been shown that excessive weight gain in pregnancy relates directly to an increased capacity of infant blood cells to produce TNF- α, which is associated with asthma by age 9.[19,20] In turn, TNF- α production very early in life (<3 months) is predictive of childhood asthma.[19]

Childhood asthma and wheeze prevalence has been observed to differ between boys and girls, with boys having a higher prevalence than girls.[28,29,30,40,41] This difference switches after puberty, where females then have a higher prevalence of asthma and wheeze through adulthood than males.[28,29,30,40] It is suggested that the overall mechanism behind these sex differences is caused by differential physiologic morphology, maturation, and hormonal changes that occur during puberty, but these mechanisms are

not well understood. More specifically, some potential causes of the sex differences in asthma and wheeze prevalence include pulmonary dysanapsis, testosterone, hormonal changes' influence on airway size, β2 adrenoceptor regulation, sex differences in the antioxidant response to oxidative stress, gender-influenced genetic polymorphisms and smooth muscle and vascular function, though it remains unclear which mechanism or mechanisms are the likely cause.[28,29,30, 40]

C. Epidemiology of Exposure-Outcome Relationship

Four epidemiologic studies have addressed the relationship between gestational weight gain and childhood asthma.[10, 19-21] All four were prospective cohort studies.

Two of these studies measured gestational weight gain exclusively through self-reported post-partum questionnaire data[20,21], one study used birth certificate weight,[19] and one study used medical record extraction.[10] Three of these studies measured childhood asthma using parent questionnaires, [10,19,21] whereas one used self-reported data from the child.[20] Three of the studies used physician-diagnosed asthma[19,20,21] and one used active symptoms of asthma or medicine prescribed in the past year[10] as the outcome of interest. Each of these studies included children of different ages within their study population: age 4,[19] ages 9-14,[20] age 7,[21] and ages 2-9.[10] None of the studies adjusted for all, but some combination of, factors that have an established association between gestational weight gain and asthma including: family history of allergy, eczema and/or asthma, smoking during pregnancy, low-income status, and race/ethnicity. Lastly, none of the studies have evaluated an association between trimester-specific gestational weight gain and offspring asthma.

Two studies found that low or inadequate total gestational weight gain was positively associated with development of childhood asthma as compared to normal or adequate gestational weight gain,[19] though one was merely suggestive,[20] whereas the other two studies found that high or excessive total gestational weight gain was positively associated with development of childhood asthma when compared to normal or adequate total gestational weight gain.[10,22]

In the most recent prospective cohort study to date, Polinski et al. followed 6,450 children, from birth in 2001 to age 4, in the United States.[19] The authors used birth certificate data to obtain total gestational weight gain information, and if missing was obtained via self-reported values on questionnaires.[19] The presence of childhood asthma was assessed at three time points: 9-month after birth, 2 years, and 4 years.[19] At each time point, a parent or guardian of the child was asked during an interview whether a doctor had ever told them that their child has asthma.[19] The authors found a 56% increased odds of having a child with asthma when the mother gained less than 5 kg, as compared to gaining 10-15 kg, after adjustment (aOR: 1.56; 95% CI: 1.04-2.35).[20] This study was limited in that it relied upon self-reported total gestational weight gain for 19% of mothers who had missing birth certificate data. In addition, childhood asthma diagnosis in children under 4 years of age is difficult to diagnose and therefore subject to misclassification. Lastly, the study did not adjusted for several well-known risk factors such as family history of allergy, eczema and/or asthma and low-income status.

Three epidemiologic studies have addressed the relationship between gestational weight gain and offspring wheezing.[21, 32,39] All three were prospective cohort studies.

One study measured gestational weight gain through self-reported post-partum questionnaire data,[21] one study used the difference between self-reported pre-pregnancy weight and weight in the third trimester from medical records,[39] and one study provided no information on how the gestational weight gain was measured.[32] All three of these studies measured offspring wheeze using parental questionnaires.[21, 32.39] Two of the studies used wheeze phenotypes, including early transient, persistent and late-onset, as the outcomes of interest[21,32] while one study used dichotomous wheeze as the outcome.[39] Each of the three epidemiologic studies included children of different ages in their studies: ages 1-4 years,[39] 18 months to 7 years,[21] and 6-7 years.[32] Two of the studies adjusted for a number of factors that have an established association between gestational weight gain and offspring wheeze including family history of allergy, eczema and/or asthma, smoking during pregnancy, low-income status, and race/ethnicity,[39,32] while one study did not include family history of eczema and asthma, low-income status nor race/ethnicity.[21] None of the studies evaluated an association between trimester-specific gestational weight gain and offspring wheeze.

The findings of one study was null,[32] whereas one study found an increased risk of persistent wheeze with 5-9 kg gestational weight gain, as compared to 10-15 kg gestational weight gain,[21] and one study found an increased risk of offspring wheeze at 1 year and at 4 years with increasing gestational weight gain.[39]

In the most recent prospective cohort study to date evaluating the relationship between gestational weight gain and offspring wheeze, Harpsoe et al. followed 38,874 mothers and children from 1996 to 2002, in Denmark as part of the Danish National Birth Cohort.[21] The authors used maternal self-reported gestational weight gain information at

6 months post-partum as the exposure of interest.[21] Parental reported wheezing was obtained via telephone interview at 18 months and via questionnaire at 7 years.[21] Wheezing was categorized into early transient (>1 episode of wheezing from birth to 18 months), persistent (both early and current wheezing), and late onset (current but not early wheezing).[21] The authors found an increased risk of offspring persistent wheeze among mothers who had a gestational weight gain of 5-9 kg in comparison to mothers who had a gestational weight gain of 10-15 kg, after adjustment (aOR = 1.24, 95% CI: 1.01-1.40). This study was limited for a number of reasons. First, there was a potential selection bias introduced since the study sample had a higher socioeconomic status than the source population, particularly concerning since low socioeconomic status is a risk factor for childhood wheezing. Second, the authors loosely used the temporal wheezing phenotypes based on GINA guidelines, but used wheeze assessment at 18 months as a proxy for the recommended 3 years. This would potentially cause misclassification of wheezing phenotypes since wheezing information between 18 months and 3 years would be lost and could change the classification of the wheeze phenotype present. Lastly, Harpsoe et al. lacked adjustment for some well-known risk factors for wheezing including family history of eczema and paternal allergy, low-income status and race/ethnicity.

Additionally, one study evaluated if sex of the child modified the association between gestational weight gain and offspring asthma.[20] This was a prospective cohort study which measured gestational weight gain via maternal self-report on questionnaires and asthma status via child self-report on questionnaires given between age 9 years to 14 years.[20] Sex of the child did not modify the association between gestational weight gain

and offspring asthma.[20] There have been no studies that have specifically evaluated if sex of the child modifies the association between gestational weight gain and offspring wheeze phenotypes, as wheezing is often considered as a symptom of asthma.

D. Summary of Significance and Innovation

In summary, the prior epidemiologic studies of gestational weight gain and offspring asthma and wheeze phenotypes have several limitations: 1) the majority relied upon self-reported gestational weight gain, [19,20,21] 2) offspring asthma was assessed among children of an unreliable age to be diagnosed with asthma in two of four studies, [10,19] 3) offspring wheezing was assessed among children of an age where they would be unable to determine distinct phenotypes in one of three studies,[39] 4) well known confounders were inconsistently adjusted for across studies,[10, 19,20,21,] and 5) no prior study has evaluated the potential association between trimester-specific gestational weight gain and offspring asthma nor wheeze phenotypes. These limitations may explain the conflicting results of prior epidemiologic studies. Therefore, we have prospectively studied the association between gestational weight gain, measured at multiple time points throughout pregnancy via medical visits, and offspring asthma and wheeze phenotypes among children age 7 years and 1 year to 9 years, respectively, using Project Viva cohort data. This study is significant because gestational weight gain is a potentially modifiable factor and if associated with childhood asthma and/or wheeze phenotypes, could direct new primary prevention efforts. This study is also significant because it evaluates whether the timing of gestational weight gain across trimesters is clinically relevant in the development of offspring asthma and/or wheeze, which could provide directed clinical recommendations

for prevention as well as insight into the etiology of asthma and/or wheeze phenotypes. This study is innovative because we have access to multiple, measured points of gestational weight gain via medical record abstraction, a 7 year follow-up period among children to more accurately diagnose asthma and a 9 year follow-up period among children to determine specific wheeze phenotypes, along with comprehensive information on potential covariates. Additionally, this study is innovative because it is the first to evaluate an association between trimester-specific gestational weight gain and offspring asthma and wheeze phenotypes.

CHAPTER II

SPECIFIC AIIMS AND HYPOTHESES

Specific Aim #1: *To evaluate the association of gestational weight gain and offspring risk of asthma.*

Hypothesis #1a: There will be a U-shaped association between total gestational weight gain and offspring asthma.

Hypothesis #1b: Excessive total gestational weight gain will be positively associated with offspring asthma, as compared to adequate total gestational weight gain.

Hypothesis #2a: Second and third trimester gestational weight gain will be positively associated with offspring asthma.

Hypothesis #2b: Excessive trimester-specific gestational weight gain will be associated with offspring asthma, as compared to adequate trimester-specific gestational weight gain.

Hypothesis #3: There will be a stronger positive association between gestational weight gain and offspring asthma among boys, as compared to girls.

Specific Aim #2: *To evaluate the association of gestational weight gain and offspring wheezing phenotypes.*

Hypothesis #4a: There will be a U-shaped association between total gestational weight gain and offspring persistent wheeze.

Hypothesis #4b: Excessive total gestational weight gain will be positively associated with offspring persistent wheeze, as compared to adequate total gestational weight gain.

Hypothesis #5a: Second and third trimester gestational weight gain will be positively associated with offspring persistent wheeze.

Hypothesis #5b: Excessive trimester-specific gestational weight gain will be associated with offspring persistent wheeze, as compared to adequate trimester-specific gestational weight gain.

Hypothesis #6: There will be a stronger positive association between gestational weight gain and offspring persistent wheeze among boys, as compared to girls.

CHAPTER III

STUDY DESIGN AND METHODS

A. Overall Strategy

We assessed the relationship between gestational weight gain and childhood asthma and wheeze phenotypes using data from Project Viva. Project Viva is a prospective cohort study based in Massachusetts, which enrolled mothers and now includes their singleton children.[22] A total of 2341 women were recruited at their first prenatal visit in eastern Massachusetts between 1999 and 2002 and enrolled in the study.[22] In-person visits were conducted with mothers during pregnancy in the late first (median 9.9 weeks of gestation) and second (median 27.9 weeks) trimesters.[22] Mothers and children were later seen in the hospital during the delivery admission and then during infancy (median age 6.3 months), early childhood (median 3.2 years) and mid-childhood (median 7.7 years), with in-person visits presently continuing through the children's teenage years.[22] Prenatal visits occurred during pregnancy, from which medical records were drawn, and annual questionnaires were mailed to mothers between in-person visits.[22] Out of the 2341 women enrolled, a total of 2128 women had a live birth and 1279 mother-child pairs provided information at the mid-childhood visit.[22]

B. Study Population

Eligible participants were pregnant women less than 22 weeks gestation.[22] Women were excluded if they: 1) had a multiple gestation, 2) were unable to answer questions in English, 3) had a gestational age ≥ 22 weeks at recruitment, or 4) had plans to move away prior to delivery.[22] For the purposes of this study, mothers who were

missing information on offspring asthma status were excluded for the analysis between gestational weight gain and offspring risk of asthma. As for the analysis between gestational weight gain and offspring risk of wheeze phenotypes, mothers who did not provide at least one offspring wheeze measurement from 1 year to 5 years, inclusively, and at least one measurement from 6 years to 9 years, inclusively, were excluded from the study.[41] Due to the use of multiple imputation, women who had missing information on exposures and/or covariates were able to be included in modeling and therefore were not excluded from the analyses.

C. Exposure Assessment

Gestational weight gain was gathered from self-reported prepregnancy weight data and weight measurements from prenatal visits, ending with the last prenatal visit prior to birth via medical record abstraction. Trimester-specific gestational weight gain was interpolated from medical record weight given during prenatal visits.

