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by

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DEDICATION

This work is dedicated to my family and friends in appreciation for their encouragement and support.

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ABSTRACT

Data from the 2001 Early Childhood Longitudinal Study – Birth Cohort were used to examine the association between maternal gestational weight gain (GWG) and the risk of obesity in the offspring, and the possible mediating role of birth weight. The Centers for Disease Control's growth 2000 reference charts and child's height and weight measured at age 4 or 5 years old were used to determine child's body mass index (BMI) Z-scores or obesity status ($\geq 95^{th}$ percentile). Multiple linear or logistic regression models were used to adjust for maternal age, race, education, smoking status and prepregnancy BMI. In this population (unweighted n=6400), 43.4% of mothers exceeded the 2009 Institute of Medicine (IOM) weight gain recommendation, while 30.2% gained weight below the recommendation. 17.6% of children were obese. We found that a 1 kg increase in the weekly rate of GWG in the second and third trimesters was associated with 0.37-unit increase in BMI Z-score (95% CI: 0.14-0.61), and 2.31 times higher odds of being obese (95% CI: 1.51-3.54). Gaining weight exceeding IOM recommendations was positively associated with a 0.14 unit increase child BMI Z-scores compared to gaining adequate GWG (95% CI: 0.01-0.26). In a subsample of offspring who were born full term (unweighted n=5400), a 5-kilogram increase in total GWG was also associated with 0.07 unit increase in BMI Z-scores (95% CI: 0.02-0.26) and 1.19 times the odds of being obese (95% CI: 1.08-1.30). Mediation analysis was conducted to decompose the total effects into direct and indirect effects. There were stronger direct effects than indirect effects. Birth weight is a moderate mediator between the association of maternal GWG

and offspring’s weight status. In conclusion, targeting maternal GWG is a promising approach to prevent childhood obesity.

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List of Abbreviations

BMI .... Body Mass Index

ECLS-B .... Early Childhood Longitudinal Study-Birth Cohort

GWG .... Gestational Weight Gain

IOM .... Institute of Medicine

LMP .... Last normal Menstrual Period

NDE .... Natural Direct Effects

NIE .... Natural Indirect Effects

CHAPTER 1

INTRODUCTION

Childhood obesity is a major public health issue in the United States. American children have experienced a large increase in the prevalence of obesity in last three decades.[1] Researchers have evaluated the association between gestational weight gain and offspring's adiposity. As illustrated in the next chapter, the findings from a majority of these studies[2-13] are consistent with a few exceptions.[14-17] The main limitations of this body of literature are as follows. Most of these studies used retrospective data or data from old cohorts when the prevalence of obesity was lower. Very few studies conducted in the United States used a nationally representative sample. Moreover, none of the published studies have used novel methods such as mediation analysis to help understand the mechanisms explaining this association.

The purpose of this thesis was to examine the association between gestational weight gain and the risk of obesity in children before age 5 using data from the Early Childhood Longitudinal Study – Birth Cohort (ECLS-B), a nationally representative study conducted in the United States. We also evaluated the role of birth weight as a potential mediator in the relationship between gestational weight gain and obesity in the offspring using mediation analysis. The results from this thesis will add to the existing literature by providing new insight about this association and the role of potential mediators. The findings from this study may also be used to design interventions to prevent childhood obesity by considering intrauterine environments.

CHAPTER 2

LITERATURE REVIEW

2.1 Childhood obesity: Trends and consequences

The prevalence of childhood obesity has increased in the past three decades in the United States (U.S.). [1]Data from National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of obesity in children aged 6 to 11 increased from 7% in 1980 to approximately 18% in 2010 in the US.[1] Likewise, the prevalence of obesity in adolescents aged 12-19 years increased from 5% to 18% during the same time interval[1]. The increase in the prevalence of obesity during this period was observed in both boys and girls. Furthermore, obesity levels among preschool children aged 2 to 5 have also increased from 5% to 12.1% between 1976-1980 and 2009-2010. [1]

The increase in the prevalence of obesity is a major public health concern because obesity in children has serious health consequences. Children and adolescents who are overweight are at increased risk for high blood pressure, high cholesterol, fatty liver disease, and chronic diseases such as type 2 diabetes and cardiovascular disease. [18] Other health problems associated with overweight in children include asthma and sleep apnea.[19] Obesity in children is also associated with an increased risk of adult obesity, disability in adulthood, and premature death. For instance, one study found that children who were obese as young as age 2 were more prone to be obese in adulthood.[19] Moreover, obesity also impacts children's social and psychological development including their academic performance. Overweight children are at a higher risk of low self-esteem and prejudice including bullying.[18]

The causes of childhood obesity are complex and attributable to multiple factors. In order to curtail this epidemic, researchers have been exploring genetic factors and modifiable social, behavioral, and environmental risk factors. The risk factors that have been investigated include rapid weight gain in preschool years[20-22], physical activity[23,24], diet/nutrition [25,26], increased food portion sizes[27,28], consumption of sugar sweetened beverages[29,30], breast feeding[31-33], infant birth weight[34,35], gestational diabetes[36-38], and maternal smoking during pregnancy.[39-41] Recently, increasing attention has been paid to intrauterine environment[42,43] and early life factors[44] on the development of childhood obesity. Mother's weight gain in pregnancy as an indicator of intrauterine nutritional environment may impact the birth size of the offspring.[11]

2.2 Potential mechanism between the association of gestational weight gain and childhood adiposity

Gestational weight gain (GWG) is a mother's weight gained during pregnancy starting at conception until delivery. Investigators have proposed potential mechanisms to explain how GWG is associated with childhood overweight and obesity. Mothers who easily gain weight due to genetic and lifestyle factors could possibly have children who gain weight due to their shared gene and lifestyle factors.[7] Studies conducted in animal studies show that mother's over-nutrition in pregnancy leads to enhanced fat mass, modified genes in the adipose tissue, and modifications in appetite centers of the brain in offspring.[45-47] Therefore, investigators hypothesize that excessive weight gain during pregnancy means over nutrition during pregnancy which may control the child's energy balance system through altering the developmental programming of appetite control and metabolism of adiposity in fetuses. Hence, children with modified systems might experience increased risk of childhood obesity.

Another explanation for the association of GWG and offspring overweight or obesity is one through insulin resistance. Higher GWG and hyperglycemia may stimulate β fetal pancreatic cells in excess leading to fetal hyperinsulinism.[7,35] The growth hormone insulin is associated with weakened glucose tolerance and obesity among adolescents.[7]

2.3 Maternal weight gain during pregnancy

In 2009, the Institute of Medicine (IOM) updated the recommended levels of weight gain during pregnancy according to mother's pre-pregnancy body mass index (BMI) categories (i.e., underweight, normal weight, overweight, and obese).[48] Table 2.1 illustrates the IOM recommended gestational weight gain guidelines for women with a singleton pregnancy.

Table 2.1 Institute of Medicine total weight gain and rate of weight gain for single pregnancy recommendations[32]

Prepregnancy weight category	Body Mass Index(BMI)[a]	Range of recommended total weight gain (kg)	Rates of weight gain in the second and third trimesters (kg) Mean (range in kg/week)
Underweight	Less than18.5	12.5-18	0.51 (0.44-0.58)
Normal weight	18.6-24.9	11.5-16	0.42 (0.35- 0.50)
Overweight	25.0- 29.9	7.0-11.5	0.28 (0.23- 0.33)
Obese	30 and more	5.0-9.0	0.22 (0.17- 0.27)

[a] BMI calculated as weight in kg divided by height in meters^2

[b] Calculations assume a 1.1–4.4 lb weight gain in the first trimester.

