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Maternal Obesity, Gestational Weight Gain And Offspring's Asthma

Kristen Polinski
University of South Carolina

MATERNAL OBESITY, GESTATIONAL WEIGHT GAIN AND OFFSPRING'S ASTHMA

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Kristen Polinski

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Accepted by:

Jihong Liu, Director of Thesis

Alexander McLain, Reader

Nansi Boghossian, Reader

Lacy Ford, Senior Vice Provost and Dean of Graduate Studies

ABSTRACT

Introduction: Obesity is common among women of childbearing age and intrauterine exposures may influence the development of early childhood asthma. A handful of studies have investigated pre-pregnancy obesity, but even fewer have thoroughly explored gestational weight gain as possible childhood asthma risk factors. Gaps remain in the literature and to our knowledge, none have longitudinally explored these relationships in a nationally representative sample of U.S. children.

Methods: We used data from the Early Childhood Longitudinal Study – Birth Cohort, in which children were followed through age four (n≈5,200). Asthma was based on parent report of a physician's diagnosis. Four definitions of gestational weight gain were used. Generalized estimating equation binomial models were used to compute adjusted odds ratios (aOR) and 95% confidence intervals.

Results: Compared to children of normal weight mothers, children born to obese mothers had an overall increased risk of early childhood asthma (aOR: 1.63 95% CI: 1.25-2.11); whereas pre-pregnancy overweight fell just below statistical significance (aOR: 1.26 95% CI 0.99-1.60). Extreme weight gains (<5kg and ≥25kg) were also independently associated with increased risks of asthma; however, no other significant associations were observed for weight gain and offspring's asthma.

Conclusions: We found that in the U.S., extreme weight gain levels, maternal obesity, and to a lesser extent maternal overweight are risk factors of early childhood asthma. Exceeding weight gain recommendations was not a risk factor for asthma. Our study

provides further evidence for the long-term effects intrauterine exposures may have on children and the need to target preconception care in improving child health indicators.

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CHAPTER 1

BACKGROUND

1.1 Asthma

Asthma is a chronic condition that inflames and narrows the airways. Both children and adults can be diagnosed with asthma; however, children experience different challenges than adults. Young children have smaller airways than adults, making an asthma attack an even more serious condition (1). Additionally, childhood asthma is the leading cause of emergency department visits, hospitalizations and missed school days among youth. Childhood asthma is also one of the most common chronic diseases affecting children in the United States (2). Approximately 14 percent of children under the age of eighteen and 7 percent under the age of four have been diagnosed with asthma (3).

As many as 50 to 80 percent of children with asthma develop symptoms before the age of five, such as wheeze, cough, trouble breathing, and recurring bronchitis (4) (5). Wheeze is perhaps the most common symptom, and has been used in lieu of asthma in the literature. Despite being a strong risk factor for asthma, wheezing in different age periods in childhood may be indicative of varying physiological mechanisms (6).

Prevention and early diagnosis of asthma are particularly important in childhood. Asthma can invoke detrimental consequences to a child's development, such as permanent narrowing of the airways. Furthermore, as a chronic condition, asthma management/therapeutic interventions only target symptoms and contribute to huge

health care expenditures. In 2007, the total incremental cost of asthma to society was $56 billion (7). A review article summarized the findings of several birth cohorts, in which, preschool children with wheeze may already have permanent deficits in lung function by the age of six (8). Impaired lung growth in this age group will continue to afflict individuals into adulthood, "setting the stage for lifelong persistent asthma." (8). Furthermore, asthma in early childhood is also said to be underdiagnosed resulting in young children not receiving adequate therapy (5). Childhood asthma also contributes to utilization of emergency care, poor sleep and fatigue, interferences with physical activity and missed school days (4). For instance, between 2005 and 2007 the rate of emergency department visits for asthma among children under the age of five was about 133 visits per 10,000 children (9). Also in 2007, 41.4 hospitalizations for asthma per 10,000 children under the age of five occurred (9).

1.2 Maternal Obesity and GWG

Over the past decade, more and more women have entered pregnancy being overweight or obese (10, 11) with a body mass index (BMI) of 30 or more prior to pregnancy. Research has shown that maternal pre-pregnancy obesity can be associated with adverse outcomes such as adiposity and metabolic risk markers in offspring by the age of 10 (12). Maternal pre-pregnancy obesity is also associated with increased risks for maternal complications during pregnancy (e.g. gestational diabetes) and is linked to excessive gestational weight gain (GWG) (13, 14). GWG is the weight a woman gains during pregnancy and is based on Institute of Medicine (IOM) recommendations (see

Table 1.1). Overweight or obese pregnant women are more likely to exceed the IOM recommendations compared to women who begin their pregnancy at a normal BMI (12).

Maternal pre-pregnancy obesity is a modifiable risk factor among women who are planning to conceive and preconception programs promoting optimal pre-pregnancy weight are ideal. However, in 2006, 49 percent of pregnancies were unplanned (15) limiting the ability to target high pre-pregnancy BMI. Therefore, GWG becomes an important modifiable risk factor because it can be largely controlled during pregnancy. Furthermore, studies have shown that pregnancy is a great window of opportunity for interventions because women are more likely to make behavioral changes if they believe the changes will benefit the child (16). Therefore, GWG is an ideal risk factor to modify in interventions.

Excessive GWG is common in the United States. During pregnancy only 33-40 percent of women gain the amount of weight recommended by the IOM (13). In fact, the CDC reported that 48 percent of women gain more than the recommended amount during pregnancy(17). Women who are already overweight or obese entering pregnancy may also be at higher risk of gaining too much weight during pregnancy. One study found that 68 percent of overweight and obese women exceeded the IOM's recommendations; whereas 50 percent of normal weight women exceed the recommendations (12).

Excessive GWG is associated with many of the same pregnancy complications and poor health outcomes present in mothers with a high pre-pregnancy BMI (18, 19). Also, higher weight gain during pregnancy regardless of the mother's pre-pregnancy BMI, increases the risk of macrosomia (≥4500g) or infants that are large for gestational

age (LGA) (20). Furthermore, increased weight gain in pregnancy among obese women is also associated with newborn infant adiposity and childhood obesity (21). Low GWG has also been associated with preterm birth and low birthweight (22).

1.3 Introduction

Recent literature has identified possible links between maternal pre-pregnancy BMI, GWG and risk of asthma in the offspring. A review of the literature can be found in Chapter 2. Other studies exploring the biological mechanisms of childhood asthma have acknowledged that maternal pre-pregnancy BMI and GWG may play a role. However, the complete etiology of childhood asthma in association with maternal pregnancy obesity remains unknown.