Total gestational weight gain was assessed both continuously and categorically. Categorical gestational weight gain was divided into three groups based on the Institute of Medicine (IOM) guidelines: inadequate, adequate and excessive weight gain.[23] These guidelines recommend varying levels of weight gain for each woman dependent on their prepregnancy BMI.[23] For women with a 'normal' prepregnancy BMI (18.5-24.9 kg/m^2), weight gain should fall within 11.5-16.0 kg.[23] For women with an underweight prepregnancy BMI (<18.5 kg/m^2), weight gain should fall within 12.5-18.0 kg.[23] For women with an overweight prepregnancy BMI (25.0-29.9 kg/m^2), weight gain should fall

within 7.0-11.5 kg.[23] For women with an obese prepregnancy BMI (≥ 30.0 kg/m^2), weight gain should fall within 5.0-9.0 kg.[23]

Trimester-specific gestational weight gain was also assessed both continuously and categorically, the latter based on IOM guidelines. The Institute of Medicine assumes a 0.5-2.0 kg weight gain in the first trimester and then varying levels of kilogram per week weight gain across the second and third trimesters, dependent on prepregnancy BMI.[23] For women with a 'normal' prepregnancy BMI (18.5-24.9 kg/m^2), mean weight gain per week should be 0.45 kg (range: 0.36-0.45 kg).[23] For women with an underweight prepregnancy BMI (<18.5 kg/m^2), mean weight gain per week should be 0.45 kg (range: 0.45-0.59 kg).[23] For women with an overweight prepregnancy BMI (25.0-29.9 kg/m^2), mean weight gain per week should be 0.27 kg (range: 0.23-0.32 kg).[23] For women with an obese prepregnancy BMI (≥ 30.0 kg/m^2), mean weight gain per week should be 0.23 kg (range: 0.18-0.27 kg).[23]

Self-reported prepregnancy weight has been validated in a previous Project Viva study against clinically measured weights among 170 study participants who had weight recorded in the medical record within 3 months prior to their last menstrual period.[24] The observed association between the self-reported and clinically measured weight was linear with correlation coefficients of 0.99 overall and mean underreporting of weight of approximately 1 kg or 2.2 pounds.[24] Findings did not differ by race/ethnicity, gestational age at study enrollment, or weight itself.[24]

D. Outcome Assessment

Presence of childhood asthma was assessed during the mid-childhood in-person visit, occurring at a median age of 7.7 years. During the in-person visit, mothers were asked: "Have you ever been told by a health care professional, such as a doctor, physician assistant or nurse practitioner, that your child has…asthma?" Mothers were additionally asked: "Have you ever been told by a health care professional, such as a doctor, physician assistant or nurse practitioner, that your child has…wheezing or reactive airways?" If the mother responded to either question affirmatively then she was then asked: "In the past 12 months, has your child taken any of the following medications?" which included a number of medications often used for asthma, wheezing and/or reactive airways. Current mid-childhood asthma was considered to be present when a mother had reported that her child had health care professional-diagnosed asthma and had experienced wheezing or reactive airways and/or had taken asthma medications within the past 12 months; otherwise the child was considered to not have current mid-childhood asthma. Therefore, mid-childhood current asthma was assessed as a dichotomous outcome.

Mother-report of health-care-professional-diagnosed childhood asthma has been validated in previous studies.[25,26] One validation study found a high level of sensitivity (88.5%) and specificity (95.7%) between parental report of doctor-diagnosed asthma in their child and the general practitioner's recorded diagnosis.[25] A second validation study found a high level of agreement between parental report of offspring early onset asthma (<10 years of age, Cohen's kappa 0.72) and medically-recorded diagnosis.[26]

Presence of childhood wheeze was assessed during annual questionnaires from 1 to 9 years inclusively. In each questionnaire, mothers were asked: "Since your child was

[age at last questionnaire], had he/she ever had wheezing (or whistling in the chest)?" Childhood wheeze was considered to be present when a mother had responded with a "Yes" to this question, otherwise the child was not considered to have wheeze at that time.

After wheezing status was determined, wheeze trajectories, or phenotypes, were derived using latent class mixed modeling as performed by Tse et al.[41] Only those children who had at least one wheeze measurement between 1 year and 5 years and 6 years and 9 years, inclusively, were included in this modeling.[41] Tse et al. specified 3 latent classes, which provided the best fit.[41] Three distinct wheeze phenotypes were identified and did not differ by sex of the child: never or infrequent wheeze, early transient wheeze and persistent wheeze, labeled as such based on the observed temporal pattern and patterns reported in the prior literature.[41]

Parental report of current wheezing during early childhood has been validated in two studies.[45, 46] Both studies found a high level of sensitivity (86%,[45] 82.8%[46]) and specificity (91.8%,[45] 85%[46]) between parental report of their infants' current wheezing status and physician report.[45, 46] Both validation studies assessed only short-term parental report of wheezing and included only infants.

E. Covariate Assessment

We identified established risk factors for childhood asthma based on prior literature.[10,19,20,21] Mother's age at enrollment, mother's prepregnancy BMI, nulliparity, maternal asthma, allergy and eczema, maternal smoking during pregnancy, household income, maternal and paternal college graduate, maternal race/ethnicity, distance to the

nearest major roadway, and age in days at the mid-childhood visit were considered *a priori* confounders of the relationship between gestational weight gain and offspring asthma and wheeze phenotypes, respectively. Additionally, paternal asthma, allergy and eczema and maternal secondhand smoke exposure during pregnancy were considered risk factors for offspring asthma and wheeze phenotypes, respectively. Sex of the child was assessed as a potential effect modifier; if it did not modify the relationship between gestational weight gain and offspring asthma nor wheeze phenotypes then it would be included as an *a priori* confounder. All variables were obtained from questionnaires and in-person visits except gestational weight gain measurements during pregnancy, which were obtained through medical record abstraction, and distance to the nearest roadway, which was calculated using distance to the nearest A1 or A2 road (U.S. Census Features Class) from the home address at the time of study enrollment, as performed by Rice et al.[42]

CHAPTER IV

DATA ANALYSIS

Specific Aim #1: *To evaluate the association of gestational weight gain and offspring risk of asthma.*

Specific Aim #2: *To evaluate the association of gestational weight gain and offspring wheezing phenotypes.*

A. Univariate Analysis

The study population size after accounting for exclusion criteria, as numbers and percents, is presented in Table 1. We also present the mean and standard deviation of continuous gestational weight gain, as well as the percent distribution of categorical gestational weight gain in Table 2. The percent distribution of observed offspring asthma and wheeze phenotypes is presented in Table 3.

B. Bivariate Analyses

Covariate distributions were assessed against total and trimester-specific gestational weight gain, both continuously and categorically (Table 4) and against asthma status and wheeze phenotypes (Table 5). Continuous variables were assessed using t-tests and Pearson's correlation coefficients. Categorical variables were assessed using chi-square tests and analysis of variance (ANOVA). P-values from these tests are reported.

Additionally, the association between total and trimester-specific gestational weight gain, both continuously and categorically, and current mid-childhood asthma were modeled using unconditional logistic regression, presented in Table 6. Odds ratios and

95% confidence intervals are reported. The association between total and trimester-specific gestational weight gain, both continuously and categorically, and wheeze phenotypes were modeled using unconditional multinomial logistic regression, presented in Table 7. Adequate gestational weight gain, no current mid-childhood asthma, and never or infrequent wheeze served as reference.

We explored potential non-linear relationships of continuous total gestational weight gain and offspring current mid-childhood asthma using generalized additive models (GAMs) with penalized smoothing regression splines (Figure 3), and visually inspected plots of the smoothed data.

C. Multivariate Analyses

Multivariable logistic regression was used to evaluate the association between gestational weight gain and offspring current mid-childhood asthma. Multinomial logistic regression was used to evaluate the association between gestational weight gain and offspring wheeze phenotypes. For both procedures two adjusted models were produced and are presented in Tables 6 and 7, respectively. In the first adjusted model, all *a priori* confounders were included due to their established association with both gestational weight gain and offspring asthma and wheeze phenotypes in the prior literature. In the second adjusted model, all *a priori* risk factors were included, in addition to the *a priori* confounders, due to their established association with offspring asthma and wheeze in the prior literature.

Due to how common current mid-childhood asthma and wheezing are in the general population, we determined that the resulting odds ratios would not be a

reasonable approximation of the risk ratio: the statistic to be expected from a cohort study, such as this. Therefore, we calculated risk differences for current mid-childhood asthma (Table 6) and wheeze phenotypes (Table 7), respectively, using predicted probabilities.

To assess whether sex of the child modified the relationship between gestational weight gain and offspring current mid-childhood asthma, inclusion of an interaction term into a multivariable logistic regression was used. The same procedure was performed in order to assess whether sex of the child modified the relationship between gestational weight gain and offspring wheeze, but through inclusion of an interaction term into a multivariable multinomial regression.

To prevent potential bias associated with missing data, we imputed missing data on exposures and covariates using multiple imputation by chained equations. We specified an adequate number of iterations (n=50) according to the proportion of missing information.[46] Mean estimates and variances were computed from the 50 imputed data sets using Rubin's rule.[47]

Additionally, we performed a sensitivity analysis to ascertain if the length of gestational age affected the estimates in comparison to the study population including all gestational ages. We limited the analyses to include only those who had experienced a full-term pregnancy, defined as having delivered the baby at 37 weeks gestation or later, and compared these estimates to those among the full study cohort.

CHAPTER V

RESULTS

Of the 2128 live births in the Project Viva cohort, we excluded 896 mother-child pairs that did not have information on their asthma status at mid-childhood and 833 mother-child pairs that did not have an available wheeze trajectory (Table 1). This yielded an analytic cohort of 1232 mother-child pairs for the current mid-childhood asthma assessment and 1295 mother-child pairs for the wheeze phenotypes assessment. Women and their partners were predominately white, college educated and had a household income greater than $70,000 per year.

Women had a mean total gestational weight gain of 15.54 kg (SD: 5.69); 13% had inadequate total gestational weight gain, 31% had adequate total gestational weight gain and 56% had excessive total gestational weight gain (Table 2). Women in their first trimester had a mean weight gain of 2.94 kg (SD: 2.87), in their second trimester had a mean weight gain of 6.31 kg (SD: 2.49) and in their third trimester had a mean weight gain of 6.31 kg (SD: 3.02) (Table 2). Women across all trimesters were most likely to have had excessive gestational weight gain, though the proportion of women having excessive weight gain decreases across the trimesters from 63% in the first trimester to 57% in the third trimester (Table 2). Current mid-childhood asthma was present in 17.8% of children whereas 74% of children were classified as having never wheezed or had infrequent wheeze, 13% had early transient wheeze and 13% had persistent wheeze (Table 3).

Women who had excessive total gestational weight gain had a higher pre-pregnancy BMI than inadequate and adequate total gestational weight gain, with women who had adequate weight gain having the lowest pre-pregnancy BMI (Table 4). Additionally, women with excessive total gestational weight gain were more likely to be nulliparous, be a smoker during pregnancy, have a higher income, be of other or white race/ethnicity, and have a boy, than women who had inadequate or adequate total gestational weight gain. Women who had excessive gestational weight gain during the first trimester were older, had a lower pre-pregnancy BMI, be a smoker during pregnancy, have a higher income, be a college graduate, and be of white race/ethnicity, than women who had inadequate or adequate first trimester gestational weight gain (Table 4). Women who had excessive second trimester gestational weight gain were more likely to be nulliparous, not have a history of asthma, be a smoker during pregnancy, have a higher income, be a college graduate, be of Hispanic, other or white race/ethnicity, and lived closer to a major roadway, than women who had inadequate or adequate second trimester gestational weight gain (Table 4). Women who had excessive third trimester gestational weight gain were younger, had a higher prepregnancy BMI, were nulliparous, be of other race/ethnicity, and have a boy than women who had inadequate or adequate gestational weight gain (Table 4).

Children with current mid-childhood asthma were more likely to be male and to have younger mothers, mothers with higher pre-pregnancy BMI, maternal and paternal history of asthma, paternal history of allergy, a mother who smoked during the pregnancy, a household income less than $70,000, mothers and fathers who did not graduate college, mothers and fathers of African American or Hispanic race/ethnicity,

than children without current mid-childhood asthma (Table 5). Other covariates did not differ significantly among participants who did and did not have current mid-childhood asthma. Children with persistent wheeze were more likely to be male and to have younger mothers, mothers with a higher pre-pregnancy BMI, have siblings, maternal and paternal history of asthma, allergy and eczema, a household income less than $70,000, mothers and fathers who did not graduate college, mothers and fathers of African American or Hispanic race/ethnicity, and living closer to a major roadway than children with never/infrequent or early transient wheeze (Table 5). Other covariates did not differ significantly among participants who did and did not have persistent wheeze.