2.4 Epidemiological evidence on the association between maternal weight gain and obesity in children

There has been an increasing focus on maternal pre-pregnancy BMI and excessive weight gain during pregnancy as important risk factors for undesirable childhood and pregnancy complications.[16] More women of childbearing age are overweight or obese (body mass index (BMI) ≥30 kg/m^2). Of these women, almost 75% of African American women and 50% of non-Hispanic white in the US are overweight or obese (overweight and obesity combined BMI ≥25 kg/m^2).[4] In addition, 46% of pregnant women in the US gained more weight than the recommended IOM's weight gain during pregnancy guidelines.[49] Women who are overweight or obese before pregnancy are almost twice as likely to surpass the IOM recommended weight gain than women with normal weight.[50-52]

A number of studies have examined the association between maternal weight gain during pregnancy and offspring's adiposity. The following is a review of literature to describe the available evidence from published studies and how this current study will contribute to the existing literature.

A total of 24 studies were identified in this review**.** Of these, only three were cross-sectional studies[3,6,15] and twenty one were cohort studies,[2,4,5,7,9-12,14-17,53-60] three of which were retrospective cohort studies.[5,7,61] The majority of studies were conducted in populations in Europe and North America. Ten studies were conducted in USA[2,4,5,7,10-

[12,16,17,62] and three were conducted in Germany[6,13,15]. All of these studies explored the relationship between GWG and overweight in children. A total of 15 studies investigated this topic in children aged 9 years or younger.[2,7,9,10,12-14,16,17,53,54,56,61,62] Four studies investigated this topic in adolescents aged 16-18.[5,55,57,58] Two studies considered children and adolescents in Germany in the ages of 3-17.[6,15] The study conducted by Moreira focused on this effect in children between the ages of 6-12 years in Portugal.[3] One study by Schack-Nielsen et al. assessed the relationship from childhood through age 42.[59] This study evaluated data from the 1959-1961 prospective birth cohort in Denmark to determine the association between maternal weight gain in relation to the children's BMI and obesity from childhood through adulthood.[59]

These studies showed varying results. Some studies found that GWG exceeding the recommended weight gain increases the risk of obesity in children and adolescents.[2-12,14,17] The magnitude of the positive association ranges from weak (odds ratio: 1.2-1.5) to moderate (Odds ratio: 1.5-3.0). Oken et al. showed that the odds of having a child who is overweight are higher among women with adequate gestational weight gain (OR=3.77 ; 95% CI: 1.38, 10.27) or excessive weight gain (OR= 4.35; 95% CI: 1.69, 11.24) compared to women who have inadequate weight gain.[10] This study evaluated this association in children aged 3 years in the US from the Project Viva cohort study.[10] Wrotniek et al. found that the odds of a child being overweight at the age of 7 years old is 3% higher for each 1kg increase in gestational weight gain (adjusted OR= 1.03; 95% CI: 1.02, 1.05).[7] Also Wrotniek et al. analyzed data from the 1959 –1972 Collaborative Perinatal Project (CPP) and found that the odds of overweight was 48% higher in children whose mothers gained more than the IOM weight gain recommendations than in children whose mothers adhered to weight gain recommendations (adjusted OR= 1.48; 95% CI: 1.06, 2.06).[7] Branum et al. also evaluated data from CPP and found a positive relationship between prepregnancy BMI, GWG and the child's BMI z score at 4 years. Branum et al. [16] found that a 2 unit change in pre-pregnancy BMI was associated with a 0.09 unit increase in child BMI z scores (95% CI: 0.08, 0.11) and a 5kg increase in GWG was associated with a 0.07 unit increase in child BMI z-scores (95% CI: 0.04, 0.11) using generalized estimating equations.[16] In a study conducted in Portugal, Moreira et al. showed that children aged 9-16 years whose mothers gained greater than or equal to 16kg in pregnancy had higher odds of overweight or obesity than children whose mothers gained less than 9kg.[3]

Other studies have shown mixed results. Kleiser et al. in the KIGGS study showed that in overweight mothers, high gestational weight gain was not associated with obesity in children in Germany aged 3-10 year olds (OR= 0.71 95% CI: 0.3–1.6).[15] However, in this same study, children whose mothers were normal weight and gained ≥20kg during pregnancy were 2.8 times more likely to be overweight or obese (OR=2.81 95%CI: 1.6-5.0)[15]. The study by Hinkle did not find a significant relationship between GWG and child BMI z-scores in obese or underweight mothers.[17] However, the small sample size of mothers who are underweight before pregnancy is its limitation.[17] Also, Hinkle et al found that there is an association between excess GWG and a rise in child BMI z-scores in normal and overweight women.[17]

While many studies evaluated the association between GWG during pregnancy and overweight in the offspring, other studies evaluated timing of GWG and other measures of child obesity. One study by Margerison- Zilko assessed the relationship between GWG in trimesters and the child's BMI at 5 years old. They found that in the first trimester, for every kilogram increase in GWG, the odds of their offspring being overweight increased by 5% (OR for child overweight = 1.05; 95% CI = 1.02, 1.09).[2] However, there was no significant association between GWG in the second and third trimester and child overweight.[2] In another study Anderson et al. found that there was a small positive association between GWG and the children's BMI at age 7 years during the first and second but not the third trimester of pregnancy.[53] The study by Fraser considered the association of maternal prepregnancy weight and GWG with adiposity in the offspring which was measured by fat mass, BMI and waist circumference which had not been considered by other studies[55]. GWG within the first fourteen weeks of pregnancy was associated with higher adiposity in children. However, GWG during weeks 14-36 of pregnancy was only associated with adiposity in children whose mothers gained more than 500g/week.[55] There is an association between higher maternal pre-pregnancy weight and GWG during 36 weeks of pregnancy and larger offspring adiposity and undesirable cardiovascular risk factors.[55] Some studies assessed additional measurements of adiposity in children such as subscapular and triceps skinfold thicknesses.[10] Oken et al found that women with higher GWG had children with more adiposity at the age of 3 assessed by skinfold thicknesses (0.26mm).[10] Furthermore, one study by Crozier considered body composition measurements using dual-energy X-ray absorptiometry (DXA) in children.[14] The results from this study showed that children whose mothers had excessive weight gain had higher fat mass at birth (7% higher) and 6years (10% higher) old compared to children of mothers with adequate weight gain during pregnancy.[14]

In these studies, different criteria were used to define maternal obesity. Obesity in pregnancy is defined as body mass index (BMI) ≥ $30kg/m^2$ at the initial antenatal assessment. In some of the studies, maternal height and weight measurements were self reported [10,13,16,17,53-56,62] while in other studies these measurements were assessed by either trained health care workers[2,12,14,17,58,61] or trained research staff. [15,61] In general, self-report of weight status tends to be under reported or underestimated. Underestimations of gestational weight gain (particularly in women with the most weight gain) likely bias the estimates towards the null.[26] Maternal pregnancy BMI and total gestational weight gain in some studies were categorized using the 2009 IOM recommendations.[48] The BMI cut points as stated by the 2009 IOM recommendations are used to group women into underweight (BMI<18.5), normal weight (BMI:18.5-24.9), overweight (BMI:25.0-29.9), and obese categories(BMI≥30) before pregnancy.[48]