The intrauterine environment is thought to play a critical role on offspring's health (23). One cohort study found that about 40 percent of children with asthma by age 7, had reduced air flow and bronchial responsiveness as neonates (24). Such a finding lends support to the notion that the mechanisms of asthma may begin in the prenatal period. Inadequate or excessive GWG and maternal obesity are both believed to change the intrauterine environment (25). For example, a recent study found that GWG can alter the expressions of genes regulating placenta nutrient transport (26) and another found that pre-pregnancy obesity can alter placental leptin DNA methylation (27).

In terms of childhood asthma, GWG and maternal BMI may affect childhood asthma through non-allergic inflammatory mechanisms. Both high pre-pregnancy BMI and GWG, particularly in the second and third trimesters, have been associated with higher levels of cord blood leptin (28-30). In further support of these findings, another

study identified increased weight gain during pregnancy as a strong predictor for elevated TNF-α (tumor necrosis factor alpha) in the infant; subsequently observing an association between TNF-α and asthma by age 9 (31).

Leptin and TNF-α are cell signaling proteins called cytokines that are involved in systemic inflammation. More specifically, leptin is a pro-inflammatory adipokine which is a type of cytokine that is secreted from adipose tissue. Smooth muscles in the airways release interleukin-8 (IL-8) through interactions with these inflammatory cells; which in turn, contribute to airway inflammation and remodeling (32, 33). Additionally, maternal obesity and excess GWG have been shown to contribute to childhood obesity (25, 34-36), which in turn may increase the risk for asthma development (37, 38).

Overall, childhood asthma is a complex disease with significant public health implications. The purpose of this thesis is to investigate the associations between GWG, maternal pre-pregnancy BMI and offspring's risk of asthma in a multiethnic, nationally representative U.S. sample of children in early childhood.

Table 1.1: IOM 2009 Recommendations for Total and Rate of Weight Gain During Pregnancy (18)

Pre-pregnancy BMI	BMI (kg/m2)	Total Weight Gain Range (lbs)	Rates of weight gain 2nd and 3rd trimester (mean range in lbs/wk)	Total Weight Gain Range (kg)	Rates of weight gain 2nd and 3rd trimester (mean range in kg/wk)
Underweight	<18.0	28-40	1 (1-1.3)	12.5-18	0.51 (0.44-0.58)
Normal weight	18.5-24.9	25-35	1 (0.8-1)	11.5-16	0.42 (0.35-0.50)
Overweight	25-29.9	15-25	0.6 (0.5-0.7)	7-11.5	0.28 (0.23-0.33)
Obese	≥30.0	11-20	0.5 (0.4-0.6)	5-9	0.22 (0.17-0.27)

Note: IOM = Institute of Medicine

CHAPTER 2

LITERATURE REVIEW

The literature on the associations of maternal obesity and childhood asthma is limited. In July 2014, Forno et al. published a meta-analysis on maternal obesity, GWG, and the risk of asthma in offspring (39). Based on the 14 studies included in the meta-analysis, the authors concluded that high maternal BMI is associated with asthma in the offspring (31, 40-52). Compared with children from mothers with a normal pre-pregnancy weight, children whose mothers were overweight before pregnancy had higher odds of asthma (OR = 1.52; 95% CI: 1.05-2.18) in a prospective Dutch birth cohort (51). In another prospective birth cohort of multiethnic children in 20 U.S. cities, the odds of obese mothers having a child with asthma was 1.34 (95% CI: 1.03-1.76) times that of non-obese mothers, after adjusting for sociodemographic, medical, obstetric and behavioral factors. Overall, the meta-analysis concluded that the magnitudes of association of maternal obesity and ever or current asthma in offspring were between 1.15 and 4.20 and were mostly statistically significant.

In addition to the articles included in the Forno et al.'s review paper (39), a PubMed search was conducted to search for articles published since the review. Only one new article on maternal BMI and offspring asthma was identified (53). Table 2.1 provides a complete listing of studies from the review and the updated PubMed search that included only the maternal pre-pregnancy BMI exposure. Table 2.2 provides a list of studies that included GWG as an exposure.

As presented in Table 2.1, pre-pregnancy BMI was obtained in six studies via medical records or direct height and weight measurements (31, 47-49, 52, 53). Seven studies relied on self-reported height and weight estimates (40-45, 51). Self-reported weight tends to be underestimated and height tends to be overestimated, which may lead to an underestimate of pre-pregnancy BMI and could weaken the association between BMI and childhood asthma.

Forno et al. also evaluated the association of GWG and asthma. The authors expressed the need for future studies to explore the association between GWG and asthma because only a few studies measured GWG (39). Among the five studies that examined this association, two demonstrated statistically significant increased risk (magnitudes 1.09 and 3.4) of asthma in children with mothers who experienced higher GWG, which was independent of maternal pre-pregnancy BMI (31, 43). One study observed that for every unit increase in GWG there was a slightly increased risk of wheeze in offspring (OR: 1.10; 95% CI: 1.04-1.16) (45). Another study also found an increased risk of wheeze among children born to mothers with GWG greater than 15kg, although these results were insignificant (OR: 1.23; 95% CI: 0.85-1.40) (50). Lastly, a 1996 case-control study found that mothers of asthmatic children were more likely (OR: 3.42; 95% CI:1.72-6.79) to have low GWG (<20lbs or <9kg) than mothers of non-asthmatic children (46). Furthermore, in the studies that adjusted for pre-pregnancy BMI, the variable was either treated categorically or was not used in the analysis, as shown in Table 2.2.

2.1 Methodological Issues:

Four of the five studies that included GWG measures were prospective birth cohorts from predominantly white populations in Denmark (43), Tucson, AZ (31), Italy (50), and the Netherlands (45). Only one study included a primarily African American sample from Cleveland, Ohio (46). The Generation R Netherlands cohort study followed children from birth through age four (45). In the Denmark, Italy and Tucson studies children were followed from birth through age seven and nine, respectively (31, 43, 50). Therefore, to our knowledge, no studies examining the association between GWG and offspring's asthma have been conducted using a U.S. nationally representative sample of multiethnic children.

GWG was measured differently across the studies. One study measured total GWG as the difference of weight at the time of delivery and pre-pregnancy weight (46). However, this definition of total GWG does not adjust for gestational age which can impact the amount of weight gained (i.e. the shorter the pregnancy duration, the lower the weight gain). Due to the availability of data, some studies examined the weight gain from pre-pregnancy to weight in the third trimester (45) or weight in the last office visit (31), which does not represent the total weight gain during pregnancy leading to limitations in measuring the exposure. One study relied on the self-reported total weight gain in pregnancy being reported after delivery (43), which may introduce inaccuracies in the exposure. Furthermore, GWG was often presented inconsistently across studies (e.g. continuous, tertiles, varying cut-offs) limiting comparability. Overall, measures of GWG have limitations regarding the absence of gestational age and the current coding of GWG (i.e. varying cut-offs) are not easily comparable across studies.