After visual inspection of the generalized additive models, we determined there was a departure from linearity of total gestational weight gain and offspring current mid-childhood asthma (Figure 3). There was no such observation among any of the three trimester-specific gestational weight gain and offspring current mid-childhood asthma (results not shown).

We evaluated associations between total and trimester-specific gestational weight gain and offspring current mid-childhood asthma via logistic regression, but findings were not statistically significant after adjustment (Table 6). In the unadjusted analyses we observed an increased odds of offspring current mid-childhood asthma among children whose mothers had inadequate second trimester gestational weight gain (OR=2.06; 95% CI: 1.30-2.23), as compared to adequate second trimester gestational weight gain, though this was attenuated after adjustment (Table 6).

We evaluated associations between total and trimester-specific gestational weight gain and offspring wheeze phenotypes via logistic regression (Table 7). We found a 36%

decreased odds of offspring current mid-childhood asthma among children whose mother had excessive third trimester gestational weight gain, as compared to adequate third trimester gestational weight gain (aOR: 0.64; 95% CI: 0.42-0.98) (Table 7).

Additionally, we evaluated associations between total and trimester-specific gestational weight gain and offspring current mid-childhood asthma via conditional predicted probabilities (Table 8). We found an approximately 5% increased probability of having a child with current mid-childhood asthma among mothers who had inadequate total and inadequate second trimester gestational weight gain, respectively, as compared to adequate total and adequate second trimester gestational weight gain (Table 8). We also found an approximately 3% increased probability of having a child with current mid-childhood asthma among mothers who had inadequate third trimester gestational weight gain, as compared to mothers who had adequate third trimester gestational weight gain (Table 8).

Lastly, we evaluated associations between total and trimester-specific gestational weight gain and offspring wheeze phenotypes via conditional predicted probabilities (Table 9). We found an approximately 5-6% decreased probability of having a child with early transient wheeze among mothers who had inadequate or excessive third trimester gestational weight gain, as compared to mothers who had adequate third trimester gestational weight gain (Table 9). We also found an approximately 2-4% decreased probability of having a child with early transient wheeze among mothers who had inadequate or excessive first trimester gestational weight gain, as compared to mothers who had adequate first trimester gestational weight gain (Table 9). Additionally, we found a 2.5% increased probability of having a child with persistent wheeze among

mothers who had inadequate total gestational weight gain, as compared to mothers who had adequate total gestational weight gain (Table 9).

We found that there is no effect modification by sex of the child in the association between gestational weight gain and offspring current mid-childhood asthma nor offspring wheeze phenotypes (results not shown). Lastly, after removing preterm gestational age from the overall sample in a separate analysis, findings were similar (results not shown).

CHAPTER VI

DISCUSSION

In this prospective cohort study, we found a non-linear association between total gestational weight gain and offspring current mid-childhood asthma. We found increased probabilities of offspring current mid-childhood asthma among mothers with inadequate second trimester, third trimester and total gestational weight gain, as compared to adequate gestational weight gain during those times. We also found a 36% decreased odds of early transient wheeze among children whose mothers had excessive gestational weight gain during the third trimester (aOR: 0.64; 95% CI: 0.42-0.98), as compared to adequate third trimester gestational weight gain. Additionally, we found a suggestive decreased odds of early transient wheeze among children whose mothers had inadequate third trimester gestational weight gain (aOR: 0.60; 95% CI: 0.36-1.02), as compared to adequate third trimester gestational weight gain. Lastly, we found decreased probabilities of offspring early transient wheeze among mothers with inadequate and excessive gestational weight gain during the first and third trimesters, as compared to adequate gestational weight gain during those times.

Our findings for the associations between gestational weight gain and offspring current mid-childhood asthma are consistent with some prior literature while being inconsistent with others. Polinski et al. found a 56% increased odds of having a child with asthma when women gained less than 5 kg, as compared to women who gained 10-15 kg (aOR: 1.56; 95% CI: 1.04-2.35). Dumas et al. found a 28% increased odds of childhood asthma when women had low gestational weight gain as compared to normal

gestational weight gain (aOR: 1.28; 95% CI: 0.98-1.66). Additionally, Harpsoe et al. found a 97% increased odds of current severe childhood asthma at 7 years among mothers who had a greater than or equal to 25 kg total gestational weight gain as compared to mothers who had a 10-15 kg total gestational weight gain. Our findings suggest that there are increased probabilities of offspring current mid-childhood asthma among children whose mothers had inadequate gestational weight gain during the second trimester, third trimester and overall.

Our finding of a non-linear association between total gestational weight gain and offspring current mid-childhood asthma is consistent with Harpsoe et al. Harpsoe et al. found U-shaped associations between total gestational weight gain and offspring ever having asthma and offspring having previous asthma. Our findings suggest a U-shaped association between total gestational weight gain and offspring current mid-childhood asthma.

Our findings for the associations between gestational weight gain and offspring wheeze phenotypes are inconsistent with prior literature. Leermakers et al. found a 9% increased odds of wheezing from 1 to 4 years with continuous gestational weight gain, per standard deviation increase in weight gain (aOR: 1.09; 95% CI: 1.04-1.14). Harpsoe et al. found a 24% increased odds of persistent wheeze among children whose mothers had 5-9 kg gestational weight gain, as compared to mother with 10-15 kg gestational weight gain (aOR: 1.24; 95% CI: 1.01-1.40). Rusconi et al. found no association between wheeze phenotypes and inadequate or excessive total gestational weight gain, as compared to adequate total gestational weight gain. We found a 36% decreased odds of early transient wheeze among children whose mothers had excessive third trimester

gestational weight gain (aOR: 0.64; 95% CI: 0.42-0.98) and, suggestively, inadequate third trimester gestational weight gain (aOR: 0.60; 95% CI: 0.36-1.02), as compared to adequate third trimester gestational weight gain. We also found decreased probabilities of early transient wheeze among children whose mothers had inadequate or excessive first or third trimester gestational weight gain, as compared to adequate first or third trimester gestational weight gain.

Differences in study findings may be due to smaller sample size in our study and failure of prior studies to have complete adjustment for potential confounders. Previous studies have oftentimes not adjusted for a number of important risk factors including, but not limited to: parental history of asthma, allergy and/or eczema, maternal smoking during pregnancy, low-income status and maternal race/ethnicity. Our study adjusted for all of these important risk factors and a multitude of others. Additionally, study populations vary widely between studies with much of the prior literature having been conducted outside of the United States.

This study has several strengths. First, this was the first study to evaluate the relationship between gestational weight gain and offspring wheeze phenotypes, an informative symptomatic pattern used to clinically diagnose childhood asthma. Second, we measured gestational weight gain using medical records, offspring asthma at approximately 7 years and offspring wheeze phenotypes until 9 years. These measurements increase validity of both the exposure and outcome assessments since medically recorded weight gain is the gold standard and both asthma and wheezing should be measured through childhood in order to obtain the most accurate diagnoses and

identification. Lastly, we adjusted for all *a priori* confounders and risk factors based on prior literature and direct acyclic graphs (DAGs).

Total gestational weight gain was calculated by taking the difference between self-reported prepregnancy weight and medical record weight at the last prenatal visit before delivery. There is the possibility that self-reported prepregnancy weight was incorrectly reported. This would cause either an overestimation or underestimation of total gestational weight gain depending on whether women overstated or understated their prepregnancy weight, due to conscious misreport or rounding. If women misreported their prepregnancy weight this would lead to an underestimate of the true odds ratio (OR), though self-reported prepregnancy weight has been validated against clinically measured weights in a previous Project Viva study.[24] It seems likely that there is some misclassification of total gestational weight gain due to misreporting of prepregnancy weight, but we expect that the impact of this misreporting is minimal since it has been adequately validated in this study population and was further minimized when evaluating gestational weight gain categorically based on the IOM guidelines.

Offspring current mid-childhood asthma status was determined via maternal report at the Mid-Childhood Visit, which occurred at a mean child age of 7.7 years. Due to the nature of parental reporting and the accuracy of asthma diagnoses, it is possible that there is misclassification of offspring asthma. This means that some mothers will report that a doctor had told them their child has asthma when in actuality they do not, and vice versa. However, validation studies on parental reporting of childhood asthma have found a high level of agreement between parental, particularly maternal, report of doctor-diagnosed asthma in their child and the general practitioner's recorded

diagnosis.[25,26] Additionally, we held current mid-childhood asthma to a stringent criterion in order to minimize the possibility of misdiagnosis by physician. Mothers needed to report that their child had doctor-diagnosed asthma plus had wheezing symptoms in the past 12 months and/or were taking asthma medications within the past 12 months. Based on this stringent criterion, it seems less likely that misclassification of current mid-childhood asthma would occur. If mothers misreported their child's asthma status or the child had a misdiagnosis of asthma and met the other criterion, then this would lead to an underestimation of the true OR. It seems possible that there is misclassification of offspring asthma status but we expect that the impact is modest and will be minimized by the combination of validated maternal report of doctor-diagnosed offspring asthma and strict current mid-childhood asthma criterion.

Offspring wheezing was determined via maternal report on yearly questionnaires between ages 1 year and 9 years inclusively and then offspring wheeze phenotypes were derived using latent class mixed models. There is the possibility of non-differential misclassification of wheeze phenotypes due to the nature of parental reporting of symptoms and the latent class mixed models categorization procedure. This means that some mothers may have reported their child as having not wheezed in the past year when in actuality they had, or vice versa. However, validation studies on parental report of current wheeze symptoms have found a high agreement between parental report and doctor-recognized wheeze symptoms. If mothers misreported their child's wheezing symptoms then this would lead to an underestimation of the true OR. It seems possible that there is misclassification of offspring wheeze status, which was later used to derive wheeze trajectories, but we expect the impact of this to be minimal since wheeze status

was later categorized into latent classes of wheeze trajectories and multiple wheeze statuses were used in these derivations, therefore misclassification would be minimized. Additionally, by utilizing latent classes in order to categorize wheeze phenotypes there is the potential for the latent class procedure to have misclassified observations into inaccurate wheeze phenotypes. This would have lead to an underestimation of the true OR. It is likely that some misclassification of wheeze phenotypes occurred during the latent class mixed models procedure.

A limitation of the study was the large loss to follow-up. At the Mid-Childhood in-person visit, 58% (N=1232) of women from the original study sample (N=2128) provided information about asthma status in their child. With regard to the wheeze trajectories, 61% (N=1295) of women from the original study sample had provided sufficient information about their child's wheezing status across 1 to 5 years and 6 to 9 years.

Selection bias in this study may have occurred through differential loss to follow-up. For example, mothers who had either inadequate or excessive gestational weight gain and a child who was diagnosed with asthma may drop out of the study at a higher rate than other mother-child pairs. This specific situation could be caused by either overall poor health of the mother and/or child or low socioeconomic status, which could limit the access to resources or transportation needed to continue participation in the study, particularly attending the Mid-Childhood Visit where asthma assessment took place. If these mother-child pairs were lost from the study, this would bias the OR towards the null. This scenario seems likely given the large loss to follow-up in the study, particularly during the in-person visits.

In order to limit the affect of loss to follow-up, we utilized multiple imputation. Through this method we were able to include mother-child pairs in the analyses who originally had missing information on exposures and/or covariates. These mother-child pairs with missing information on these factors would have otherwise been excluded from the analyses, if not for the use of multiple imputation. This increased our sample size, in comparison to a complete case analysis, and therefore increased the power of this study, maximizing all participant information considering our relatively small sample size.

In this prospective cohort study, information on offspring asthma was not collected differentially for those with different gestational weight gain. Therefore, there should be no information bias because asthma questions within the questionnaires and in-person visits were a small subset of all questions asked. In addition, it would be highly unlikely that women would misreport their child's asthma status differentially based on their gestational weight gain years prior.

Data on possible confounders and risk factors were gathered using numerous questionnaires, in-person visits and medical records. Additionally, our study had adequate power to include all *a priori* confounders and risk factors in our models. However, it is possible that a confounder not suggested by the literature may be missed or that the collection of data for the confounder left residual confounding. For example, if maternal dietary patterns were positively associated with gestational weight gain and positively associated with offspring asthma and was not controlled for in statistical models, the reported OR would be an overestimation of the true effect of gestational weight gain on offspring asthma. The impact of unmeasured confounders such as dietary

factors could be moderate, but thorough evaluation of prior literature for potential confounders and risk factors has been done and therefore it is unlikely there are major confounders or risk factors missing from our analyses.