Furthermore, the researchers used different definitions for overweight and obesity in children. Five studies used the Centers for Disease Control (CDC) 2000 growth charts in the US to determine the children's BMI percentile.[4,10,12,16,62] According to the CDC growth charts, overweight is defined as a BMI more than or equal to the 85^{th} percentile but lower than the 95^{th} percentile for children of similar age and sex. On the other hand, obesity is defined as a BMI more than or equal to the 95^{th} percentile.[63] One study by Fuiano et al. conducted in Italy used Italian 2006 growth charts to define overweight and obesity in children.[61] The study by Beyerlin et al. used the European guidelines where overweight is defined as BMI greater than the 90^{th} reference percentile and obesity is defined as BMI greater than the 97^{th} reference percentile.[13]

2.5 Gaps in Literature

In brief, a majority of studies have found a positive association between GWG and the risk of childhood obesity[2-14,17] with exceptions that one study did not identify any significant association of GWG and fat mass in children aged 4.[14] One of the gaps in the literature is that most of these studies used data from old cohorts where behavioral habits and obesogenic environments may be different from individuals today and the obesity epidemic was not as severe as today. For example, Wrotniak et al. used data from the National Collaborative Perinatal Project, a cohort of children born in USA from 1959-1965.[7] This cohort was followed during pregnancy and birth until the child reached age 7.[7] The prevalence of obesity in children in the United States aged 6-11 from 1963 to 1965 was 4.2%, significantly lower than the prevalence of childhood obesity in this age group in 2008 (19.6%). [64] Children aged 2-5 years old were excluded in the surveys conducted in the 1960s.[64]

Another common limitation is that the results from some of these studies may not generalize to other populations because they used data from a specific geographic area.[5,9,10,12,13] We identified 19 studies that used data from a nationally representative population. [2-4,6-8,11,14-17,53-58,62] Of these, only seven were conducted in the United States.[2,4,7,11,16,17,54] However, some studies were questionable in terms of generalizing their findings to a large population. For example, Gillman et al and Oken et al analyzed data from the Project Viva cohort study who were mostly non-Hispanic white women with health insurance, fairly high levels of household income and education, and their children from Massachusetts. [9,10] Other studies had relatively small sample sizes.[56,65] The study by Fuiano et al. determined the prevalence of overweight and obesity among 632

Italian school children between the ages of 3 and 8.[65] In another study, Jedrychowski et al. assessed data from 312 children aged 5 years in Cracow, Poland to determine the impact of GWG among non-smoking mothers on body fatness between infancy and early childhood.[56] A small sample size may have impacted the statistical power of the study. If the sample size is very small, then they might not have enough power to detect a significant association between GWG and childhood obesity if one exists in a study. Hence, there is a greater likelihood of committing a Type II error when the sample size is smaller.

The fourth limitation is that some of these studies are retrospective studies[5,7,65] or cross-sectional studies.[3,6,15] Thus, misclassification is more likely to occur due to the long time period of recalling weight gain during pregnancy. Also, in retrospective studies, GWG might be more susceptible to misclassification error compared to the studies where GWG is based on data obtained from reviewing medical records.[5]

Finally, only a few studies assessed the mediating role of birth weight between the association of GWG and childhood adiposity.[7,17] Hinkle et al. used the measured variable path analysis (MVPA) to estimate direct and indirect effects of GWG on offspring's BMI z scores.[17] The authors considered birth weight as a mediating variable and determined birth weight for gestational age Z-scores that are sex specific.[17] Also Hinkle et al. assessed the direct effect of GWG on child BMI z scores separately for sub-groups based on prepregnancy BMI. The results from the MVPA model showed that there was a positive relationship between GWG and infant birth weight-for-gestational age in all pre-pregnancy BMI sub-groups. The direct effects of GWG on the child's BMI were significant among mothers with normal weight only.[17]

There was no significant association between GWG and child BMI Z-score in overweight or obese mothers after controlling for potential confounders.

Recent mediation analysis method developed by VanderWeele[66] et al. using causal inference framework provides an alternative method for reexamining the mediating role of birth weight in this association. This method has the advantage of partitioning the total effect of exposure on the risk of an outcome into two components: the direct and indirect effects.[67] This method also has the advantage of evaluating possible mediator-outcome confounding covariates which can't be done in the previous methods.[68] Furthermore, this method is useful to take possible exposure-mediator interactions into consideration. [69]

2.6 Motivation for current research

Although many studies have analyzed data to determine the associations between GWG and childhood overweight and obesity, more research is needed using data from recent prospective cohort studies conducted in the United States with racially diverse and nationally representative samples. Also, novel methods such as mediation analysis can be used to show insight about the role of birth weight in the association between GWG and obesity in the offspring. Better understanding of this association and related mediators will be useful for the design of future interventions in the prevention of childhood obesity.

2.7 Purpose and Objectives

The purpose of this study is to investigate the association between maternal weight gain during pregnancy and obesity in the offspring at ages 4 or 5 using a US national database. Below we will first present the study aims, followed by the respective study questions and hypotheses.

Aim 1: To determine the relationship between maternal weight gain during pregnancy and offspring's weight status at age 4 or 5years.

Question 1.1 Are there associations between GWG and the offspring's BMI z-scores and childhood obesity in preschool children after adjusting for mother's age, race/ethnicity, education, prepregnancy BMI, and maternal smoking?

Hypothesis 1.1: We hypothesize that the rate of GWG in the second and third trimester during pregnancy is positively associated with higher child BMI Z-scores and higher odds of childhood obesity at age 4-5 years.

Hypothesis 1.2: Gaining weight exceeding IOM recommendations (or excessive GWG) is positively associated with higher child BMI Z-scores and higher odds of childhood obesity at age 4-5 years

Hypothesis 1.3: High total GWG is positively associated with higher child BMI Z-scores and higher odds of childhood obesity in preschoolers.

Aim 2: To determine the role of birth weight as a potential mediator in the association between GWG and weight status of the offspring.

Question 2.1: Is birth weight a mediating variable for the association between GWG and offspring's weight status at age 4-5?

Hypothesis 2.1: Birth weight for gestational age Z-score is a mediating variable for the relationship between GWG measures and obesity in the offspring.

Question 2.2: What proportion of the increased weight status is directly the consequence of GWG through pathways other than birth weight?

Hypothesis 2.1: After partitioning the total effects of the GWG-childhood obesity association, there are still direct effects between GWG and offspring's weight measures.

Question 2.3: Is there an interaction between GWG and birth weight and their effects on offspring's weight status at age 4-5?

Hypothesis 2.3: The effect of GWG on offspring's weight status at ages 4 or 5 might be modified by birth weight.

CHAPTER 3

METHODS

3.1 Study Population and Setting

The Early Childhood Longitudinal Study–Birth Cohort (ECLS-B) is a longitudinal study that consists of a nationally representative cohort of children born in the United States in 2001. The ECLS-B study is sponsored by the US Department of Education in cooperation with many other agencies. This birth cohort study mainly concentrates on the children's experiences in education from birth to kindergarten.

The ECLS-B cohort was chosen from the 2001 U.S. birth certificates from the National Center for Health Statistics Vital Statistics System. Children whose mothers were below the age of 15 were excluded. Also, infants who died or were adopted before the first period of data collection were excluded (approximately when participants were 9 months old). ECLS-B also oversampled American Indian and Asian/Pacific Islanders to increase the sample's diversity. A total of 10,700 children from diverse racial backgrounds participated in the study with a weighted response rate of 74.1%. In addition, twins and low birth weight babies were oversampled.

3.2 ECLS-B Data Collection Methods

In the ECLS-B study, children were measured 5 times, that is, approximately at the ages of 9 months (2001-2002 n= 10,700), 2 years (2003-2004 n= 9,850), 4 years (2005-2006 n= 10,700), 5 years (2006-2007 n= 6,950) and 6 years (2007-2008 n=1,900).