Asthma and/or wheeze were the outcomes of interest among all of the studies included in Table 2.1 and Table 2.2. Eight studies included child's asthma as an outcome (31, 43, 46-49, 51, 53) and twelve studies included wheeze as the outcome (31, 40-45, 47, 48, 50-52). Asthma in the child was determined via medical records, parental report of physician diagnosis, or as parental report without physician diagnosis. Wheeze was entirely based on parental report with the exception of one study (44). Overall, studies that do not include wheeze as a substitute for asthma are preferable. Furthermore, medical records as a source of asthma status are preferable, but parent report of a physician diagnosis is also acceptable, particularly in large cohort studies.

Overall, few studies have examined the role of GWG in asthma risk among offspring and most have used poor quality measures of GWG and asthma. The IOM report has called for more research to assess the impact of GWG on childhood asthma (18). Furthermore, more studies are needed to understand the independent effect of BMI and GWG. In this study, we will attempt to fill in gaps in existing literature by using a large, nationally representative sample of multiethnic children. To address the variability among previous studies in the reporting of exposures (e.g. categorical vs. continuous GWG) and in the definition of asthma or wheeze, we will use four GWG definitions (1. total GWG from birth certificate, 2. weekly rate of weight gain in the 2^{nd} and 3^{rd} trimesters, 3. meeting IOM recommendations in weight gain, and 4. Categorical GWG by 6 levels) and parent report of physician diagnosis of asthma in this study.

Table 2.1: Studies Researching Pre-pregnancy Weight with Risk of Asthma/Wheeze among Offspring

Author, year	Location	Sample Size	Main Exposure	Outcome(s) of interest	Results
Caudri, 2013 (40)	Netherlands	2,728	Pre-pregnancy BMI - continuous‡	Wheeze‡	Per interquartile increase in BMI, crude OR: 1.26 (95% CI: 1.01-1.57)
Ekstrom, 2015 (53)*	Sweden	4089	Pre-pregnancy BMI - categorical§	Asthma‡	AOR for obese vs. normal: 1.53 (95%CI: 1.04-2.26)
Guerra, 2013 (41)	Spain	1,107	Pre-pregnancy BMI-categorical‡	Wheeze ‡	Adjusted RR for obese vs. normal: 4.2 (95% CI: 1.5-11.3)
Haberg, 2009 (42)	Norway	33,192	Pre-pre-pregnancy BMI - categorical‡	Wheeze‡	Risk difference for obese vs. normal: 3.3% (p-value: <0.01)
Kumar, 2010 (44)	Boston, MA	1,191	Pre-pregnancy BMI - categorical‡	Recurrent wheeze§	AOR for obese mothers vs. BMI <25: 3.51 (95% CI: 1.68-7.32)
Patel, 2011 (47)	Finland	6,945	Pre-pregnancy weight & BMI – categorical, continuous‡	Wheeze‡	1-unit increase in BMI, AOR: 1.028 (1.005-1.051). AOR for obese vs. normal: 0.99 (95% CI: 0.66-1.48)
Pike, 2013 (48)	United Kingdom	940	Pre-pregnancy BMI - continuous§	Asthma†; wheeze‡	Per 5-unit increase in BMI, RR of ever asthma: 1.08 (95% CI: 0.92-1.26) and RR of ever wheeze: 1.08 (95% CI: 1.02-1.14)
Reichman, 2008 (49)	United States	1,971	Pre-pregnancy BMI-categorical§	Asthma†	AOR for obese vs non-obese: 1.44 (95% CI: 1.12-1.86)
Scholtens, 2010 (51)	Netherlands	3,963	Pre-pregnancy weight/BMI – categorical and continuous‡	Asthma; wheeze‡	Asthma AOR for overweight vs. normal: 1.58 (95% CI: 1.10-2.26). 1-unit increase in BMI, asthma AOR: 1.05 (95% CI: 1.01-1.10)
Wright, 2013 (52)	Boston, MA	261	Pre-pregnancy BMI - categorical‡	Wheeze‡	AOR for obese vs. non-obese: 2.56 (95% CI: 0.99-6.32)

‡ Based on parent/self-report

† Based on parent report of physician diagnosis

§ Based on medical records/measured

* Not included in 2014 meta-analysis

AOR and ARR indicates adjusted odds ratio

Table 2.2: Studies Researching GWG with Risk of Asthma/Wheeze among Offspring

Author, year	Location	Sample Size	Main Exposure	Outcome(s) of interest	Results
Halonen, 2013 (31)	Tucson, AZ	430	Maternal BMI - categorical; GWG - categorical[§]	Asthma[†]	Asthma AOR for high tertile BMI comparted to low: 0.4 (95% CI: 0.2-1.1). Asthma AOR 3.4 (95% CI: 1.6-7.2) for high tertile GWG vs. low.
Harpsoe, 2012 (43)	Denmark	38,874	Maternal pre-pregnancy BMI - categorical; GWG - categorical[‡]	Asthma (ever)[†]; wheeze[‡]	Asthma AOR for obese vs. normal: 1.54 (95% CI: 1.34-1.76). Asthma AOR for ≥25kg GWG compared to 10-15kg GWG: 1.17 (95% CI: 1.02-1.33). Persistent wheeze AOR for obese vs. normal: 1.62 (95% CI: 1.26-2.09). Persistent wheeze AOR for 20-24kg GWG vs. 10-15kg: 0.96 (95% CI: 0.79-1.18)
Leermakers, 2013 (45)	Netherlands	4,656	Maternal pre-pregnancy BMI - categorical[‡]; GWG - continuous[‡]	Wheeze[‡]	AOR for obese vs. normal: 1.47 (95% CI: 1.12-1.95). 1-unit increase in GWG, AOR: 1.09 (95% CI: 1.04-1.14)
Oliveti, 1996 (46)	Cleveland, OH	256	GWG[§]	Asthma[§]	AOR for weight gain <20lbs (low GWG) among mothers with asthmatic children vs. non asthmatic children: 3.42 (95% CI 1.72-6.79)
Rusconi, 2007 (50)	Italy	15,609	GWG - categorical[‡]	Wheeze[‡]	AOR for weight gain >15kg among persistent wheezers vs. nonwheezers: 1.20 (95% CI: 0.98-1.48)

[‡] Based on parent/self-report

[†] Based on parent report of physician diagnosis

[§] Based on medical records/measured

AOR indicates adjusted odds ratio

CHAPTER 3

METHODS

3.1 Purpose & Objectives

Based on the literature review, this thesis is the first to use a multiethnic, nationally representative U.S. sample of children in early childhood to investigate the associations between GWG, maternal pre-pregnancy BMI, and offspring's risk of asthma. Research questions:

1. Is high GWG in mothers associated with increased risk of asthma in offspring after adjusting for various covariates (i.e. maternal age, child gender, smoking, BMI, etc.)?
2. Is high maternal BMI associated with increased risk of asthma in offspring after adjusting for various covariates (i.e. maternal age, child gender, smoking, GWG, etc.)?