We also accounted for the potential for residual confounding in our study by attempting to include multiple confounders and risk factors as proxies for a broader, or difficult to measure, confounder or risk factor. For example, low socioeconomic status has been associated with both gestational weight gain and offspring asthma and wheezing but this is difficult to measure. Therefore, we used a combination of parental college graduate status, household income, maternal race/ethnicity and others as measures of socioeconomic status. The impact of residual confounding could still be moderate, but thorough inclusion of multiple confounders and risk factors in our analyses should limit these effects.

The Project Viva cohort may have limited generalizability to other US populations. The cohort is largely white and college educated, with a most having a yearly household income over the national average in the years that information was collected.[48] Additionally, participants resided exclusively in the greater Boston area and had health insurance.[22]

Additionally, here are differences in the etiology of childhood asthma and persistent wheezing in comparison to adult or late-onset asthma and wheezing, therefore these results are not generalizable to adults who develop asthma or wheezing.[27] However, these results should be generalizable to other, diverse populations of mother-child pairs since the inflammatory and immune responses of leptin and tumor necrosis factor-α occur consistently across populations and therefore affect youth in the same way.

Table 1. Number and Percent in Study Sample; Project Viva

Original Study Sample (Number of Live Births)	2128
Asthma Status at Mid-Childhood	1232 (58%)
Wheeze Trajectories Available	1295 (61%)

Table 2. Distribution of Total and Trimester-Specific Gestational Weight Gain among Participants with Current Mid-Childhood Asthma and with Wheeze Phenotypes; Project Viva

		Current Mid-Childhood Asthma		
		N(%)	M (SD)	Range
Total Gestational Weight Gain (kg)			15.41 (5.37)	(-7.27 - 33.18)
Total Gestational Weight Gain				
	Inadequate	156 (12.68%)		
	Adequate	395 (32.03%)		
	Excessive	681 (55.29%)		
Trimester-Specific Gestational Weight Gain (kg)				
	1st Trimester		2.81 (2.76)	(-8.98 - 17.96)
	2nd Trimester		6.32 (2.39)	(-10.55 - 14.48)
	3rd Trimester		6.28 (2.90)	(-10.03 - 17.55)
Trimester-Specific Gestational Weight Gain				
	1st Trimester - Inadequate	189 (15.39%)		
	1st Trimester - Adequate	269 (21.81%)		
	1st Trimester - Excessive	774 (62.80%)		
	2nd Trimester - Inadequate	146 (11.86%)		
	2nd Trimester - Adequate	343 (27.80%)		
	2nd Trimester - Excessive	743 (60.34%)		
	3rd Trimester - Inadequate	251 (20.40%)		
	3rd Trimester - Adequate	273 (22.17%)		
	3rd Trimester - Excessive	708 (57.43%)		

Table 2 (continued). Distribution of Total and Trimester-Specific Gestational Weight Gain among Participants with Current Mid-Childhood Asthma and with Wheeze Phenotypes; Project Viva

		Wheeze Phenotypes		
		N(%)	M (SD)	Range
Total Gestational Weight Gain (kg)			15.45 (5.32)	(-7.27 - 33.18)
Total Gestational Weight Gain				
	Inadequate	165 (12.75%)		
	Adequate	411 (31.76%)		
	Excessive	719 (55.49%)		
Trimester-Specific Gestational Weight Gain (kg)				
	1st Trimester		2.79 (2.67)	(-8.98 - 17.96)
	2nd Trimester		6.38 (2.39)	(-10.55 - 15.66)
	3rd Trimester		6.29 (2.90)	(-10.03 - 17.29)
Trimester-Specific Gestational Weight Gain				
	1st Trimester - Inadequate	204 (15.71%)		
	1st Trimester - Adequate	278 (21.49%)		
	1st Trimester - Excessive	813 (62.80%)		
	2nd Trimester - Inadequate	152 (11.71%)		
	2nd Trimester - Adequate	345 (26.68%)		
	2nd Trimester - Excessive	798 (61.61%)		
	3rd Trimester - Inadequate	266 (20.55%)		
	3rd Trimester - Adequate	286 (22.12%)		
	3rd Trimester - Excessive	743 (57.33%)		

Table 3. Distribution of Current Asthma at Mid-Childhood and Wheeze Phenotypes; Project Viva

	N	Percent
Current Mid-Childhood Asthma (N=1232)		
No current childhood asthma	1013	82.22%
Yes, current childhood asthma	219	17.78%
Wheeze Phenotypes (N=1295)		
Never/infrequent wheeze	960	74.13%
Early transient wheeze	165	12.74%
Persistent wheeze	170	13.13%

Table 4. Distribution of Covariates According to Total and Trimester-Specific Gestational Weight Gain; Project Viva

	Continuous Total	p-value	Total Inadequate N = 156	Total Adequate N = 395	Total Excessive N = 681	p-value
Mother's Age at Enrollment; Mean (SD)	-0.05	0.17	31.90 (5.74)	32.52 (5.37)	32.04 (5.04)	0.27
Mother's Pre-Pregnancy BMI; Mean (SD)	**-0.26**	**<0.0001**	**24.37 (6.17)**	**23.34 (4.71)**	**25.61 (5.11)**	**<0.0001**
Nulliparous; N(%)						
No (N=1111)	**14.70 (5.26)**		**168 (15.12%)**	**343 (30.87%)**	**600 (54.01%)**	
Yes (N=1017)	**16.18 (5.38)**	**<0.0001**	**115 (11.31%)**	**306 (30.09%)**	**596 (58.60%)**	**0.02**
Maternal History of Asthma; N(%)						
No (N=1842)	**15.54 (5.27)**		245 (13.30%)	557 (30.24%)	1040 (56.46%)	
Yes (N=286)	**14.49 (5.96)**	**0.03**	38 (13.29%)	92 (32.17%)	156 (54.55%)	0.74
Paternal History of Asthma; N(%)						
No (N=1884)	**15.53 (5.25)**		241 (12.79%)	578 (30.68%)	1065 (56.53%)	
Yes (N=244)	**14.54 (6.13)**	**0.04**	42 (17.21%)	71 (29.10%)	131 (53.69%)	0.18
Maternal History of Allergy; N(%)						
No (N = 1524)	15.57 (5.42)		194 (12.73%)	464 (30.45%)	866 (56.82%)	
Yes (N=604)	15.02 (5.23)	0.10	89 (14.74%)	185 (30.63%)	330 (54.64%)	0.37
Paternal History of Allergy; N(%)						
No (N = 1582)	15.48 (5.36)		212 (13.40%)	484 (30.59%)	886 (56.01%)	
Yes (N=546)	15.22 (5.40)	0.47	71 (13.00%)	165 (30.22%)	310 (56.78%)	0.84
Maternal History of Eczema; N(%)						
No (N = 1855)	15.40 (5.32)		245 (13.21%)	567 (30.57%)	1043 (56.23%)	
Yes (N=273)	15.47 (5.67)	0.87	38 (13.92%)	82 (30.04%)	153 (56.04%)	0.88
Paternal History of Eczema; N(%)						
No (N = 2006)	**15.50 (5.32)**		263 (13.11%)	613 (30.56%)	1130 (56.33%)	
Yes (N = 122)	**14.00 (5.84)**	**0.02**	20 (16.39%)	36 (29.51%)	66 (54.10%)	0.53
Maternal Smoker Status during Pregnancy; N(%)						
Never (N = 1457)	15.26 (5.26)		**208 (14.28%)**	**476 (32.67%)**	**773 (53.05%)**	
Former (N = 401)	15.64 (5.21)		**49 (12.22%)**	**111 (27.68%)**	**241 (60.10%)**	
Smoker (N = 270)	16.09 (6.38)	0.22	**26 (9.63%)**	**62 (22.96%)**	**182 (67.41%)**	**0.0009**
Maternal Secondhand Smoke Exposure; N(%)						
1 hr/wk (N = 1761)	15.46 (5.27)		239 (13.57%)	538 (30.55%)	984 (55.88%)	
2 hr/wk (N = 264)	15.34 (5.75)		35 (13.26%)	80 (30.30%)	149 (56.44%)	
3 hr/wk (N = 51)	14.79 (6.06)		4 (7.84%)	14 (27.45%)	33 (64.71%)	
4 hr/wk (N = 13)	15.52 (6.24)		0 (0.00%)	3 (23.08%)	10 (76.92%)	
5 hr/wk (N = 28)	14.29 (5.93)	0.75	4 (14.29%)	11 (39.29%)	13 (46.43%)	0.46
Household Income; N(%)						
<= $70,000 (N = 893)	15.09 (5.88)		139 (15.57%)	253 (28.33%)	501 (56.10%)	
>$70,000 (N = 1235)	15.62 (5.00)	0.10	144 (11.66%)	396 (32.06%)	695 (56.28%)	0.09
Maternal College Graduate Status; N(%)						
No (N = 754)	14.97 (6.24)		115 (15.25%)	210 (27.85%)	429 (56.90%)	
Yes (N = 1374)	15.61 (4.92)	0.06	168 (12.23%)	439 (31.95%)	767 (55.82%)	0.23
Paternal College Graduate Status; N(%)						
No (N = 825)	15.18 (6.16)		120 (14.55%)	213 (25.82%)	492 (59.64%)	
Yes (N = 1303)	15.54 (4.88)	0.28	163 (12.51%)	436 (33.46%)	704 (54.03%)	0.09
Maternal Race/Ethnicity; N(%)						
Asian (N = 122)	**14.63 (4.15)**		**21 (17.21%)**	**51 (41.80%)**	**50 (40.98%)**	
Black (N = 354)	**14.35 (5.92)**		**57 (16.10%)**	**110 (31.07%)**	**187 (52.82%)**	
Hispanic (N = 157)	**14.80 (6.21)**		**26 (16.56%)**	**51 (32.48%)**	**80 (50.96%)**	
Other (N = 84)	**16.17 (6.36)**		**11 (13.10%)**	**18 (21.43%)**	**55 (65.48%)**	
White (N = 1411)	**15.71 (5.13)**	**0.0097**	**168 (11.91%)**	**419 (29.70%)**	**824 (58.40%)**	**0.002**
Distance to Major Roadway at Enrollment; Mean (SD)	0.03	0.15	6.69 (1.28)	6.71 (1.37)	6.84 (1.34)	0.21
Sex of the Child; N(%)						
Male (N = 1096)	**15.91 (5.30)**		**128 (11.68%)**	**329 (30.02%)**	**639 (58.30%)**	
Female (N = 1032)	**14.92 (5.39)**	**0.0013**	**155 (15.02%)**	**320 (31.01%)**	**557 (53.97%)**	**0.03**
Age of Child at Mid-Childhood Visit (Days); Mean (SD)	-0.02	0.67	2934.16 (321.42)	2885.67 (292.82)	2885.85 (282.92)	0.16

Table 4 (continued). Distribution of Covariates According to Total and Trimester-Specific Gestational Weight Gain; Project Viva