The sample sizes are rounded off to the nearest 50 in accordance to the requirements of the Department of Education. Informed consents were obtained from parents or childcare providers before the study began.

Table 3.1 summarizes the information collected at each wave. According to the ECLS-B study design, the data were collected from parents or guardians who were knowledgeable about the child, childcare providers and teachers through child assessments conducted at their schools and homes. Parent interviews were carried out during a home visit with a member of the household most well informed about the child's care and education. The child's biological mother was the most preferred respondent for the parent instruments if available, though the child's biological father (2nd preference), another parent or guardian (3rd preference) or household member (4th preference) such as a step parent, foster parent, grandparent, including relative or other non-relative guardians were used. Data were gathered by computer-assisted personal interview (CAPI) instruments and questionnaires where the interviewer asked the parents questions and documented the responses in a computer. These parent interviews were conducted predominantly in English and interpreters were used for those families who spoke languages other than English or Spanish. Also, parents filled in a self-administered questionnaire (PSAQ) which included questions concerning household income, use of child care, family structure, and support. In the ECLS-B study, data were also collected from children's birth certificate records and through the research staff's direct assessment and observation of the children's conduct and home environment during home visit.

Table 3.1 Data sources and instruments used in each wave in the ECLS-B study

9 month	2 years	Preschool

Child assessments	Child assessments	Child assessments
Parent interview (CAPI)	Parent interview (CAPI)	Parent interview (CAPI)
Parent self-administered Interview	Parent self-administered Interview	Parent self-administered Interview
Parent-child video	Parent-child video	Parent-child video
Resident father questionnaire	Resident father questionnaire	Resident father questionnaire
Non Resident father questionnaire	Non Resident father questionnaire	Parent-child video
Parent-child video	Parent-child video	Child care provider telephone interview for early care and education
Child observations and interviewer Comments questionnaire	Child observations and interviewer Comments questionnaire	Child care observation
Birth certificate	Child care provider telephone interview for early care and education	
	Child care observation	

Source: U.S. Department of Education, National Center for Education Statistics, Early Childhood Longitudinal Study, Birth Cohort (ECLS-B) User's Manual

3.3 Outcome Variables

The outcome measure is child's BMI status. Each child's height and weight measurements were collected using a standard protocol at each time point.[70] Weight (in kilograms) and height (in centimeters) were measured with a digital bathroom scale and a SECA portable stadiometer, respectively.[70] Height and weight were measured twice bytrained staff and the average of these two measures was used. The child BMI Z- scores for age and sex were determined using the CDC's 2000 Growth Charts.[71]

3.4 Exposure Variables

The main exposure is gestational weight gain (GWG). Information about GWG is found in the child's birth certificate and mother's report obtained when the child was 9 months. For this analysis, we mainly used GWG data found in the birth certificate (81%). When it was missing, we used information from the maternal report. Prepregnancy BMI was calculated as weight (kg) before pregnancy divided by height^2 (m).

To better assess the associations between GWG and offspring's adiposity at 4 or 5 years old, we measured GWG in three different ways. First, we determined the rate of GWG in the last two trimesters. The recommended mean rates of weight gain during the last two trimesters of pregnancy w ere based on the 2009 IOM guidelines. The assumption is that during the first trimester (≤13 weeks), the expected GWG (in kg) vary by prepregnancy BMI. Women with BMI<25 gain on average 2kg, while women who are overweight (BMI: 25-29.9) gain 1kg and those who are obese (BMI≥30) gain 0.5kg. We calculated the rate of GWG in the two last using the formula:

Rate of GWG in the second and third trimesters= (total weight gain – expected first trimester GWG) / (child's gestational age -13)

Second, considering that total weight gain would be smaller for women with shorter duration of pregnancy, we also used another measure which considered the gestational age at delivery. This measure was named as the adequacy ratio of GWG and has also been used in a previous study.[72] The recommended mean and ranges of weekly rate of weight gain during the last two trimesters of pregnancy based on the 2009 IOM guidelines were used to determine the expected GWG. We made the same assumption above the expected GWG (in kg) in the first trimester as mentioned above. We used the equation below to calculate mean expected GWG after the first trimester as follows: Mean expected GWG = assumed first-trimester total weight gain + (gestational age at delivery – 13weeks) * recommended rate of weight gain in the second and third trimesters.[72]

Using IOM recommended range for the rate of weekly weight gain for each prepregnancy BMI group,[48] we computed the lower and upper recommended GWGs for each gestational age. Then we calculated the bound of adequacy ratio by dividing the lower and upper recommended amount of GWGs by the mean expected GWG: (0.79-1.14) for underweight, for normal weight, (0.86-1.2) for overweight (0.81-1.34), and (0.78-1.41) for women who are obese.[73] We further calculated each woman's adequacy ratio as the observed GWG divided by mean expected GWG based on her gestational age at delivery. Compared to the bound of adequacy ratio by IOM's guidelines, each participant was classified as inadequate if her own ratio was lower than the lower cutoff of recommendations, being adequate if it was within the range of adequacy, or being excessive if it was more than the upper cutoff of the recommendations.[73] For our third exposure, we also used total weight gain as a measure by itself but we restricted this analysis to those who had full-term babies (≥ 37 weeks) considering the relationship between total GWG and pregnancy duration.

3.5 Mediating variable

Birth weight is one of the important variables to be considered in the association between GWG and childhood obesity. Prior studies have found a positive linear association between birth weight and later childhood obesity, which may persist through adulthood.[74-76] Some studies have found J- or U-shaped associations where there is also a relationship between low birth weight and overweight and obesity.[77,78] Furthermore, GWG is also associated with increased birth weight.[79-81] The impact of GWG on childhood obesity might be mediated through birth weight. It is important to evaluate whether the association between GWG and childhood obesity is mediated through birth weight and whether birth weight would interact with GWG while impacting childhood obesity. Performing mediation analysis without considering the interaction between the exposure and mediator may result in biased estimates. [82]

Using birth weight and gestational age obtained from the child's birth certificate, we calculated sex-specific birth-weight for-gestational-age Z-scores according to the US national reference.[83] In this calculation, we mainly used clinical estimates of gestation data found in birth certificates (83.9%) and if missing, we used last normal menstrual period (LMP) based gestational age from birth certificates. The correlation between the two gestational age measures was high (0.89) for those with gestational age data from both clinical estimates of gestation and LMP-based gestational ages from birth certificate

3.6. Confounders

The causes of overweight and obesity are multidimensional. A number of potential confounders of the association have been identified from previous literature. A directed acyclic graph (DAG) was used to guide the selection of confounders. As shown in Figure 3.1, the variables such as maternal race/ethnicity, age, education,maternal pre pregnancy BMI, and smoking during pregnancy were identified as confounders. These variables were adjusted for in our analyses.

Previous studies have shown that racial/ethnic differences occur in pregnancy-associated risk factors for childhood obesity. Some studies have evaluated maternal race/ethnicity as a potential confounder.[2,9-12,16,54] In one prospective study which was based on a total of 1,343 White, 355 non-Hispanic black, and 128 Hispanic pairs of mothers and children in the Project Viva study, the authors found that Hispanic and non-Hispanic black women were more likely to enter pregnancy being overweight or obese compared to Caucasian women.[84] Thus maternal race/ethnicity was included in the model. Maternal race/ethnicity was grouped as White, non-Hispanic; Black, non-Hispanic; Hispanic; and other non-Hispanic races that include Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native and those in more than one race.