3.2 Study Population

We used data from the Early Childhood Longitudinal Study Birth Cohort (ECLS-B), a longitudinal study conducted by the National Center for Education Statistics (NCES) designed to collect health, developmental, care and educational information from birth through kindergarten entry. A nationally representative sample of about 14,000 children born in the U.S. in 2001 were followed through kindergarten entry as part of the ECLS-B (54). The ECLS-B sampled births from birth certificates maintained by the

NCES. Data collection took place when the children were 9 months old, 2 years old, 4 years old/preschool and at kindergarten entry (54). The reduction in sample size at the fourth assessment occurred because the sample of participating children did not enter kindergarten at the same time. Approximately 75 percent of the sampled children entered kindergarten by the fourth assessment, the remaining 25 percent were followed up the following year in a fifth assessment(54). For our analysis we used data from the first three assessment periods (9 month, 2 year, and 4 years/preschool).

The University of South Carolina is licensed with the NCES for analysis of the ECLS-B restricted-use data.

3.3 Definitions and Measures

Outcome:

Data on childhood asthma were available across all assessments. In each interviewer-administered assessment, a guardian of the child was asked, "Since your child turned (x) years of age, has a doctor, nurse or other medical professional ever told you that your child has asthma?" Therefore, the answer option was dichotomous, Y/N.

Main exposures:

Data on maternal pre-pregnancy weight were available in the 9 months assessment. In the 9 months assessment, a trained interviewer asked the mother "How much did you weigh just before you became pregnant with child?" The mother was also asked to provide her height. These two questions were used to obtain the mother's pre-pregnancy BMI. Analyses treating BMI as a continuous and categorical variable were

performed. Maternal BMI was classified as follows: underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obese (≥30.0 kg/m^2) (55).

Total GWG was obtained from the birth certificate and was assessed in four different ways. First, GWG was treated continuously as reported on the birth certificate. Second, IOM weight gain adequacy was obtained by a ratio of the observed total GWG (from birth certificate) to the expected GWG that was then categorized by the percentage of IOM recommendations met (i.e. inadequate, adequate and excessive) based on pre-pregnancy BMI in Table 1.1 (56). The expected GWG used in the ratio was determined by the following equation: Expected GWG = recommended first-trimester total weight gain + (gestational age at weight measurement at or before delivery – 13 wk) × recommended rate of gain in second and third trimesters (56, 57) where recommended first trimester total weight gain is assumed to be 2kg in women of underweight and normal pre-pregnancy BMI and 1kg or .5kg in overweight or obese women, respectively. Recommended rate of weight gain in second and third trimesters is based on the assumption that underweight, normal, overweight and obese women are gaining weight at the rate of .51kg, .42kg, .28kg and .22kg, respectively (Table 1.1). Therefore, the expected weight gain for a normal BMI woman delivering at 40 weeks is 13.34kg = [2kg + (40-13) * .42kg]. Next, percentage of IOM weight gain recommendations met was classified as inadequate, adequate and excessive based on cutoffs of the range of total GWG for each pre-pregnancy BMI. As an example, normal weight women with a gestational age of 40 weeks have a recommended range of 11.5-16kg (Table 1.1), so 86% (11.5/13.34kg) to 120% is considered within the 'adequate' range and anything below or above received the 'inadequate' or 'excessive' labels, respectively. IOM weight gain

adequacy, which has been previously used and described, takes into account the fact that total GWG varies by gestational age (56, 57). Accounting for gestational age is important when measuring GWG so the relationship between GWG and asthma can be separated from that of gestational age, particularly because gestational age plays an important role in asthma risk. A meta-analysis found that childhood asthma outcomes were positively associated with children of gestational age younger than 32 weeks (58). Third, the weekly rate of GWG based on the second and third trimesters was used and was treated continuously. Fourth, categorical GWG was organized into 6 levels in order to better compare our results to current literature: <5kg, 5-9kg 10-15kg, 16-19kg, 20-24kg and ≥25kg where the first and last levels are considered 'extremes' and 10-15kg is the reference level (43).

Other Covariates:

Directed acyclic graphs (DAGs) are used to identify potential confounders and to determine which covariates need to be adjusted (see Figure 3.1). All covariates are one-time measurements taken from either the birth certificate or 9 months assessment. In addition to the common sociodemographic variables (e.g. race, SES, child gender, maternal age), the following covariates were selected based on existing literature: birth weight, parity, gestational age, WIC, and smoking in pregnancy.

3.4 Statistical Analyses:

As per NCES data-use guidelines all presented sample sizes are rounded to the nearest 50. Before any exclusions, the sample size was approximately n≈10,700. After

exclusions for twins, children with birth weight ≤500g, and gestational age <28 weeks or >45 weeks, the sample was reduced to n≈8,750. We then removed missing observations for all covariates, leaving an analytic sample of approximately n≈5,200.

All analyses were adjusted for the appropriate clustered sample design and weighted to account for oversampling of particular groups and attrition. Weighting schemes were for birth certificate and parent interview data. Weighted percentages, means and accompanying standard errors were used to obtain baseline descriptive characteristics from the total analytic sample. Bivariate analyses were performed on maternal exposure variables (i.e. GWG measures and pre-pregnancy BMI) by ever asthma diagnosis in the offspring. For the inferential analysis, logistic regression models via generalized estimating equation (GEE) were used to obtain odds ratios and 95% confidence intervals. Four models were created, one for each definition of GWG (i.e. total GWG, weekly rate in 2^{nd} and 3^{rd} trimesters, IOM Recommendations Met, and categorical GWG). Each of the four models included pre-pregnancy BMI and adjusted for all covariates presented in the DAG.

In traditional logistic regression each participant contributes only one binary outcome observation, but when using longitudinal data there are multiple binary observations over time. GEEs take the correlation between repeated measures in the same individual into account. In this study a compound symmetry correlation matrix was applied which assumes the correlation between the binary responses is the same..

As a sensitivity analysis, we applied multiple imputation methods to impute missing data for total GWG, rate of weight gain, and BMI. Ten multiply imputed datasets were created and were analyzed separately with the four GEE binomial models, after

which results were combined to obtain estimates of the imputation. We assumed that missing data were missing completely at random (MCAR). We additionally modeled offspring's asthma at 9 months and 4 years, to check for variations in associations at these two time points. Results are presented in Appendix A. SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used for our analyses.