	1st Trimester Continuous	p-value	2nd Trimester Continuous	p-value	3rd Trimester Continuous	p-value
Mother's Age at Enrollment; Mean (SD)	**0.07**	**0.01**	-0.02	0.77	**-0.15**	**<0.0001**
Mother's Pre-Pregnancy BMI; Mean (SD)	-0.6	0.26	**-0.37**	**<0.0001**	**-0.13**	**<0.0001**
Nulliparous; N(%)						
No (N=1111)	2.80 (2.84)		**6.09 (2.35)**		**5.81 (2.84)**	
Yes (N=1017)	2.83 (2.67)	0.86	**6.56 (2.40)**	**0.0006**	**6.79 (2.87)**	**<0.0001**
Maternal History of Asthma; N(%)						
No (N=1842)	2.80 (2.69)		**6.41 (2.33)**		6.33 (2.85)	
Yes (N=286)	2.92 (3.26)	0.60	**5.67 (2.64)**	**0.0003**	5.91 (3.20)	0.10
Paternal History of Asthma; N(%)						
No (N=1884)	2.86 (2.67)		6.36 (2.35)		6.32 (2.90)	
Yes (N=244)	2.49 (3.35)	0.14	6.04 (2.61)	0.15	6.00 (2.87)	0.23
Maternal History of Allergy; N(%)						
No (N = 1524)	2.83 (2.87)		6.39 (2.36)		6.35 (2.92)	
Yes (N=604)	2.77 (2.49)	0.72	6.15 (2.44)	0.11	6.10 (2.82)	0.17
Paternal History of Allergy; N(%)						
No (N = 1582)	2.94 (2.71)		6.30 (2.47)		6.24 (2.96)	
Yes (N=546)	2.45 (2.88)	0.0083	6.36 (2.14)	0.70	6.41 (2.70)	0.38
Maternal History of Eczema; N(%)						
No (N = 1855)	2.83 (2.77)		6.31 (2.39)		6.27 (2.88)	
Yes (N=273)	2.71 (2.72)	0.64	6.41 (2.36)	0.62	6.35 (3.02)	0.75
Paternal History of Eczema; N(%)						
No (N = 2006)	2.83 (2.76)		6.34 (2.34)		**6.34 (2.86)**	
Yes (N = 122)	2.57 (2.88)	0.46	5.99 (3.00)	0.24	**5.44 (3.31)**	**0.01**
Maternal Smoker Status during Pregnancy; N(%)						
Never (N = 1457)	2.75 (2.78)		6.30 (2.31)		6.21 (2.74)	
Former (N = 401)	2.77 (2.45)		6.46 (2.37)		6.40 (3.19)	
Smoker (N = 270)	3.35 (3.14)	0.09	6.15 (2.92)	0.48	6.59 (3.35)	0.3
Maternal Secondhand Smoke Exposure; N(%)						
1 hr/wk (N = 1761)	2.78 (2.69)		6.38 (2.32)		6.30 (2.83)	
2 hr/wk (N = 264)	2.96 (2.69)		6.07 (2.49)		6.32 (3.07)	
3 hr/wk (N = 51)	3.02 (4.53)		6.04 (3.27)		5.73 (3.72)	
4 hr/wk (N = 13)	4.25 (2.55)		5.99 (2.64)		5.28 (2.54)	
5 hr/wk (N = 28)	2.22 (2.63)	0.47	5.82 (3.04)	0.41	6.25 (3.32)	0.67
Household Income; N(%)						
<= $70,000 (N = 893)	2.95 (3.26)		**6.01 (2.67)**		6.12 (2.97)	
>$70,000 (N = 1235)	2.72 (2.39)	0.17	**6.52 (2.16)**	**0.0006**	6.38 (2.84)	0.14
Maternal College Graduate Status; N(%)						
No (N = 754)	2.92 (3.31)		**5.97 (2.85)**		6.08 (3.21)	
Yes (N = 1374)	2.76 (2.48)	0.35	**6.47 (2.14)**	**0.0008**	6.37 (2.74)	0.10
Paternal College Graduate Status; N(%)						
No (N = 825)	2.97 (3.35)		**5.99 (2.80)**		6.23 (3.12)	
Yes (N = 1303)	2.73 (2.38)	0.17	**6.50 (2.11)**	**0.0005**	6.31 (2.77)	0.62
Maternal Race/Ethnicity; N(%)						
Asian (N = 122)	2.61 (2.37)		**6.33 (1.69)**		5.69 (2.47)	
Black (N = 354)	2.93 (3.71)		**5.53 (2.96)**		5.89 (3.19)	
Hispanic (N = 157)	2.90 (3.04)		**5.96 (2.57)**		5.94 (3.11)	
Other (N = 84)	3.47 (4.07)		**6.30 (2.41)**		6.40 (2.94)	
White (N = 1411)	2.75 (2.39)	0.36	**6.53 (2.23)**	**<0.0001**	6.43 (2.82)	0.05
Distance to Major Roadway at Enrollment; Mean (SD)	-0.05	0.22	**0.05**	**0.02**	0.04	0.05
Sex of the Child; N(%)						
Male (N = 1096)	2.95 (2.94)		**6.49 (2.41)**		**6.47 (2.96)**	
Female (N = 1032)	2.67 (2.56)	0.08	**6.15 (2.36)**	**0.02**	**6.09 (2.81)**	**0.02**
Age of Child at Mid-Childhood Visit (Days); Mean (SD)	0.03	0.14	-0.05	0.15	-0.04	0.32

Table 4 (continued). Distribution of Covariates According to Total and Trimester-Specific Gestational Weight Gain; Project Viva

		1st Trimester Inadequate	1st Trimester Adequate	1st Trimester Excessive	p-value
Mother's Age at Enrollment; Mean (SD)		**30.39 (5.91)**	**31.95 (4.62)**	**32.69 (5.17)**	**<0.0001**
Mother's Pre-Pregnancy BMI; Mean (SD)		**26.72 (6.21)**	**24.22 (5.02)**	**24.41 (4.93)**	**<0.0001**
Nulliparous; N(%)					
	No (N=1111)	173 (15.57%)	229 (20.61%)	709 (63.82%)	
	Yes (N=1017)	163 (16.03%)	207 (20.35%)	647 (63.62%)	0.89
Maternal History of Asthma; N(%)					
	No (N=1842)	279 (15.15%)	385 (20.91%)	1177 (63.93%)	
	Yes (N=286)	57 (19.86%)	51 (17.77%)	179 (62.37%)	0.13
Paternal History of Asthma; N(%)					
	No (N=1884)	284 (15.07%)	390 (20.70%)	1210 (64.23%)	
	Yes (N=244)	52 (21.31%)	46 (18.85%)	146 (59.84%)	0.05
Maternal History of Allergy; N(%)					
	No (N = 1524)	241 (15.81%)	325 (21.33%)	958 (62.86%)	
	Yes (N=604)	95 (15.73%)	111 (18.38%)	398 (65.89%)	0.32
Paternal History of Allergy; N(%)					
	No (N = 1582)	245 (15.50%)	322 (20.37%)	1014 (64.14%)	
	Yes (N=546)	92 (16.82%)	113 (20.66%)	342 (62.52%)	0.63
Maternal History of Eczema; N(%)					
	No (N = 1855)	292 (15.74%)	373 (20.11%)	1190 (64.15%)	
	Yes (N=273)	44 (16.12%)	63 (23.08%)	166 (60.81%)	0.48
Paternal History of Eczema; N(%)					
	No (N = 2006)	320 (15.95%)	402 (20.04%)	1284 (64.01%)	
	Yes (N = 122)	17 (13.93%)	34 (27.87%)	71 (58.20%)	0.31
Maternal Smoker Status during Pregnancy; N(%)					
	Never (N = 1457)	238 (16.32%)	318 (21.81%)	902 (61.87%)	
	Former (N = 401)	61 (15.21%)	80 (19.95%)	260 (64.84%)	
	Smoker (N = 270)	38 (14.13%)	37 (13.75%)	194 (72.12%)	0.06
Maternal Secondhand Smoke Exposure; N(%)					
	1 hr/wk (N = 1761)	277 (15.73%)	366 (20.78%)	1118 (63.49%)	
	2 hr/wk (N = 264)	44 (16.67%)	51 (19.32%)	169 (64.02%)	
	3 hr/wk (N = 51)	9 (17.65%)	11 (21.57%)	31 (60.78%)	
	4 hr/wk (N = 13)	0 (0.00%)	3 (23.08%)	10 (76.92%)	
	5 hr/wk (N = 28)	5 (17.86%)	3 (10.71%)	20 (71.43%)	0.67
Household Income; N(%)					
	<= $70,000 (N = 893)	180 (20.16%)	161 (18.03%)	552 (61.81%)	
	>$70,000 (N = 1235)	156 (12.63%)	275 (22.27%)	804 (65.10%)	0.0006
Maternal College Graduate Status; N(%)					
	No (N = 754)	**155 (20.56%)**	**140 (18.57%)**	**459 (60.88%)**	
	Yes (N = 1374)	**181 (13.17%)**	**296 (21.54%)**	**897 (65.28%)**	**0.0002**
Paternal College Graduate Status; N(%)					
	No (N = 825)	**166 (20.10%)**	**154 (18.64%)**	**506 (61.26%)**	
	Yes (N = 1303)	**171 (13.13%)**	**282 (21.66%)**	**849 (65.21%)**	**0.0007**
Maternal Race/Ethnicity; N(%)					
	Asian (N = 122)	**21 (17.21%)**	**27 (22.13%)**	**74 (60.66%)**	
	Black (N = 354)	**75 (21.25%)**	**53 (15.01%)**	**225 (63.74%)**	
	Hispanic (N = 157)	**36 (22.93%)**	**33 (21.02%)**	**88 (56.05%)**	
	Other (N = 84)	**16 (19.05%)**	**14 (16.67%)**	**54 (64.29%)**	
	White (N = 1411)	**189 (13.39%)**	**308 (21.81%)**	**915 (64.80%)**	**0.004**
Distance to Major Roadway at Enrollment; Mean (SD)		6.76 (1.27)	6.94 (1.24)	6.73 (1.39)	0.08
Sex of the Child; N(%)					
	Male (N = 1096)	170 (15.51%)	210 (19.16%)	716 (65.33%)	
	Female (N = 1032)	167 (16.18%)	225 (21.80%)	640 (62.02%)	0.24
Age of Child at Mid-Childhood Visit (Days); Mean (SD)		2889.96 (268.80)	2878.71 (285.78)	2896.99 (298.81)	0.67

Table 4 (continued). Distribution of Covariates According to Total and Trimester-Specific Gestational Weight Gain; Project Viva

	2nd Trimester Inadequate	2nd Trimester Adequate	2nd Trimester Excessive	p-value
Mother's Age at Enrollment; Mean (SD)	31.87 (6.15)	32.52 (5.07)	32.09 (5.11)	0.33
Mother's Pre-Pregnancy BMI; Mean (SD)	**26.51 (7.62)**	**22.96 (4.12)**	**25.17 (4.85)**	**<0.0001**
Nulliparous; N(%)				
No (N=1111)	**180 (16.20%)**	**296 (26.64%)**	**635 (57.16%)**	
Yes (N=1017)	**100 (9.83%)**	**276 (27.14%)**	**641 (63.03%)**	**<0.0001**
Maternal History of Asthma; N(%)				
No (N=1842)	**225 (12.22%)**	**500 (27.16%)**	**1116 (60.62%)**	
Yes (N=286)	**55 (19.16%)**	**72 (25.09%)**	**160 (55.75%)**	**0.01**
Paternal History of Asthma; N(%)				
No (N=1884)	250 (13.27%)	498 (26.43%)	1136 (60.30%)	
Yes (N=244)	30 (12.30%)	75 (30.74%)	139 (56.97%)	0.46
Maternal History of Allergy; N(%)				
No (N = 1524)	189 (12.40%)	401 (26.31%)	934 (61.29%)	
Yes (N=604)	91 (15.07%)	171 (28.31%)	342 (56.62%)	0.07
Paternal History of Allergy; N(%)				
No (N = 1582)	222 (14.04%)	411 (26.00%)	948 (59.962%)	
Yes (N=546)	58 (10.60%)	161 (29.43%)	328 (59.96%)	0.17
Maternal History of Eczema; N(%)				
No (N = 1855)	252 (13.58%)	491 (26.47%)	1112 (59.95%)	
Yes (N=273)	28 (10.26%)	81 (29.67%)	164 (60.07%)	0.30
Paternal History of Eczema; N(%)				
No (N = 2006)	265 (13.21%)	535 (26.67%)	1206 (60.07%)	
Yes (N = 122)	14 (11.48%)	38 (31.15%)	70 (57.38%)	0.65
Maternal Smoker Status during Pregnancy; N(%)				
Never (N = 1457)	**202 (13.85%)**	**404 (27.71%)**	**852 (58.44%)**	
Former (N = 401)	**37 (9.23%)**	**111 (27.68%)**	**253 (63.09%)**	
Smoker (N = 270)	**42 (15.61%)**	**56 (20.82%)**	**171 (63.57%)**	**0.02**
Maternal Secondhand Smoke Exposure; N(%)				
1 hr/wk (N = 1761)	217 (12.32%)	483 (27.43%)	1061 (60.25%)	
2 hr/wk (N = 264)	44 (16.67%)	63 (23.86%)	157 (59.47%)	
3 hr/wk (N = 51)	6 (11.76%)	13 (25.49%)	32 (62.75%)	
4 hr/wk (N = 13)	3 (23.08%)	2 (15.38%)	8 (61.54%)	
5 hr/wk (N = 28)	7 (25.00%)	10 (35.71%)	11 (39.29%)	0.09
Household Income; N(%)				
<= $70,000 (N = 893)	**142 (15.90%)**	**236 (26.43%)**	**515 (57.67%)**	
>$70,000 (N = 1235)	**138 (11.17%)**	**337 (27.29%)**	**760 (61.54%)**	**0.01**
Maternal College Graduate Status; N(%)				
No (N = 754)	**130 (17.24%)**	**179 (23.74%)**	**445 (59.02%)**	
Yes (N = 1374)	**150 (10.92%)**	**393 (28.60%)**	**831 (60.48%)**	**0.01**
Paternal College Graduate Status; N(%)				
No (N = 825)	130 (15.74%)	198 (23.97%)	498 (60.29%)	
Yes (N = 1303)	150 (11.52%)	374 (28.73%)	778 (59.75%)	0.09
Maternal Race/Ethnicity; N(%)				
Asian (N = 122)	**21 (17.21%)**	**33 (27.05%)**	**68 (55.74%)**	
Black (N = 354)	**76 (21.53%)**	**88 (24.93%)**	**189 (53.54%)**	
Hispanic (N = 157)	**25 (15.92%)**	**35 (22.29%)**	**97 (61.78%)**	
Other (N = 84)	**10 (11.90%)**	**19 (22.62%)**	**55 (65.48%)**	
White (N = 1411)	**149 (10.55%)**	**396 (28.05%)**	**867 (61.40%)**	**<0.0001**
Distance to Major Roadway at Enrollment; Mean (SD)	6.58 (1.50)	6.73 (1.33)	6.84 (1.31)	0.08
Sex of the Child; N(%)				
Male (N = 1096)	131 (11.95%)	284 (27.52%)	681 (62.147%)	
Female (N = 1032)	149 (14.44%)	288 (27.91%)	595 (57.66%)	0.06
Age of Child at Mid-Childhood Visit (Days); Mean (SD)	2919.99 (350.19)	2881.43 (277.65)	2890.27 (283.49)	0.40