Maternal smoking during pregnancy has also been recognized as a potential risk factor childhood overweight and obesity. Several studies have found that there is a positive association between smoking during pregnancy and childhood obesity. [39-41,52,56] In a meta-analysis , Oken et al. found that the odds of being overweight in children were 50% higher if their mothers smoked during pregnancy compared with those whose mothers did not smoke (pooled adjusted odds ratio (OR) 1.50, 95% CI: 1.36, 1.65). [21] Women who stop smoking during pregnancy tend to have higher GWG than either persistent smokers or non smokers.[85,86] [87,88] Thus, smoking was included in the model as a potential confounder for this analysis.

Maternal smoking during pregnancy in the last 3months of pregnancy was assessed during the 9-month interview and was categorized as yes or no.

Other important maternal characteristics considered as confounders include mother's age at baseline, education and maternal pre-pregnancy BMI. Maternal age at baseline was categorized as 15-19, 20-24, 25-29, 30-34 and ≥ 35. Maternal education was categorized as ≤ 12th grade, high school diploma or equivalent, vocational/technical or some college and bachelor's degree or higher. Maternal pre-pregnancy BMI was used in all models as a continuous variable to control for residual confounding.

3.6.1 Variable Table

Table 3.2 shows all the variables in the analyses, its sources in ECLS, and how these variables were coded

Table 3.2 List of variables included in the statistical analyses

Variable Name Description	Source	Type	Levels
Gestational Age	Birth certificate record	Continuous	
Birth Weight	Birth certificate record	Continuous	
Gestational Weight Gain	Birth certificate record & 9-mo parent interview	Continuous	
Maternal Race/ethnicity	9-mo parent interview	Categorical	4
Maternal Age	9-mo parent interview	Categorical	4
Maternal Education	9-mo parent interview	Categorical	4

Pre-pregnancy BMI	9-mo parent interview	Continuous	
Smoking in the Last 3 Months of Pregnancy	9-mo parent interview	Categorical	2

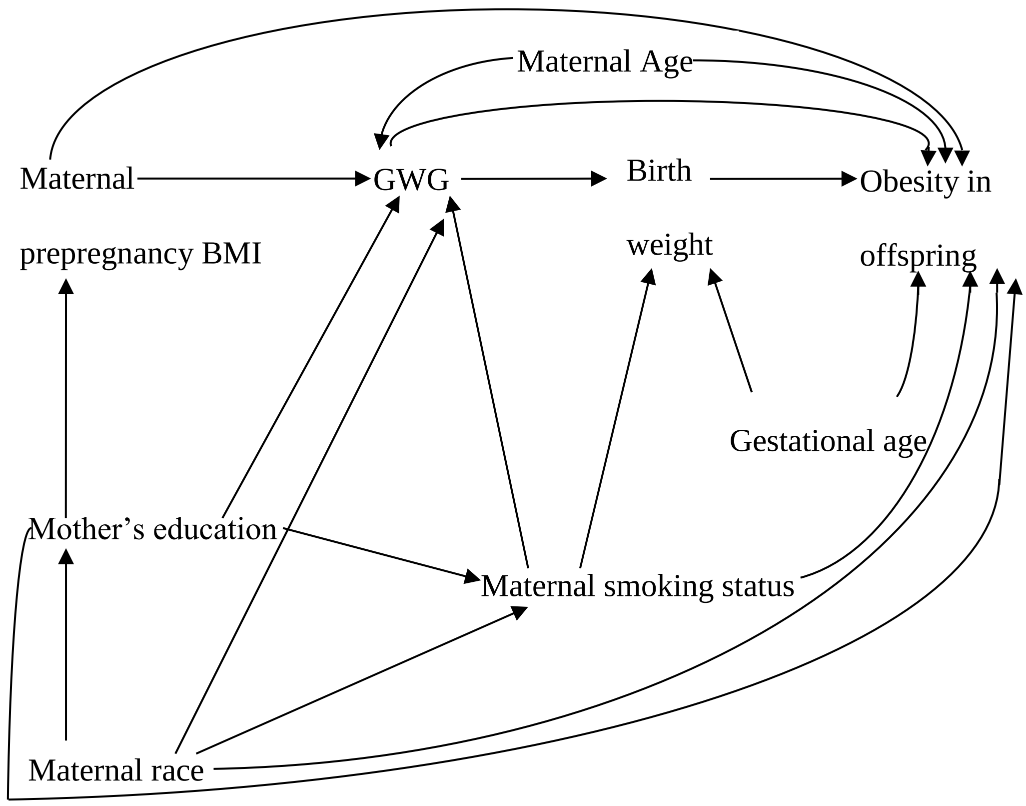

Figure 3.1 Directed acyclic graph used to select potential confounders.

3.7 Mediation Analysis

Increasing attention has been paid to new methods for mediation analysis and approaches to divide the total effect of an exposure on the likelihood of an outcome into direct and indirect effects.[69] An indirect effect occurs through a mediator whereas a direct effect is one that occurs on the outcome or as a result of other pathways.[69] Mediation analysis has a number of unmeasured confounding assumptions that need to be met.[67] One of the assumptions is that the group of covariates that are adjusted are able to control for confounding of the exposure-outcome, mediator-outcome and exposure–mediator associations.[67] Total effects can also be partitioned into direct, indirect and interactive effects.[69] The two-way decomposition is easier to perform, making it possible for one toevaluate the proportion of the total indirect effect that is due to a mediated interaction compared to a pure indirect effect.[69] Natural direct effects occur on the outcome through other pathways whereas indirect effects occur through a mediator.[67] The role of interaction is more distinct in mediation analysis. [69]

3.8 Statistical Analysis

Statistical analyses were conducted using SAS version 9.3 (SAS Institute Cary, NC) and SAS-Callable SUDAAN software release 11 taking the complex survey design into consideration. Also sampling weights were included to account for unequal probabilities in sampling and responses. We considered p-values less than 0.05 to be statistically significant. We used a SAS macro to evaluate mediation analysis.[82]

There were 10,700 infants enrolled in the ECLS-B study. Considering ECLS-B's response rates at each wave as well as the timing of each wave, we decided to focus on offspring's weight status among preschool children, which included those who were interviewed at Wave 3 or Wave 4. We kept all children who were interviewed in both Wave 4 and Wave 3 (n=7,000) and had non-missing values for child's BMI covariates. Those who were only interviewed in Wave 3 (n=2,000) but not in Wave 4 were also included in our analysis. The initial sample size of included participants was 8,700. Of these, we excluded infants with gestational age of less than 28 weeks (n=460) and those born after 45 weeks of gestation (n=32). Also, 157 infants with a birth weight less than 500g were excluded. In addition, twins and triplets were excluded (n=1283). We also excluded participants with missing information on maternal race (n=9), smoking in the last three months of pregnancy (n=1) and 395 participants with missing information on height, weight and gestational weight gain. Therefore, our final analytical sample was limited to 6,400 participants who met the inclusion criteria, that is, singleton births without missing data for maternal and child characteristics to be considered in our analysis. The sample size was rounded off to the nearest 50 in accordance to the requirements of the US National Center for Education Statistics.

For aim 1 (to determine the association between GWG and the risk of obesity in the offspring among preschool-aged children), we calculated descriptive statistics for the demographic variables and exposure variables. The weighted means and standard deviations were computed for continuous variables, while frequency distributions (percentages) were calculated for categorical variables.

Multiple linear regression models were used to evaluate the association between GWG and offspring's BMI Z-scores while adjusting for potential confounders. For the dichotomous outcomes (i.e., being obese: BMI$\geq$ 95th percentile), multiple logistic regression models were used. For all of these models, we ran two sequential models to evaluate this association. In model 1, the crude association was presented. In model 2, we added maternal characteristics such as race/ethnicity, age, education, pre-pregnancy BMI, and mother's smoking status in the last three months of pregnancy. We also evaluated for the interaction between GWG and prepregancy BMI in all measures of GWG.