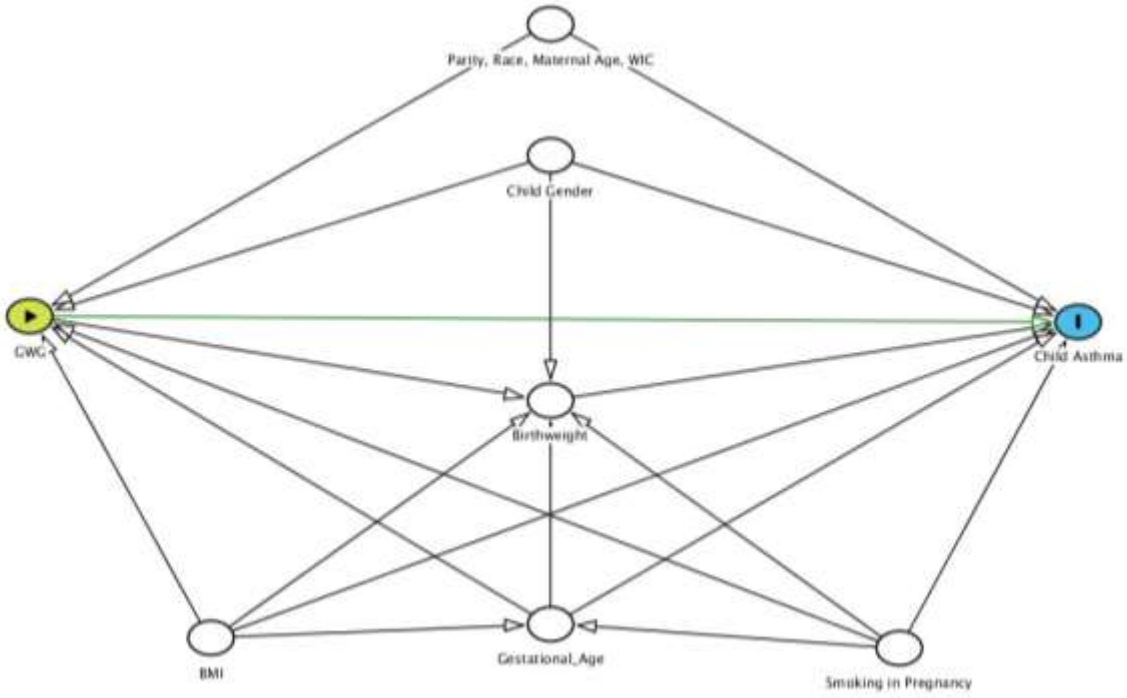

Figure 3.1: DAG representing the association between high GWG exposure and offspring's asthma

CHAPTER 4

RESULTS

Table 4.1 presents baseline descriptive statistics for the total sample. The sample included approximately 5,200 children, of whom half were male (50.4%), the majority had a normal birth weight (84.6%) and a mean gestational age of 38.8 weeks. At 9 months, almost half of the children's mothers had received WIC benefits in the past 12 months (48.2%) and the majority of mother's reported not smoking during pregnancy (87.8%).

On average, mothers in this population gained about 31 lbs. (SE=.2) throughout the entire pregnancy, and were gaining 1.07 lbs. per week in the second and third trimesters (Table 4.2). Half of the mothers exceeded IOM Recommendations for GWG (50.4%), while only 28.8% met adequate weight gain recommendations over the course of their pregnancy, and 20.8% gained inadequate weight during pregnancy. Over half of the mothers had a normal pre-pregnancy BMI (54.6%) and 40.4% were either overweight or obese.

Overall, approximately 17% of children were 'ever' diagnosed with asthma by age 4. Children with asthma were more likely to have mothers with overweight or obese pre-pregnancy BMIs compared with children without asthma (Table 4.2). Furthermore, children with asthma were more likely to have mothers with extreme GWG (i.e. <11 lbs. or ≥55 lbs.) as compared to children without asthma. No other significant differences

were found between maternal GWG among offspring with and without an asthma diagnosis in bivariate analyses (Table 4.2).

Gaining more than 25kg (≈55lbs.) during pregnancy was associated with increased risk of having a child with asthma as compared to mothers who gained between 10-15kg (OR: 1.71 95% CI: 1.14-2.55); this association fell just below significance after adjusting for all covariates (aOR: 1.51 95% CI: 0.98-2.32). Gaining less than 5kg (≈11 lbs.) as compared to gaining 10-15kg during pregnancy was associated with an increased risk of having a child with asthma (aOR: 1.55 95% CI: 1.03-2.33). In the adjusted models, continuous measures of GWG displayed a slightly positive, but statistically insignificant association with asthma in offspring from 9 months to 4 years of age (total GWG per 5 lbs OR: 1.01; 95% CI: 0.93-1.05) (1 lb weekly weight gain in 2nd and 3rd trimesters OR: 1.03 95% CI: 0.84-1.27). An inverse effect on overall asthma risk in offspring was observed among children of mothers with excessive GWG compared to children of mothers with adequate weight gain in the adjusted model (aOR: 0.84 95% CI: 0.67-1.06), however this finding was also statistically insignificant (Table 4.3).

Maternal pre-pregnancy obesity was independently associated with increased odds of having a child with asthma (Unadjusted OR: 1.80 95% CI: 1.40-2.31); whereas, maternal pre-pregnancy overweight fell just below significance (Unadjusted OR: 1.26 95% CI: 0.99-1.58). Children of mothers with an obese pre-pregnancy BMI had a statistically significant overall increased risk of asthma during the first 4 years of life, compared to children of mothers with a normal pre-pregnancy BMI, after adjusting for the covariates (Table 4.3). We found that the adjusted odds ratio (model 1) was 1.63 (95% CI: 1.25-2.11) for maternal obesity and 1.26 (95% CI: 0.99-1.60) for maternal

overweight. A secondary analysis with imputed data confirmed the results from the primary analysis (Table 4.4). Supporting findings are also presented in Appendix A, tables A.1 and A.2. Briefly, no significant odds ratios were observed between GWG and offspring's asthma at 9 months, but positive associations were detected between the extreme GWG categories and offspring's asthma at 4 years. Significant positive associations were observed between maternal overweight and offspring's asthma at 9 months, but were not significant at 4 years. Associations between maternal obesity and asthma at 9 months and then again at 4 years remained significant; although the magnitude of the association was slightly attenuated.

Table 4.1: Baseline Sample Characteristics, ECLS-B Cohort (n=5200)

Variables	**N**‡	**%**‡
Mother's race		
Non-Hispanic White	2600	64.7
Non-Hispanic Black	850	13.8
Hispanic	700	16.3
Non-Hispanic Others	1050	5.2
Maternal Age, years		
≤19	400	6.7
20-24	1350	23.8
25-29	1250	26.5
30-34	1300	25.6
≥35	900	17.4
Parity, # prior deliveries		
0	2200	41.7
1-2	2550	49.7
≥3	500	8.6
WIC participation in the past 12 months		
Yes	2700	48.2
No	2500	51.8
Smoking during pregnancy		
Yes	650	12.2
No	4550	87.8
Child's birth weight, g		
Low (<2500g)	900	5.4
Normal (2500-3999g)	3900	84.6
High (≥4000g)	400	9.9
Child gender		
Male	2650	50.4
Female	2600	49.6
		Mean (SE)‡
Maternal age, years		28.3 (0.2)
Child's gestational age at delivery, weeks		38.8 (0.0)

ECLS-B indicates the Early Childhood Longitudinal Study – Birth cohort.
WIC indicates the Supplemental Nutrition Program for Women, Infants, and Children a measure of socioeconomic status.
‡Analyses were weighted for birth certificate and 9 month data, sample sizes were rounded to nearest 50 per ECLS-B data-use agreements.