Table 4 (continued). Distribution of Covariates According to Total and Trimester-Specific Gestational Weight Gain; Project Viva

		3rd Trimester Inadequate	3rd Trimester Adequate	3rd Trimester Excessive	p-value
Mother's Age at Enrollment; Mean (SD)		**33.00 (5.32)**	**32.92 (4.95)**	**31.60 (5.24)**	**<0.0001**
Mother's Pre-Pregnancy BMI; Mean (SD)		**23.92 (5.62)**	**22.90 (4.28)**	**25.72 (5.19)**	**<0.0001**
Nulliparous; N(%)					
	No (N=1111)	**277 (24.93%)**	**248 (22.32%)**	**586 (52.75%)**	
	Yes (N=1017)	**177 (17.40%)**	**223 (21.93%)**	**617 (60.67%)**	**<0.0001**
Maternal History of Asthma; N(%)					
	No (N=1842)	390 (21.18%)	414 (22.49%)	1037 (56.33%)	
	Yes (N=286)	64 (22.30%)	57 (19.86%)	166 (57.84%)	0.67
Paternal History of Asthma; N(%)					
	No (N=1884)	402 (21.34%)	412 (21.87%)	1070 (56.79%)	
	Yes (N=244)	52 (21.31%)	59 (24.18%)	133 (54.51%)	0.69
Maternal History of Allergy; N(%)					
	No (N = 1524)	311 (20.41%)	336 (22.05%)	877 (57.55%)	
	Yes (N=604)	143 (23.68%)	135 (22.35%)	326 (53.97%)	0.15
Paternal History of Allergy; N(%)					
	No (N = 1582)	**362 (22.90%)**	**339 (21.44%)**	**880 (55.66%)**	
	Yes (N=546)	**92 (16.82%)**	**132 (24.13%)**	**323 (59.04%)**	**0.02**
Maternal History of Eczema; N(%)					
	No (N = 1855)	398 (21.46%)	412 (22.21%)	1045 (56.33%)	
	Yes (N=273)	57 (20.88%)	59 (21.61%)	157 (57.51%)	0.83
Paternal History of Eczema; N(%)					
	No (N = 2006)	423 (21.09%)	446 (22.23%)	1137 (56.68%)	
	Yes (N = 122)	32 (26.23%)	24 (19.67%)	66 (54.10%)	0.40
Maternal Smoker Status during Pregnancy; N(%)					
	Never (N = 1457)	320 (21.95%)	336 (23.05%)	802 (55.01%)	
	Former (N = 401)	83 (20.70%)	84 (20.95%)	234 (58.35%)	
	Smoker (N = 270)	51 (18.96%)	51 (18.96%)	167 (62.08%)	0.22
Maternal Secondhand Smoke Exposure; N(%)					
	1 hr/wk (N = 1761)	364 (20.67%)	391 (22.20%)	1006 (57.13%)	
	2 hr/wk (N = 264)	57 (21.59%)	64 (24.24%)	143 (54.17%)	
	3 hr/wk (N = 51)	15 (29.41%)	7 (13.73%)	29 (56.86%)	
	4 hr/wk (N = 13)	3 (23.08%)	3 (23.08%)	7 (53.85%)	
	5 hr/wk (N = 28)	10 (35.71%)	5 (17.86%)	13 (46.43%)	0.26
Household Income; N(%)					
	<= $70,000 (N = 893)	201 (22.51%)	179 (20.04%)	513 (57.45%)	
	>$70,000 (N = 1235)	253 (20.49%)	292 (23.64%)	690 (55.87%)	0.38
Maternal College Graduate Status; N(%)					
	No (N = 754)	174 (23.08%)	150 (19.89%)	430 (57.03%)	
	Yes (N = 1374)	281 (20.45%)	321 (23.36%)	772 (56.19%)	0.30
Paternal College Graduate Status; N(%)					
	No (N = 825)	189 (22.88%)	156 (18.89%)	481 (58.23%)	
	Yes (N = 1303)	265 (20.35%)	315 (24.19%)	722 (55.45%)	0.28
Maternal Race/Ethnicity; N(%)					
	Asian (N = 122)	**34 (27.87%)**	**35 (28.69%)**	**53 (43.44%)**	
	Black (N = 354)	**89 (25.21%)**	**67 (18.98%)**	**197 (55.81%)**	
	Hispanic (N = 157)	**38 (24.20%)**	**30 (19.11%)**	**89 (56.69%)**	
	Other (N = 84)	**16 (19.05%)**	**15 (17.86%)**	**53 (63.10%)**	
	White (N = 1411)	**276 (19.55%)**	**325 (23.02%)**	**811 (57.44%)**	**0.01**
Distance to Major Roadway at Enrollment; Mean (SD)		6.75 (1.29)	6.68 (1.42)	6.82 (1.33)	0.33
Sex of the Child; N(%)					
	Male (N = 1096)	**227 (20.71%)**	**220 (20.07%)**	**649 (59.22%)**	
	Female (N = 1032)	**227 (22.00%)**	**251 (24.32%)**	**554 (53.68%)**	**0.03**
Age of Child at Mid-Childhood Visit (Days); Mean (SD)		**2959.80 (331.95)**	**2844.24 (267.98)**	**2886.04 (280.32)**	**<0.0001**

Table 5. Distribution of Covariates According to Offspring Current Mid-Childhood Asthma and Wheeze Phenotypes; Project Viva

		No Current Mid-Childhood Asthma N=1013	Current Mid-Childhood Asthma N=219	p-value
Mother's Age at Enrollment; Mean (SD)		**32.35 (5.13)**	**31.36 (5.66)**	**0.01**
Mother's Pre-Pregnancy BMI; Mean (SD)		**24.47 (4.92)**	**25.92 (6.39)**	**0.001**
Nulliparous; N(%)				
	No	514 (80.56%)	124 (19.44%)	
	Yes	499 (84.01%)	95 (15.99%)	0.12
Maternal History of Asthma; N(%)				
	No	**913 (84.54%)**	**167 (15.46%)**	
	Yes	**100 (65.79%)**	**52 (34.21%)**	**<0.0001**
Paernal History of Asthma; N(%)				
	No	**913 (84.15%)**	**172 (15.85%)**	
	Yes	**100 (68.03%)**	**47 (31.97%)**	**<0.0001**
Maternal History of Allergy; N(%)				
	No	731 (83.26%)	147 (16.74%)	
	Yes	282 (79.66%)	72 (20.34%)	0.14
Paternal History of Allergy; N(%)				
	No	**763 (84.31%)**	**142 (15.69%)**	
	Yes	**250 (76.45%)**	**77 (23.55%)**	**0.003**
Maternal History of Eczema; N(%)				
	No	887 (82.67%)	186 (17.33%)	
	Yes	126 (79.25%)	33 (20.75%)	0.36
Paternal History of Eczema; N(%)				
	No	950 (82.18%)	206 (17.82%)	
	Yes	63 (82.89%)	13 (17.11%)	0.80
Maternal Smoker Status during Pregnancy; N(%)				
	Never	**714 (81.60%)**	**161 (18.40%)**	
	Fomer	**211 (87.92%)**	**29 (12.08%)**	
	Smoker	**88 (75.21%)**	**29 (24.79%)**	**0.02**
Maternal Secondhand Smoke Exposure; N(%)				
	1 hr/wk	852 (82.88%)	176 (17.12%)	
	2 hr/wk	121 (79.08%)	31 (20.92%)	
	3 hr/wk	26 (83.87%)	5 (16.13%)	
	4 hr/wk	3 (60.00%)	2 (40.00%)	
	5 hr/wk	9 (64.29%)	5 (35.71%)	0.24
Household Income; N(%)				
	<= $70,000	**368 (75.88%)**	**117 (24.12%)**	
	>$70,000	**645 (86.35%)**	**102 (13.65%)**	**<0.0001**
Maternal College Graduate Status; N(%)				
	No	**289 (76.46%)**	**89 (23.54%)**	
	Yes	**724 (84.78%)**	**130 (15.22%)**	**0.0004**
Paternal College Graduate Status; N(%)				
	No	**329 (75.98%)**	**104 (24.02%)**	
	Yes	**684 (85.61%)**	**115 (14.39%)**	**<0.0001**
Maternal Race/Ethnicity; N(%)				
	Asian	**55 (88.71%)**	**7 (11.29%)**	
	Black	**130 (68.78%)**	**59 (31.22%)**	
	Hispanic	**46 (60.53%)**	**30 (39.47%)**	
	Other	**44 (80.00%)**	**11 (20.00%)**	
	White	**738 (86.82%)**	**112 (13.18%)**	**<0.0001**
Distance to Major Roadway at Enrollment; Mean (SD)		6.79 (1.33)	6.71 (1.40)	0.44
Sex of the Child; N(%)				
	Male	**494 (79.94%)**	**124 (20.06%)**	
	Female	**519 (84.53%)**	**95 (15.47%)**	**0.04**
Age of Child at Mid-Childhood Visit (Days); Mean (SD)		2888.58 (285.16)	2907.37 (319.11)	0.40

Table 5 (continued). Distribution of Covariates According to Offspring Current Mid-Childhood Asthma and Wheeze Phenotypes; Project Viva