For Aim 2, mediation analysis was conducted to examine the role of birth weight as a potential mediator in the association between GWG and obesity in the offspring. A logistic regression model was used to estimate the causal effect when the outcome was binary (i.e., being obese: BMI$\geq$ 95th percentile) [82] Linear regression models were used for the continuous outcomes (i.e., child BMI Z-scores. We adjusted for maternal characteristics (maternal care/ethnicity, age, education, pre-pregnancy BMI and smoking during the last three months of pregnancy). Child's birth-weight-for- gestational age Z-scores were treated as the mediator. Standard errors and confidence intervals were obtained using the delta method.[82] We also evaluated the presence of an interaction between the exposure (GWG) and the mediator (birth weight). Estimates for the total effect, controlled direct effect, natural indirect effect were obtained for continuous outcomes such as BMI z-scores. The total effects, direct effects and indirect effects were presented on a risk ratio scale for binary outcomes.[82] The proportion mediated was calculated as (Natural indirect effect (NIE) / total effect) for continuous outcomes (BMI z-scores).[89] For binary outcomes, the proportion mediated was calculated using the formula:

$$\text{Proportion Mediated}^{69} = \frac{\text{Natural Direct Effects x (Natural Indirect Effect – 1)}}{\text{(Natural Direct Effects x Natural Indirect Effect – 1)}}$$

CHAPTER 4

RESULTS

4.1 Sample Characteristics of mothers and children in ECLS-B study

Table 4.1 describes the study population's characteristics. The majority of women in the study population were non-Hispanic white (60.3%), had at least a high school diploma (83.0%), an average age of 28years, did not smoke in the last three months of pregnancy (89.0%), and had infants born full term with an average gestational age of 38.8 weeks. Our participants had a mean (standard deviation) pre-pregnancy BMI of 24 kg/m^2 (0.1). The mean total gestational weight gain was 12.9kg and the weekly rate of GWG in the second and third trimesters was 0.4 ± 0.01 kg (95% CI: 0.43-0.46) per week. In addition, 43.4% of the mothers exceeded the 2009 IOM weight gain recommendations while nearly one third of the women gained inadequate weight (30.2%).

The mean age of the child at the follow-up time was 61.3 months and 17.6% were obese. Overall, similar characteristics were observed in the subsample of offspring who were born full term (Table 4.1).

4.2. Adequacy of gestational weight gain

Table 4.2 shows the status of adequacy of weight gain during pregnancy according to the 2009 IOM guidelines in our study population. Overall, 26.4% of the women gained weight within the IOM recommendations while 43.4% exceeded the recommendations. There were significant variations in the proportion of adequacy ofGWG by race/ ethnicity, prepregnancy BMI and gestational age. 46.8% of non-

Hispanic White, 44.3 % of non-Hispanic Black, 26.9 % Hispanic and 31.2% other non-Hispanic women had excessive weight gain. Among mothers who were underweight before pregnancy, 42.5% gained inadequate weight while 34.0% gained excessive GWG. Among women who had normal weight prior before pregnancy, 37% had inadequate GWG while 33.8% had excessive GWG. More than half of the women who were overweight before pregnancy (57%) gained excessive GWG while 18.6% gained inadequate weight. Among women who were obese before pregnancy, 57.8% gained excessive GWG while 21.2% gained inadequate weight. Of the children who were born full term, 43.4% were born to mothers with excessive GWG while 30% were born to mothers with inadequate weight gain. All of the children born preterm were born to mothers with inadequate GWG. The prevalence of obesity in the offspring was higher among children of mothers with excessive GWG (51.3%) compared to children of mothers with adequate weight gain (22.9%). We did not find significant variations in the proportion of adequacy of GWG by maternal age, education and smoking status.

4.3. Association between rate of GWG and child's weight status before age 5

Table 4.3 and Table 4.4 present results of the multivariable analysis to evaluate the association between the rate of GWG in the second and third trimesters and child's BMI z scores or child obesity status at age 4 or 5, respectively. Analyses showed that each 1kg increase in GWG in the second and third trimester was associated with 0.37-unit increase in child BMI Z-score (95% CI: 0.34-0.61) and 2.31 times higher odds of being obese (95% CI: 1.51-3.24).Maternal racial/ethnic group had a significant effect on the child's obesity status. Children born to women in the minority groups were more likely to be obese compared to children born to white women. The odds of obesity was

48% higher among preschoolers of mothers who were Hispanic compared to children born to white mothers (OR=1.84, 95% CI 1.37-2.47) (Table 4.4). Moreover, there was an increased risk of obesity in preschoolers among children born to mothers with a high school diploma/equivalent than those born to mothers with a bachelor's degree or higher education (OR=1.53, 95% CI 1.10-2.13). (Table 4.4)

4.4. Association between adequacy of GWG and child's weight status before age 5

Table 4.5 and Table 4.6 display the results of the multivariable analysis to examine the association between adequacy of GWG per 2009 IOM recommendations and body weight status in children at age 5. Children born to mothers with excessive GWG had higher BMI z-scores (BMI Z-score: 0.14, 95% CI 0.01-0.26) compared to children born to mothers with adequate GWG. No significant association was observed between inadequate GWG and child BMI Z-scores (-0.03, 95% CI: -0.16-0.11) and odds of obesity (OR=0.94, 95% CI: 0.67-1.33) after adjusting for maternal characteristics. (Table 4.5 and Table 4.6) Also, excessive GWG was not significantly associated with odds of obesity in the offspring. (OR=1.32, 95% CI 0.98-1.77) (Table 4.6)

4.5. Association between total GWG and child's weight status before age 5 among children who were delivered full term

The association between total GWG and child obesity status in a subsample of offspring who were born full term were reported in Table 4.7 and Table 4.8. We foundthat a 5-kilogram increase in total GWG was associated with 0.07 unit increase in BMI Z-scores (95% CI: 0.02-0.12) and 1.19 times the odds of being obese (95% CI: 1.08-1.30). Similar to the other two measures of GWG, maternal race/ethnicity was still a significant predictor of weight status in children after controlling for potential confounders. However in this association, only children of mothers who were Hispanic had higher child BMI Z-scores (0.23, 95% CI: 0.08-0.38) and higher odds of being obese (OR=1.92, 95% CI 1.37-2.69) compared to those whose mothers were white. (Table 4.8)

4.6. Birth weight as a mediator between GWG and offspring's weight status at age 4 or 5.

Table 4.10 displays the results of mediation analysis where the total effects of the association between GWG and BMI z-scores in the offspring were partitioned into direct and indirect effects mediated through gestational-for age-z-scores after adjusting for mother's age, race/ethnicity, education, prepregnancy BMI, and maternal smoking. We did not observe a significant interaction between GWG and birth weight-for gestational-age z-scores. Birth weight for gestational age Z-score was a significant mediating variable for the association between the rate of gestational weight gain in the second and third trimesters and child BMI z-scores. Overall, a little more than one third of the proportion of total effects of GWG was mediated through child's birth weight. The proportion of the total effect of the rate of GWG in the second and third trimester on the child's BMI z-scores mediated through birth weight was 35.6%. In the association between adequacy of GWG and BMI z-scores in the offspring, the proportion of BMI z-scores mediated through birth weight was among 37.2% among children born to mothers with inadequate GWG compared to those born to mothers with adequate GWG. Also, in this association, the proportion mediated through birth weight was 37.4% among those with mothers who had excessive GWG compared to those whose mothers had adequate weight gain. (Table 4.10) The proportion of increased BMI z-scores mediated through total GWG was 35.7%. There were stronger direct effects than indirect effects for the relationship between GWG measures and offspring weight status.