Table 4.2: Bivariate Associations of Maternal Gestational Weight Gain (GWG), Pre-pregnancy BMI by Ever Asthma Diagnosis in Offspring by Age 4, ECLS-B‡

Maternal Exposure	Total (n=5200)	Children Without Asthma (n=4300)	Children With Asthma (n=900)	p-value
Total GWG, lbs.	30.9 (0.2)	30.8 (0.2)	31.1 (0.7)	0.7157
Rate of weight gain, lbs./wk.	1.07 (0.0)	1.1 (0.0)	1.1 (0.0)	0.2187
IOM Recommendations Met, %				0.8650
Inadequate	20.8	20.6	21.4	
Adequate	28.8	28.8	29.1	
Excessive	50.4	50.6	49.5	
GWG, kg, %				0.0002
<5	5.8	5.4	8.0	
5-9	18.4	18.2	19.5	
10-15	43.2	43.7	40.4	
16-19	17.1	17.9	12.7	
20-24	11.3	11.0	13.1	
≥25	4.1	3.7	6.25	
Pre-pregnancy BMI, kg/m^2, %				0.0107
Underweight (<18.5)	5.0	4.9	5.5	
Normal (18.5-24.9)	54.6	55.7	48.6	
Overweight (25.0-29.9)	24.7	24.5	26.1	
Obese (≥30)	15.7	14.9	19.8	
Pre-pregnancy BMI, kg/m^2	25.0 (0.1)	24.8 (0.1)	25.7 (0.2)	0.0015

Reported as mean (SE) unless otherwise stated.
ECLS-B indicates Early Childhood Longitudinal Study – Birth cohort.
GWG indicates gestational weight gain.
BMI indicates body mass index.
IOM indicates Institute of Medicine.
Rate of weight gain indicates weekly rate of weight gained during 2nd and 3rd trimesters.
‡Analyses are weighted for birth certificate and 9 months data, sample sizes rounded to nearest 50 per ECLS-B data-use guidelines.
Chi-Square test for p-values

Table 4.3: Associations of Maternal Gestational Weight Gain (GWG), Pre-pregnancy BMI and Offspring's Asthma from GEE Binomial Models, ECLS-B (n=15,650)[‡]

Variables	Crude Model	Odds Ratio (95% CI)[†]			
		Model 1[§]	Model 2[*]	Model 3[^]	Model 4[Δ]
Total GWG, per 5 lbs increase	0.98 (0.93-1.02)	1.01 (0.96-1.05)	-	-	-
Rate of weight gain, lb	0.98 (0.78-1.22)	-	1.03 (0.84-1.27)	-	-
IOM Recommendations Met					
Inadequate	1.13 (0.86-1.47)	-	-	1.00 (0.75-1.30)	-
Adequate	Reference	-	-	Reference	-
Excessive	0.96 (0.77-1.19)	-	-	0.84 (0.67-1.06)	-
GWG, kg					
<5	2.20 (1.50-3.20)	-	-	-	1.55 (1.03-2.33)
5-9	1.25 (0.97-1.61)	-	-	-	1.05 (0.81-1.36)
10-15	Reference	-	-	-	Reference
16-19	0.79 (0.58-1.07)	-	-	-	0.83 (0.61-1.12)
20-24	1.14 (0.83-1.55)	-	-	-	1.15 (0.84-1.57)
≥25	1.71 (1.14-2.55)	-	-	-	1.51 (0.98-2.32)
Pre-pregnancy BMI					
Underweight (<18.5)	1.18 (0.80-1.74)	1.03 (0.69-1.52)	1.03 (0.69-1.52)	1.01 (0.69-1.51)	1.05 (0.71-1.57)
Normal (18.5-24.9)	Reference	Reference	Reference	Reference	Reference
Overweight (25.0-29.9)	1.26 (0.99-1.58)	1.26 (0.99-1.60)	1.26 (0.99-1.60)	1.32 (1.03-1.69)	1.23 (0.98-1.56)
Obese (≥30)	1.80 (1.40-2.31)	1.63 (1.25-2.11)	1.62 (1.25-2.09)	1.68 (1.29-2.19)	1.50 (1.15-1.95)

ECLS-B indicates Early Childhood Longitudinal Study – Birth cohort.
GEE indicates generalized estimating equations. GWG indicates gestational weight gain. BMI indicates body mass index in kg/m^2. IOM indicates Institute of Medicine.
Rate of weight gain indicates weekly rate of weight gained during 2nd and 3rd trimesters per lbs.
[‡]Analyses are weighted for birth certificate and parent interview data through preschool. Sample sizes are rounded to nearest 50 per ECLS-B data-use guidelines.
[†]Models (except Crude Model) are adjusted for: BMI, parity, mother's race, mother's age, WIC, smoking during pregnancy, birth weight, child gender, and gestational age.
[§]Model 1 uses total gestational weight gain as measure of GWG and categorical BMI.
[*]Model 2 uses rate of weight gain during 2nd and 3rd trimesters as measure of GWG and categorical BMI.
[^]Model 3 uses IOM Recommendations as measure of GWG and categorical BMI.
[Δ]Model 4 uses six categories, in kg, as measure of GWG and categorical BMI.

Table 4.4: Associations of Maternal Gestational Weight Gain (GWG), Pre-pregnancy BMI and Offspring's Asthma from Multiply Imputed Data, ECLS-B (n=20,300)[‡]

	Odds Ratio (95% CI)[†]			
Variables	**Model 1[§]**	**Model 2[*]**	**Model 3[^]**	**Model 4[Δ]**
Total GWG, 5lbs.	1.00 (0.97-1.04)	-	-	-
Rate of weight gain lbs./wk.	-	1.04 (0.86-1.25)	-	-
IOM Recommendations Met				
Inadequate	-	-	1.00 (0.77-1.29)	-
Adequate	-	-	Reference	-
Excessive	-	-	0.85 (0.67-1.07)	-
GWG, kg				
<5	-	-	-	1.30 (0.91-1.86)
5-9	-	-	-	1.06 (0.83-1.34)
10-15	-	-	-	Reference
16-19	-	-	-	0.85 (0.63-1.13)
20-24	-	-	-	1.15 (0.84-1.58)
≥25	-	-	-	1.39 (0.93-2.09)
Pre-Pregnancy BMI, kg/m^2				
Underweight (<18.5)	0.99 (0.69-1.41)	1.00 (0.70-1.44)	0.99 (0.69-1.41)	1.01 (0.70-1.44)
Normal (18.5-24.9)	Reference	Reference	Reference	Reference
Overweight (25.0-29.9)	1.19 (0.96-1.47)	1.21 (0.97-1.49)	1.24 (1.00-1.55)	1.18 (0.95-1.45)
Obese (≥30)	1.57 (1.24-1.98)	1.59 (1.26-2.01)	1.62 (1.27-2.06)	1.49 (1.17-1.89)