		Never/Inconsistent Wheeze N=960	Early Transient Wheeze N=165	Persistent Wheeze N=170	p-value
Mother's Age at Enrollment; Mean (SD)		**32.53 (5.01)**	**32.30 (4.77)**	**31.29 (5.63)**	**0.01**
Mother's Pre-Pregnancy BMI; Mean (SD)		**24.52 (5.02)**	**24.11 (4.84)**	**25.96 (6.59)**	**0.002**
Nulliparous; N(%)					
	No	**475 (70.90%)**	**93 (13.88%)**	**102 (15.22%)**	
	Yes	**485 (77.60%)**	**72 (11.52%)**	**68 (10.88%)**	**0.01**
Maternal History of Asthma; N(%)					
	No	**865 (76.62%)**	**129 (11.43%)**	**135 (11.96%)**	
	Yes	**95 (57.23%)**	**36 (21.69%)**	**35 (21.08%)**	**<0.0001**
Paernal History of Asthma; N(%)					
	No	**865 (75.94%)**	**146 (12.82%)**	**128 (11.24%)**	
	Yes	**95 (60.90%)**	**19 (12.18%)**	**42 (26.92%)**	**<0.0001**
Maternal History of Allergy; N(%)					
	No	**687 (76.08%)**	**105 (11.63%)**	**111 (12.29%)**	
	Yes	**273 (69.64%)**	**60 (15.31%)**	**59 (15.05%)**	**0.05**
Paternal History of Allergy; N(%)					
	No	**728 (76.55%)**	**117 (12.30%)**	**106 (11.15%)**	
	Yes	**232 (67.44%)**	**48 (13.95%)**	**64 (18.60%)**	**0.001**
Maternal History of Eczema; N(%)					
	No	**850 (75.29%)**	**139 (12.31%)**	**140 (12.40%)**	
	Yes	**110 (66.27%)**	**26 (15.66%)**	**30 (18.07%)**	**0.03**
Paternal History of Eczema; N(%)					
	No	**911 (74.92%)**	**149 (12.25%)**	**156 (12.83%)**	
	Yes	**49 (62.03%)**	**16 (20.25%)**	**14 (17.72%)**	**0.03**
Maternal Smoker Status during Pregnancy; N(%)					
	Never	687 (75.41%)	110 (12.07%)	114 (12.51%)	
	Fomer	185 (70.61%)	42 (16.03%)	35 (13.34%)	
	Smoker	88 (72.13%)	13 (10.66%)	21 (17.21%)	0.22
Maternal Secondhand Smoke Exposure; N(%)					
	1 hr/wk	816 (74.52%)	138 (12.60%)	141 (12.88%)	
	2 hr/wk	110 (72.37%)	21 (13.82%)	21 (13.82%)	
	3 hr/wk	20 (71.43%)	5 (17.86%)	3 (10.71%)	
	4 hr/wk	5 (83.33%)	0 (0.00%)	1 (16.67%)	
	5 hr/wk	8 (57.14%)	2 (14.29%)	4 (28.57%)	0.53
Household Income; N(%)					
	<= $70,000	**335 (68.65%)**	**68 (13.93%)**	**85 (17.42%)**	
	>$70,000	**625 (77.45%)**	**97 (12.02%)**	**85 (10.53%)**	**0.0007**
Maternal College Graduate Status; N(%)					
	No	**256 (68.82%)**	**50 (13.44%)**	**66 (17.74%)**	
	Yes	**704 (76.27%)**	**115 (12.46%)**	**104 (11.27%)**	**0.004**
Paternal College Graduate Status; N(%)					
	No	**295 (68.45%)**	**62 (14.39%)**	**74 (17.17%)**	
	Yes	**665 (76.97%)**	**103 (11.92%)**	**96 (11.11%)**	**0.003**
Maternal Race/Ethnicity; N(%)					
	Asian	**51 (78.46%)**	**8 (12.31%)**	**6 (9.23%)**	
	Black	**114 (68.67%)**	**16 (9.64%)**	**36 (21.67%)**	
	Hispanic	**44 (56.41%)**	**13 (16.67%)**	**21 (26.92%)**	
	Other	**39 (72.22%)**	**8 (14.81%)**	**7 (12.96%)**	
	White	**712 (76.39%)**	**120 (12.88%)**	**100 (10.73%)**	**0.001**
Distance to Major Roadway at Enrollment; Mean (SD)		**6.79 (1.33)**	**6.98 (1.26)**	**6.59 (1.48)**	**0.0006**
Sex of the Child; N(%)					
	Male	**463 (69.62%)**	**101 (15.19%)**	**101 (15.19%)**	
	Female	**497 (78.89%)**	**64 (10.16%)**	**69 (10.95%)**	**0.0006**
Age of Child at Mid-Childhood Visit (Days); Mean (SD)		2874.53 (283.77)	2881.13 (272.70)	2873.67 (292.06)	0.88

Table 6. Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals for Total and Trimester-Specific Gestational Weight Gain and Offspring Current Mid-Childhood Asthma; Project Viva

		Current Mid-Childhood Asthma					
		Unadjusted		Adjusted*		Adjusted**	
		RR	95% CI	RR	95% CI	RR	95% CI
Total Gestational Weight Gain		**0.96**	**0.94 - 0.99**	0.98	0.95 - 1.01	0.98	0.95 - 1.01
Categorical Total Gestational Weight Gain							
	Inadequate vs. Adequate	**1.57**	**1.01 - 2.46**	0.64	0.40 - 1.02	0.81	0.63 - 1.03
	Excessive vs. Adequate	0.88	0.63 - 1.23	1.21	0.85 - 1.73	1.09	0.91 - 1.31
Total First Trimester-Specific Gestational Weight Gain		1.00	0.94 - 1.05	0.98	0.93 - 1.04	0.99	0.94 - 1.05
Total Second Trimester-Specific Gestational Weight Gain		**0.90**	**0.85 - 0.95**	0.95	0.89 - 1.02	0.95	0.89 - 1.02
Total Third Trimester-Specific Gestational Weight Gain		0.95	0.90 - 1.00	0.97	0.92 - 1.02	0.97	0.91 - 1.02
Categorical First Trimester-Specific Gestational Weight Gain							
	Inadequate vs. Adequate	1.15	0.72 - 1.83	1.08	0.66 - 1.78	1.10	0.85 - 1.42
	Excessive vs. Adequate	0.86	0.60 - 1.24	1.25	0.85 - 1.84	1.12	0.92 - 1.37
Categorical Second Trimester-Specific Gestational Weight Gain							
	Inadequate vs. Adequate	**2.06**	**1.30 - 3.29**	0.66	0.40 - 1.10	0.79	0.61 - 1.03
	Excessive vs. Adequate	0.97	0.69 - 1.38	1.15	0.79 - 1.67	1.04	0.86 - 1.26
Categorical Third Trimester-Specific Gestational Weight Gain							
	Inadequate vs. Adequate	1.43	0.91 - 2.23	0.80	0.50 - 1.28	0.86	0.67 - 1.09
	Excessive vs. Adequate	1.09	0.74 - 1.59	1.09	0.72 - 1.65	1.03	0.83 - 1.27

*Adjusted for confounders: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, distance to a major roadway, sex of the child, and age in days of child at Mid-Childhood Visit

**Adjusted for confounders and risk factors: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, distance to a major roadway, sex of the child, age in days of child at Mid-Childhood Visit, paternal asthma, paternal allergy, paternal eczema, maternal secondhand smoking status during pregnancy

Table 7. Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals for Total and Trimester-Specific Gestational Weight Gain and Offspring Wheeze Phenotypes; Project Viva

			Wheeze Phenotypes					
			Unadjusted		Adjusted*		Adjusted**	
			OR	95% CI	RR	95% CI	RR	95% CI
Total Gestational Weight Gain								
		Early Transient Wheeze	0.99	0.96 - 1.02	0.99	0.95 - 1.02	0.99	0.95 - 1.02
		Persistent Wheeze	**0.96**	**0.93 - 0.99**	0.97	0.94 - 1.01	0.98	0.95 - 1.01
Categorical Total Gestational Weight Gain								
	Inadequate vs. Adequate	Early Transient Wheeze	1.10	0.64 - 1.92	1.16	0.65 - 2.04	1.16	0.65 - 2.06
	Excessive vs. Adequate	Early Transient Wheeze	1.02	0.71 - 1.48	1.06	0.72 - 1.57	1.08	0.72 - 1.60
	Inadequate vs. Adequate	Persistent Wheeze	1.44	0.87 - 2.38	1.35	0.80 - 2.29	1.33	0.78 - 2.29
	Excessive vs. Adequate	Persistent Wheeze	0.88	0.61 - 1.28	0.83	0.56 - 1.23	0.86	0.57 - 1.28
Total First Trimester-Specific Gestational Weight Gain								
		Early Transient Wheeze	1.01	0.95 - 1.08	1.01	0.95 - 1.08	1.02	0.95 - 1.09
		Persistent Wheeze	0.95	0.89 - 1.01	0.96	0.90 - 1.02	0.96	0.91 - 1.03
Total Second Trimester-Specific Gestational Weight Gain								
		Early Transient Wheeze	0.98	0.92 - 1.05	0.97	0.89 - 1.05	0.96	0.89 - 1.05
		Persistent Wheeze	**0.92**	**0.86 - 0.99**	0.97	0.90 - 1.05	0.98	0.91 - 1.06
Total Third Trimester-Specific Gestational Weight Gain								
		Early Transient Wheeze	0.97	0.92 - 1.03	0.97	0.91 - 1.03	0.97	0.91 - 1.03
		Persistent Wheeze	0.96	0.91 - 1.02	0.98	0.92 - 1.04	0.98	0.92 - 1.04
Categorical First Trimester-Specific Gestational Weight Gain								
	Inadequate vs. Adequate	Early Transient Wheeze	0.72	0.41 - 1.27	0.67	0.37 - 1.20	0.66	0.37 - 1.19
	Excessive vs. Adequate	Early Transient Wheeze	0.80	0.54 - 1.19	0.79	0.53 - 1.20	0.80	0.53 - 1.21
	Inadequate vs. Adequate	Persistent Wheeze	1.14	0.68 - 1.89	0.82	0.48 - 1.41	0.78	0.44 - 1.34
	Excessive vs. Adequate	Persistent Wheeze	0.80	0.53 - 1.20	0.75	0.49 - 1.15	0.76	0.50 - 1.18
Categorical Second Trimester-Specific Gestational Weight Gain								
	Inadequate vs. Adequate	Early Transient Wheeze	0.89	0.48 - 1.66	0.95	0.50 - 1.80	1.00	0.52 - 1.92
	Excessive vs. Adequate	Early Transient Wheeze	1.02	0.69 - 1.49	1.04	0.69 - 1.54	1.06	0.71 - 1.59
	Inadequate vs. Adequate	Persistent Wheeze	**1.73**	**1.01 - 2.94**	1.32	0.74 - 2.36	1.39	0.77 - 2.52
	Excessive vs. Adequate	Persistent Wheeze	1.09	0.74 - 1.62	1.00	0.66 - 1.51	1.04	0.68 - 1.59
Categorical Third Trimester-Specific Gestational Weight Gain								
	Inadequate vs. Adequate	Early Transient Wheeze	0.72	0.44 - 1.18	0.61	0.37 - 1.02	0.60	0.36 - 1.02
	Excessive vs. Adequate	Early Transient Wheeze	0.71	0.48 - 1.05	0.64	0.61 - 1.52	**0.64**	**0.42 - 0.98**
	Inadequate vs. Adequate	Persistent Wheeze	1.34	0.80 - 2.23	1.13	0.66 - 1.93	1.14	0.66 - 1.97
	Excessive vs. Adequate	Persistent Wheeze	1.19	0.77 - 1.83	0.96	0.61 - 1.52	0.97	0.61 - 1.55

*Adjusted for confounders: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, paternal race/ethnicity, distance to a major roadway, sex of the child and age in days of child at Mid-Childhood Visit

**Adjusted for confounders and risk factors: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, paternal race/ethnicity, distance to a major roadway, sex of the child, age in days of child at Mid-Childhood Visit, paternal asthma, paternal allergy, paternal eczema, maternal secondhand smoking status during pregnancy

Table 8. Conditional Predicted Probabilities for Total and Trimester-Specific Gestational Weight Gain and Offspring Current Mid-Childhood Asthma; Project Viva

		Conditional Predicted Probability*	Conditional Predicted Probability**
		%	%
Total Gestational Weight Gain	1 kg	17.87%	13.10%
	10 kg	14.91%	11.10%
	30 kg	9.78%	7.60%
Categorical Total Gestational Weight Gain			
	Inadequate	20.31%	15.22%
	Adequate	13.95%	10.45%
	Excessive	11.81%	8.93%
Total First Trimester-Specific Gestational Weight Gain	0.07 kg	13.81%	10.21%
	2.94 kg	13.26%	9.97%
	5.81 kg	12.72%	9.72%
Total Second Trimester-Specific Gestational Weight Gain	3.82 kg	15.04%	15.04%
	6.31 kg	13.50%	13.50%
	8.80 kg	12.09%	12.09%
Total Third Trimester-Specific Gestational Weight Gain	3.29 kg	14.58%	14.58%
	6.31 kg	13.38%	13.38%
	9.33 kg	12.28%	12.28%
Categorical First Trimester-Specific Gestational Weight Gain			
	Inadequate	14.15%	9.80%
	Adequate	15.12%	11.60%
	Excessive	12.43%	9.41%
Categorical Second Trimester-Specific Gestational Weight Gain			
	Inadequate	19.78%	15.26%
	Adequate	14.02%	10.11%
	Excessive	12.42%	9.35%
Categorical Third Trimester-Specific Gestational Weight Gain			
	Inadequate	16.47%	12.90%
	Adequate	13.58%	9.82%
	Excessive	12.58%	9.36%