Table 4.11 displays the results of mediation analysis where the total effects of the association between GWG and the risk of obesity in the offspring were partitioned into direct and indirect effects mediated through gestational-for age-z-scores after adjusting for mother's age, race/ethnicity, education, pre pregnancy BMI, and maternal smoking. The interaction between GWG and birth weight-for-gestational-age z-scores was not statistically significant. Birth weight for gestational age Z-score was a mediating variable for the relationship between GWG measures and obesity in the offspring. In the association between the rate of GWG in the second and third trimesters and the risk of obesity in the offspring, the proportion of the total effect on the risk of obesity in preschoolers mediated through birth weight was 24.7%. In the association between adequacy of GWG and the risk of obesity in the offspring, the proportion mediated through birth weight was 37.2% in children born to mothers with inadequate GWG compared to those born to mothers with adequate GWG. Also, in this association, the proportion of obesity in the offspring mediated through birth weight was 35.7 % among those with mothers who had excessive GWG compared to those whose mothers had adequate weight gain. We also found that in the association between total GWG and the risk of obesity, the proportion of mediated through birth weight-for gestational- age z-scores was 20.8%. (Table 4.11)

Table 4.1: Sample characteristics of mothers and children Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2007

Characteristics	**All mother-child pairs**	**Subsample of mothers and their offspring born full term (≥37 weeks gestation age)**
Study population (n)[1]	6400	5400
Maternal Characteristics		
Race/Ethnicity, %[2]		
White, Non Hispanic	60.3	61.0
Black, Non Hispanic	13.1	12.7
Hispanic	20.8	20.6
Other, Non Hispanic	5.7	5.7
Maternal Age (%)		
15-19	6.7	6.5
20-24	22.9	22.8
25-29	26.7	27.1
30-34	25.8	25.9
≥35	17.9	17.7
Maternal Education (%)		
≤ 12th grade	17.0	16.6
High School Diploma/Equivalent	27.0	26.8

Table 4.1: Sample characteristics of mothers and children Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2007

Characteristic	**All mother-child**	**Subsample of mothers and their offspring born full term (≥37 weeks gestation age)**
Vocational /Technical or Some College	28.9	29.1
Bachelor's Degree or Higher	27.1	27.5
Gestational weight gain (kg)	12.9 ± 0.2	13.1 ± 0.2
Pre-pregnancy BMI	24.9± 0.1	24.9± 0.1
Weekly rate of gestational weight gain in second and third trimester (kg/wk)	0.4 ± 0.01	0.4 ±0.01
Adequacy of gestational weight gain per 2009 Institute Of Medicine guidelines (%)		
Inadequate	30.2	30.0
Adequate	26.4	26.7
Excessive	43.4	43.3

Table 4.1: Sample characteristics of mothers and children Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2007

Characteristic	**All mother-child**	**Subsample of mothers and their offspring born full term (≥37 weeks gestation age)**
Smoking status in last three months of pregnancy (%)		
Yes	11.0	10.8
No	89.0	89.2
Child Characteristics		
Child weight status at preschool years (%)		
Not obese	82.4	82.3
Obese	17.6	17.7

[1]Unweighted samples are rounded to the nearest 50

[2]Weighted percentages

Mean ± SE values or proportions are presented

Source: US Department of Education, National Center for Education Statistics, Early Childhood Longitudinal Birth Cohort, United States, 2001-2007

Table 4.2: Sample characteristics by adequacy of GWG per the 2009 Institute Of Medicine recommendations

	Adequacy per 2009 Institute Of Medicine recommendations			
Characteristics	Inadequate	Adequate	Excessive	p-value
Study population (n)[1]	2200	1600	2600	
Study population (n)[1]	30.2	26.4	43.4	
Maternal characteristics				
Race/Ethnicity (%)[2]				<0.0001
White, Non Hispanic	25.8	27.4	46.8	
Black, Non Hispanic	31.4	24.3	44.3	
Hispanic	39.3	23.8	26.9	
Other, Non Hispanic	40.3	28.5	31.2	
Maternal Age (%)				0.7162
15-19	31.9	24.9	43.2	
20-24	27.5	26.8	45.7	
25-29	32.7	25.2	42.1	
30-34	29.5	28.1	42.4	
≥35	30.2	25.5	44.3	
Maternal Education (%)				0.1635
≤ 12^{th} grade	35.5	23.8	40.7	

Table 4.2: Sample characteristics by adequacy of GWG per the 2009 Institute Of Medicine recommendations

	Adequacy per 2009 Institute Of Medicine recommendations			
Characteristics	**Inadequate**	**Adequate**	**Excessive**	**p-value**
High School Diploma/Equivalent	30.4	25.3	44.3	
Vocational /Technical or Some College	28.1	25.6	46.3	
Bachelor's Degree or Higher	28.2	29.8	41.4	
Pre-pregnancy BMI				
Underweight	42.5	23.5	34.0	<0.0001
Normal Weight	37.0	29.2	33.8	
Overweight	18.6	23.8	57.6	
Obese	21.2	21.0	57.8	
Smoking status in last three months of pregnancy (%)				0.1495
Yes	26.0	25.0	49.0	
No	30.6	26.5	42.8	
Gestational age				
Full term (≥37weeks)	30.0	26.6	43.4	<0.00011

Table 4.2: Sample characteristics by adequacy of GWG per the 2009 Institute Of Medicine recommendations

	Adequacy per 2009 Institute Of Medicine recommendations			
Characteristics	**Inadequate**	**Adequate**	**Excessive**	**p-value**
Preterm (<37 weeks)	100	0	0	
Child weight status at preschool years				
Not obese	31.1	27.1	41.8	0.0067
Obese	25.8	22.9	51.3	

[1]Unweighted samples are rounded to the nearest 50

[2]Weighted percentages

Mean ± SE values or proportions are presented

Source: US Department of Education, National Center for Education Statistics, Early Childhood Longitudinal Birth Cohort, United States, 2001-2007

Table 4.3: Association between the rate of weekly GWG per 1kg increment at the second and third trimesters and child BMI Z-scores status at 4 or 5 years[1]

Characteristics	**Model 1**	**Model 2**
	β (95% CI)	**β (95% CI)**
Main Independent Variable		
Rate of weekly gestational weight gain at second and third trimesters(kg/week)	0.27 (0.04, 0.51)	0.37 (0.14, 0.61)
Control Variables		
Maternal characteristics		
Race/Ethnicity (%)		
White, Non Hispanic		Reference
Black, Non Hispanic		-0.02 (-0.19, 0.14)
Hispanic		0.21 (0.08, 0.35)
Other, Non Hispanic		0.26 (-0.12, 0.16)
Maternal Age		
15-19		0.10 (-0.17, 0.37)
20-24		0.03 (-0.18, 0.24)
25-29		0.03 (-0.15, 0.20)
30-34		-0.03 (-0.20, 0.13)
≥35		Reference

Table 4.3: Association between the rate of weekly GWG per 1kg increment at the second and third trimesters and child BMI Z-scores status at 4 or 5 years[1]