ECLS-B indicates Early Childhood Longitudinal Study – Birth Cohort.
GWG indicates gestational weight gain. BMI indicates body mass index. IOM indicates Institute of Medicine. Rate of weight gain indicates weekly rate of weight gained during 2nd and 3rd trimesters per lb.
[‡]Analyses are weighted for birth certificate and parent interview data through preschool. Sample sizes are rounded to nearest 50 per ECLS-B data-use guidelines.
[†]Models are adjusted for: BMI, parity, mother's race, mother's age, WIC, smoking during pregnancy, birth weight, child gender, and gestational age.
[§]Model 1 uses total gestational weight gain as measure of GWG and categorical BMI.
[*]Model 2 uses rate of weight gain during 2nd and 3rd trimesters as measure of GWG and categorical BMI.
[^]Model 3 uses IOM Recommendations as measure of GWG and categorical BMI.
[Δ]Model 4 uses six categories, in kg, as measure of GWG and categorical BMI.

CHAPTER 5

DISCUSSION

Using data from a large, nationally representative birth cohort, we longitudinally examined associations of asthma risk in early childhood with maternal GWG and pre-pregnancy BMI. Modest positive associations were found for pre-pregnancy obesity in asthma risk and there is evidence to support that pre-pregnancy overweight may also have a positive but lesser effect. Likewise, extreme levels of GWG (i.e. <5kg and ≥25kg were also associated with offspring's asthma. However, we found no significant associations between asthma in offspring and continuous maternal GWG measures, although the effect was in the positive direction. Furthermore, no significant difference in asthma status was observed for populations with excessive vs. adequate weight gain by the IOM 2009 Recommendations.

Our findings are mostly consistent with other studies presented in the literature review. Among the studies that examined pre-pregnancy BMI and offspring's asthma – rather than wheeze – positive associations of similar magnitude were observed (43, 49, 51, 53). In three large birth cohorts, pre-pregnancy obesity was associated with increased risk of asthma in childhood (43, 49, 53). In another birth cohort pre-pregnancy BMI, per unit increase, was positively associated with asthma (51). In that same study, maternal overweight (BMI of ≥25) was also associated with an increased risk of asthma in offspring (51). Furthermore, a recent meta-analysis concluded that children of obese

mothers had higher odds of asthma ever and current asthma compared to children of mothers with normal BMI; however, maternal pre-pregnancy overweight showed insignificant trends (39).

The literature on high maternal GWG and offspring's asthma is sparse, although positive associations were observed using categorical GWG (31, 43). One small birth cohort, comparing the high GWG tertile to the low 2 tertiles, found a positive association with asthma in the offspring, although this finding produced a wide confidence interval (31). Harpsoe et al. had a larger sample than the present study and observed significant associations with asthma at 7 years in GWG categories <5kg, 5-9kg, 20-24kg and ≥25kg in comparison to the reference level (10-15kg) with the highest increased risks associated with the two extreme GWG categories in a crude model (<5kg OR: 1.62 95% CI: 1.32-1.98; >25 kg OR: 1.27 95% CI: 1.12-1.45) (43). In our study population, the magnitude of associations were slightly greater but in the same direction, and only the two extreme GWG levels were significant in the crude model and GWG of <5kg remained significant in the adjusted model.

Overall, no significant associations were observed among the gestational weight gain definitions and asthma in this study. Several possible reasons may explain our results. First, BMI rather than GWG more directly influences childhood asthma outcomes. Second, the IOM recommendations are not sensitive to the effects of weight gain that occur at specific and/or crucial time points in fetal development (48). Third, the IOM weight gain adequacy ratio assumes that women of underweight and normal pre-pregnancy BMI gain 2kg in the first trimester, while overweight and obese women gain 1kg and .5kg, respectively. Therefore, if an obese woman gains more than .5kg in the first

trimester this will affect the adequacy ratio when taking gestational age into account; furthermore the estimates of average weight gain in the first trimester were based on the 1980s' weight gain patterns which may not be as accurate in the more recent ECLS-B cohort (59).

Strengths of the present study include the use of a large, multiethnic, nationally representative population based cohort that is generalizable to U.S. children born in 2001. Several covariates were available in the dataset and we were able to assess our outcome with a longitudinal design. GWG data were obtained from birth certificates and our inclusion of four definitions of GWG is unique to the current literature investigating intrauterine exposures and asthma outcomes in the offspring. To our knowledge, we are the first study to include the IOM weight gain recommendations in exploring the relationship between GWG and asthma. Even though we did not observe a significant association between meeting IOM recommendations and asthma in the offspring, we see the need for future studies to verify the relationship. The secondary analysis with imputed data for missing covariates duplicated our findings and strengthened our study further.

However, our study has several limitations. First, our outcome relied on parent-report of a physician's diagnosis of asthma in the child; however, other studies have shown parent-report of chronic illness in the child to be reliable (60, 61). Second, pre-pregnancy BMI was calculated using self-reported height and weight, which may have introduced bias as associations between pregnancy outcomes and self-reported pre-pregnancy BMI have been shown to be overestimated (62). Third, unmeasured confounders such as diet were not controlled in the analysis. For example, overweight and obese women are more likely to have lower levels of vitamin D (63). Maternal intake

of vitamin D during pregnancy is believed to influence the likelihood of asthma in the offspring (64).

The IOM report in 2009 called for investigation into the long-term effects of GWG on child health, including childhood asthma. The present study has addressed this need and has filled gaps in existing literature through the use of a large, nationally representative and ethnically diverse sample. Further investigation will be needed to confirm the relationship between GWG and asthma. These future studies may benefit from the use of multiple definitions of GWG to increase comparability among studies. However, improved measures of GWG are needed to better separate any potential effects of GWG on asthma from the effects of gestational age. As an example, a recent study used a predictive model that standardized the length of time over which GWG was calculated (65). Additionally, more studies will be needed to further explore the underlying biological mechanisms of intrauterine exposures on asthma outcomes in the child. For instance, the influence of GWG on asthma in the offspring may differ by the timing of weight gain; therefore, measuring weight gain at multiple time points during pregnancy may allow investigators to determine which patterns of weight gain may have the most impact, if any.