*Adjusted for confounders: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, paternal race/ethnicity, distance to a major roadway, sex of the child and age in days of child at Mid-Childhood Visit

**Adjusted for confounders and risk factors: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, paternal race/ethnicity, distance to a major roadway, sex of the child, age in days of child at Mid-Childhood Visit, paternal asthma, paternal allergy, paternal eczema, maternal secondhand smoke exposure during pregnancy

Table 9. Conditional Predicted Probabilities for Total and Trimester-Specific Gestational Weight Gain and Offspring Wheeze Phenotypes; Project Viva

			Conditional Predicted Probability*	Conditional Predicted Probabilities**
			%	%
Total Gestational Weight Gain				
	Never/Infrequent	1 kg	69.73%	75.71%
		10 kg	73.53%	78.35%
		30 kg	80.65%	83.37%
	Early Transient	1 kg	14.12%	13.25%
		10 kg	13.03%	12.22%
		30 kg	10.63%	10.07%
	Persistent	1 kg	16.16%	11.04%
		10 kg	13.45%	9.43%
		30 kg	8.72%	6.56%
Categorical Total Gestational Weight Gain				
	Never/Infrequent	Inadequate	70.88%	76.32%
		Adequate	75.40%	79.98%
		Excessive	76.51%	80.38%
	Early Transient	Inadequate	12.71%	12.12%
		Adequate	11.70%	10.94%
		Excessive	12.63%	11.82%
	Persistent	Inadequate	16.40%	11.55%
		Adequate	12.90%	9.08%
		Excessive	10.85%	7.80%

*Adjusted for confounders: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, paternal race/ethnicity, distance to a major roadway, sex of the child and age in days of child at Mid-Childhood Visit

**Adjusted for confounders and risk factors: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, paternal race/ethnicity, distance to a major roadway, sex of the child, age in days of child at Mid-Childhood Visit, paternal asthma, paternal allergy, paternal eczema, maternal secondhand smoke exposure during pregnancy

Table 9 (continued). Conditional Predicted Probabilities for Total and Trimester-Specific Gestational Weight Gain and Offspring Wheeze Phenotypes; Project Viva

		Conditional Predicted Probability*	Conditional Predicted Probabilities**
		%	%
Total First Trimester Gestational Weight Gain			
Never/Infrequent	0.07 kg	74.89%	79.64%
	2.94 kg	75.83%	79.96%
	5.81 kg	76.63%	80.19%
Early Transient	0.07 kg	11.93%	11.11%
	2.94 kg	12.45%	11.66%
	5.81 kg	12.98%	12.23%
Persistent	0.07 kg	13.18%	9.25%
	2.94 kg	11.71%	8.38%
	5.81 kg	10.39%	7.59%
Total Second Trimester Gestational Weight Gain			
Never/Infrequent	3.82 kg	74.03%	78.51%
	6.31 kg	75.51%	79.76%
	8.80 kg	76.93%	80.95%
Early Transient	3.82 kg	13.26%	12.56%
	6.31 kg	12.41%	11.65%
	8.80 kg	11.61%	10.80%
Persistent	3.82 kg	12.71%	8.93%
	6.31 kg	12.07%	8.58%
	8.80 kg	11.46%	8.25%
Total Third Trimester Gestational Weight Gain			
Never/Infrequent	3.29 kg	73.88%	78.43%
	6.31 kg	75.56%	79.79%
	9.33 kg	77.15%	81.09%
Early Transient	3.29 kg	13.49%	12.58%
	6.31 kg	12.40%	11.63%
	9.33 kg	11.38%	10.73%
Persistent	3.29 kg	12.63%	8.99%
	6.31 kg	12.04%	8.58%
	9.33 kg	11.46%	8.18%

*Adjusted for confounders: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, paternal race/ethnicity, distance to a major roadway, sex of the child and age in days of child at Mid-Childhood Visit

**Adjusted for confounders and risk factors: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, paternal race/ethnicity, distance to a major roadway, sex of the child, age in days of child at Mid-Childhood Visit, paternal asthma, paternal allergy, paternal eczema, maternal secondhand smoke exposure during pregnancy

Table 9 (continued). Conditional Predicted Probabilities for Total and Trimester-Specific Gestational Weight Gain and Offspring Wheeze Phenotypes; Project Viva

		Conditional Predicted Probability*	Conditional Predicted Probabilities**
		%	%
Categorical First Trimester Gestational Weight Gain			
Never/Infrequent	Inadequate	74.80%	82.20%
	Adequate	75.40%	76.56%
	Excessive	75.94%	80.65%
Early Transient	Inadequate	11.89%	9.57%
	Adequate	12.23%	13.47%
	Excessive	12.56%	11.31%
Persistent	Inadequate	13.31%	8.22%
	Adequate	12.38%	9.97%
	Excessive	11.49%	8.04%
Categorical Second Trimester Gestational Weight Gain			
Never/Infrequent	Inadequate	74.41%	79.18%
	Adequate	75.19%	79.63%
	Excessive	75.84%	79.99%
Early Transient	Inadequate	11.43%	10.86%
	Adequate	12.04%	11.33%
	Excessive	12.65%	11.81%
Persistent	Inadequate	14.15%	9.96%
	Adequate	12.77%	9.04%
	Excessive	11.51%	8.20%
Categorical Third Trimester Gestational Weight Gain			
Never/Infrequent	Inadequate	75.57%	80.15%
	Adequate	71.71%	75.99%
	Excessive	76.63%	80.74%
Early Transient	Inadequate	10.85%	10.12%
	Adequate	16.84%	15.92%
	Excessive	11.59%	10.91%
Persistent	Inadequate	13.58%	9.73%
	Adequate	11.45%	8.09%
	Excessive	11.78%	8.36%

*Adjusted for confounders: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, paternal race/ethnicity, distance to a major roadway, sex of the child and age in days of child at Mid-Childhood Visit

**Adjusted for confounders and risk factors: mother's age at enrollment, mother's pre-pregnancy BMI, nulliparity, maternal asthma, maternal allergy, maternal eczema, maternal smoking status during pregnancy, household income above $70,000, maternal college graduate, paternal college graduate, maternal race/ethnicity, paternal race/ethnicity, distance to a major roadway, sex of the child, age in days of child at Mid-Childhood Visit, paternal asthma, paternal allergy, paternal eczema, maternal secondhand smoke exposure during pregnancy

Figure 1. Physiologic Mechanisms #1: Leptin

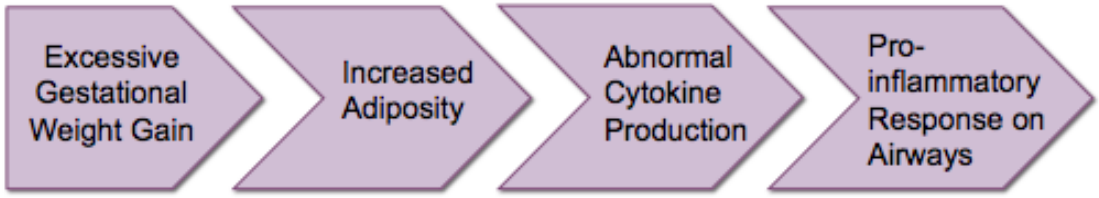


Figure 2. Physiologic Mechanism #2: Tumor Necrosis Factor – α

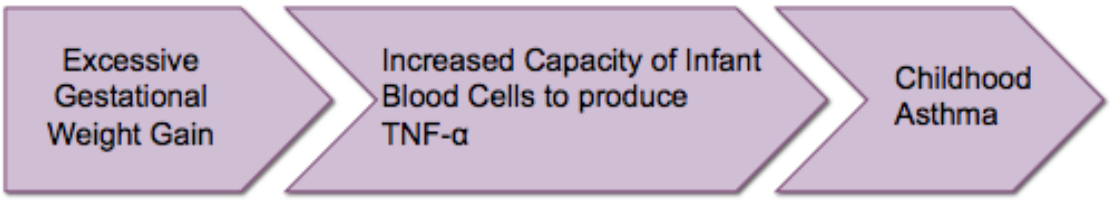
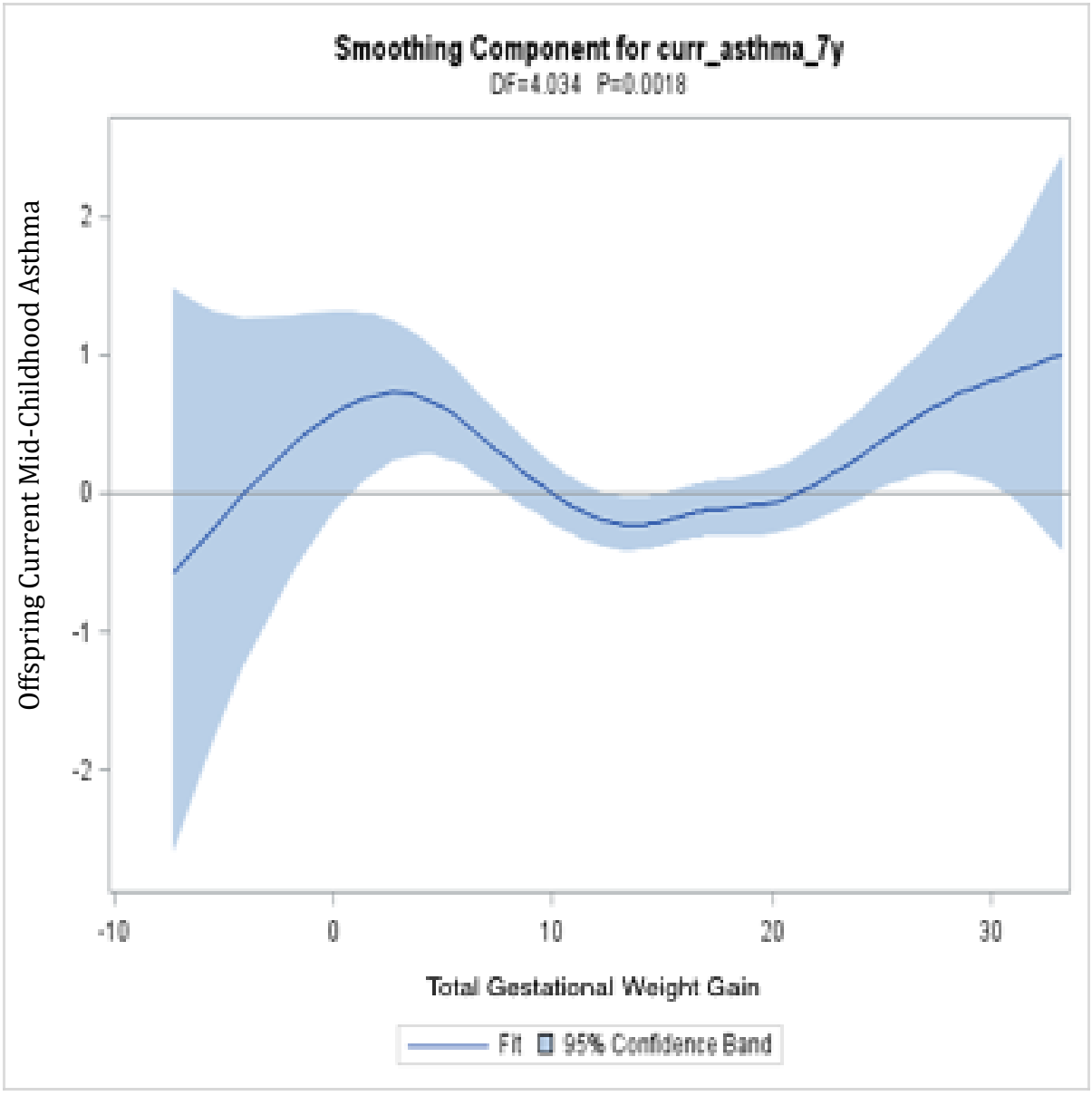


Figure 3. Generalized Additive Model of Continuous Total Gestational Weight Gain and Offspring Current Mid-Childhood Asthma; Project Viva



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