Overall, our findings have significant public health importance in terms of disease prevention and healthy lifestyle behaviors. Asthma is the most common chronic condition in childhood and creates a huge burden on the child's well-being as well as on the society. Childhood asthma has been associated with other chronic comorbid diseases, such as increased respiratory infections, cystic fibrosis, lung cancer, pneumonia, etc.; therefore, prevention of childhood asthma may eliminate these comorbidities (33).

Furthermore, maternal obesity is a risk factor for multiple pregnancy complications that impact both the mother and child, which in itself is a major public health issue. As a modifiable risk factor, pre-pregnancy obesity should be targeted in preconception programs that promote optimal preconception weight and help women achieve and maintain a healthy weight throughout pregnancy. While no single risk factor can entirely account for childhood asthma, such a prevention strategy may reduce early childhood asthma incidence in future generations. However, this will be a challenging task, particularly because almost half of U.S. pregnancies are unplanned.

5.1 Conclusions

Using data from a large nationally representative U.S. birth cohort, our longitudinal study supports the role of maternal pre-pregnancy obesity and to a lesser extent pre-pregnancy overweight in the etiology of early childhood asthma. GWG has also been hypothesized to partly explain childhood asthma, and we provided evidence to support this for the two extreme GWG categories. However, in this population excessive weight gain by the IOM definition does not appear to be a risk factor for asthma in the offspring and future studies are needed to confirm the relationship. Although a better understanding of the mechanisms behind early childhood asthma is needed, the present study provides evidence for the long-term effects that intrauterine exposures (i.e. obesity) may have on children. Efforts should be made to target pre-conception care in order to help women achieve and maintain a healthy pre-pregnancy weight and promote ideal weight gain during pregnancy.

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APPENDIX A: SUPPORTING ANALYSES

Table A.1: Associations of Maternal Gestational Weight Gain, Pre-pregnancy BMI and Offspring's Asthma at 9 months, ECLS-B (n=5,200)‡

	Odds Ratio (95% CI)†			
Variables	**Model 1§**	**Model 2***	**Model 3^**	**Model 4Δ**
Total GWG, per 5 lbs increase	0.98 (0.91-1.05)	-	-	-
Rate of weight gain, lb	-	0.94 (0.65-1.35)	-	-
IOM Recommendations Met				
Inadequate	-	-	1.19 (0.77-1.82)	-
Adequate	-	-	Reference	-
Excessive	-	-	0.83 (0.59-1.17)	-
GWG, kg				
<5	-	-	-	1.67 (0.88-3.16)
5-9	-	-	-	1.31 (0.87-1.98)
10-15	-	-	-	Reference
16-19	-	-	-	0.96 (0.57-1.61)
20-24	-	-	-	1.03 (0.57-1.87)
≥25	-	-	-	1.40 (0.61-3.21)
Pre-pregnancy BMI				
Underweight (<18.5)	0.85 (0.37-1.95)	0.84 (0.37-1.96)	0.83 (0.36-1.92)	0.86 (0.37-1.99)
Normal (18.5-24.9)	Reference	Reference	Reference	Reference
Overweight (25.0- 29.9)	1.80 (1.31-2.46)	1.81 (1.31-2.50)	1.95 (1.36-2.80)	1.76 (1.28-2.40)
Obese (≥30)	2.20 (1.58-3.07)	2.24 (1.60-3.12)	2.40 (1.68-3.44)	2.02 (1.45-2.83)

ECLS-B indicates Early Childhood Longitudinal Study – Birth cohort. GWG indicates gestational weight gain. BMI indicates body mass index in kg/m^2. IOM indicates Institute of Medicine. Rate of weight gain indicates weekly rate of weight gained during 2nd and 3rd trimesters per lbs.

‡Analyses are weighted for birth certificate and parent interview data through 9 month interview. Sample sizes are rounded to nearest 50 per ECLS-B data-use guidelines.

†Models adjusted for: BMI, parity, mother's race, mother's age, WIC, smoking during pregnancy, birth weight, child gender, and gestational age.

§Model 1 uses total gestational weight gain as measure of GWG and categorical BMI.

*Model 2 uses rate of weight gain during 2nd and 3rd trimesters as measure of GWG and categorical BMI.

[^]Model 3 uses IOM Recommendations as measure of GWG and categorical BMI.
[Δ]Model 4 uses six categories, in kg, as measure of GWG and categorical BMI.

Table A.2: Associations of Maternal Gestational Weight Gain, Pre-pregnancy BMI and Offspring's Asthma at 4 years, ECLS-B (n=5,200)[‡]

	Odds Ratio (95% CI)[†]			
Variables	**Model 1[§]**	**Model 2[*]**	**Model 3[^]**	**Model 4[Δ]**
Total GWG, per 5 lbs increase	1.02 (0.98-1.07)	-	-	-
Rate of weight gain, lb	-	1.13 (0.92-1.40)	-	-
IOM Recommendations Met				
Inadequate	-	-	0.96 (0.72-1.26)	-
Adequate	-	-	Reference	-
Excessive	-	-	0.84 (0.65-1.07)	-
GWG, kg				
<5	-	-	-	1.62 (1.08-2.42)
5-9	-	-	-	1.03 (0.77-1.39)
10-15	-	-	-	Reference
16-19	-	-	-	0.80 (0.61-1.05)
20-24	-	-	-	1.39 (1.01-1.89)
≥25	-	-	-	1.70 (1.00-2.89)
Pre-pregnancy BMI				
Underweight (<18.5)	0.94 (0.52-1.68)	0.94 (0.52-1.67)	0.93 (0.53-1.66)	0.97 (0.53-1.75)
Normal (18.5-24.9)	Reference	Reference	Reference	Reference
Overweight (25.0- 29.9)	1.04 (0.80-1.36)	1.03 (0.78-1.34)	1.07 (0.81-1.41)	1.01 (0.77-1.32)
Obese (≥30)	1.48 (1.13-1.95)	1.46 (1.11-1.94)	1.49 (1.13-1.96)	1.34 (1.01-1.79)

ECLS-B indicates Early Childhood Longitudinal Study – Birth cohort. GWG indicates gestational weight gain. BMI indicates body mass index in kg/m^2. IOM indicates Institute of Medicine. Rate of weight gain indicates weekly rate of weight gained during 2nd and 3rd trimesters per lbs.
[‡]Analyses are weighted for birth certificate and parent interview at the 4 year (preschool) assessment. Sample sizes are rounded to nearest 50 per ECLS-B data-use guidelines.
[†]Models adjusted for: BMI, parity, mother's race, mother's age, WIC, smoking during pregnancy, birth weight, child gender, and gestational age.
[§]Model 1 uses total gestational weight gain as measure of GWG and categorical BMI.
[*]Model 2 uses rate of weight gain during 2nd and 3rd trimesters as measure of GWG and categorical BMI.
[^]Model 3 uses IOM Recommendations as measure of GWG and categorical BMI.
[Δ]Model 4 uses six categories, in kg, as measure of GWG and categorical BMI.