Characteristics	Model 1	Model 2
	β (95% CI)	**β (95% CI)**
Maternal Education		
≤ 12th grade		0.12 (-0.12, 0.36)
High School Diploma/Equivalent		0.15 (0.02, 0.28)
Vocational /Technical or Some College		0.05 (-0.10, 0.21)
Bachelor's Degree or Higher		Reference
Pre-pregnancy BMI		0.04 (0.04, 0.05)
Smoking status in last three months of pregnancy		
Yes		0.10 (-0.09, 0.28)
No		Reference

Source: US Department of Education, National Center for Education Statistics, Early Childhood Longitudinal Birth Cohort, United States, 2001-2007

[1]All estimates are per 1kg GWG, unweighted sample size (n=6,400)

Model 1: Unadjusted

Model 2: Adjusted for maternal characteristics (maternal race/ethnicity, age, pre-pregnancy BMI and status of smoking in the last three months of pregnancy)

Table 4.4: Association between the rate of weekly GWG in the last two trimesters and the risk of obesity in the offspring at 5years[1]

Characteristics	Model 1	Model 2
	OR (95% CI)	**OR (95% CI)**
Main Independent Variable		
Rate of weekly gestational weight gain in the last two trimesters (kg/week)	1.83 (1.19, 2.82)	2.31 (1.51, 3.54)
Control Variables		
Maternal characteristics		
Race/Ethnicity		
White, Non Hispanic		Reference
Black, Non Hispanic		1.30 (0.95, 1.78)
Hispanic		1.86 (1.38, 2.51)
Other, Non Hispanic		1.28 (0.85, 1.94)
Maternal Age		
15-19		0.94 (0.50, 1.80)
20-24		0.91 (0.60, 1.39)
25-29		1.06 (0.72, 1.56)
30-34		0.92 (0.64, 1.33)
≥35		Reference
Maternal Education		

Table 4.4: Association between the rate of weekly GWG in the last two trimesters and the risk of obesity in the offspring at 5years[1]

Characteristics	Model 1	Model 2
	OR (95% CI)	OR (95% CI)
≤ 12th grade		1.43 (0.89, 2.28)
High School Diploma/Equivalent		1.54 (1.10, 2.15)
Vocational /Technical or Some College		1.16 (0.79, 1.71)
Bachelor's Degree or Higher		Reference
Pre-pregnancy BMI		1.07 (1.05, 1.10)
Smoking status in last three months of pregnancy		
Yes		1.38 (0.97, 1.97)
No		Reference

Source: US Department of Education, National Center for Education Statistics, Early Childhood Longitudinal Birth Cohort, United States, 2001-2007

[1]All estimates are per 1kg GWG, unweighted sample size (n=6,400)

[2]Weighted percentages

Model 1: Unadjusted

Model 2: Adjusted for maternal characteristics (maternal race/ethnicity, age, pre pregnancy BMI and smoking status of smoking in the last three months of pregnancy)

Table 4.5: Change in child BMI Z-scores at 5years old with adequacy of GWG[1]

Characteristics	Model 1	Model 2
	β (95% CI)	**β (95% CI)**
Main Independent Variable		
Change in child BMI Z-scores at 5years old with adequacy of Gestational weight gain [2]		
Inadequate	-0.02 (-0.17, 0.12)	-0.03 (-0.16, 0.11)
Adequate	Reference	Reference
Excessive	0.20 (0.07, 0.33)	0.14 (0.01, 0.26)
Control Variables		
Maternal characteristics		
Race/Ethnicity		
White, Non Hispanic		Reference
Black, Non Hispanic		-0.03 (-0.19, 0.14)
Hispanic		0.21 (0.08, 0.34)
Other, Non Hispanic		0.02 (-0.13, 0.16)
Maternal Age		
15-19		0.12 (-0.15, 0.39)
20-24		0.04 (-0.17, 0.25)
25-29		0.03 (-0.14, 0.20)
30-34		-0.03 (-0.19, 0.13)
Maternal Education		

Table 4.5: Change in child BMI Z-scores at 5years old with adequacy of GWG[1]

Characteristics	**Model 1**	**Model 2**
	β (95% CI)	**β (95% CI)**
≤ 12th grade		0.11 (-0.13, 0.35)
High School Diploma/Equivalent		0.15 (0.01, 0.28)
Voc /Tech or Some College		0.05 (-0.10, 0.21)
Bachelor's Degree or Higher		Reference
Pre-pregnancy BMI		0.04 (0.03, 0.05)
Smoking status in last three months of pregnancy		
Yes		0.10 (-0.08, 0.28)
No		Reference

Source: US Department of Education, National Center for Education Statistics, Early Childhood Longitudinal Birth Cohort, United States, 2001-2007

[1]All estimates are per 1kg GWG, unweighted sample size (n=6,400)

[2]Adequacy of GWG by 2009 IOM recommendations

Model 1: Unadjusted

Model 2: Adjusted for maternal characteristics (maternal race/ethnicity, age, pre pregnancy BMI and smoking status in the last three months of pregnancy)

Table 4.6: Association between adequacy of GWG and the risk of obesity in the offspring at 5years[1]

Characteristics	Model 1	Model 2
	OR (95% CI)	**OR (95% CI)**
Main Independent Variable		
Adequacy of gestational weight gain[2]		
Inadequate	0.98 (0.69, 1.40)	0.94 (0.67, 1.33)
Adequate	Reference	Reference
Excessive	1.45 (1.09, 1.93)	1.32 (0.98, 1.77)
Maternal Characteristics		
Race/Ethnicity		
White, Non Hispanic		Reference
Black, Non Hispanic		1.30 (0.95, 1.78)
Hispanic		1.84 (1.37, 2.47)
Other, Non Hispanic		1.27 (0.84, 1.92)
Maternal Age		
15-19		0.99 (0.52, 1.87)
20-24		0.94 (0.62, 1.43)
25-29		1.08 (0.74, 1.57)
30-34		0.93 (0.64, 1.35)
≥35		Reference
Maternal Education		

Table 4.6: Association between adequacy of GWG and the risk of obesity in the offspring at 5years[1]

Characteristics	Model 1	Model 2
	OR (95% CI)	**OR (95% CI)**
≤ 12th grade		1.40 (0.88, 2.23)
High School Diploma/Equivalent		1.53 (1.10, 2.13)
Vocational /Technical or Some College		1.16 (0.79, 1.70)
Bachelor's Degree or Higher		Reference
Pre- pregnancy BMI		1.07 (1.04, 1.09)
Smoking status in last three months of pregnancy		
Yes		1.39 (0.97, 1.99)
No		Reference

Source: US Department of Education, National Center for Education Statistics, Early Childhood Longitudinal Birth Cohort, United States, 2001-2007

[1]All estimates are per 1kg GWG, unweighted sample size (n=6,400)

[2]Adequacy of Gestation weight gain per 2009 IOM recommendations

Model 1: Unadjusted

Model 2: Adjusted for maternal characteristics (maternal race/ethnicity, age, pre-pregnancy BMI and smoking status in the last three months of pregnancy)

Table 4.7: Change in child BMI Z-scores at 5years old per 5kg increment in GWG among full term (≥37 weeks) [1]

Characteristics	Model 1	Model 2
	β (95% CI)	**β (95% CI)**
Main Independent Variable		
Change in child BMI Z-scores per 5kg increment in gestational weight gain	0.04 (-0.01, 0.08)	0.07 (0.02, 0.12)
Control Variables		
Maternal Characteristics		
Race/Ethnicity		
White, Non Hispanic		Reference
Black, Non Hispanic		0.01 (-0.18, 0.20)
Hispanic		0.23 (0.08, 0.38)
Other, Non Hispanic		0.06 (-0.08, 0.20)
Maternal Age		
15-19		0.14 (-0.15, 0.44)
20-24		0.06 (-0.16 , 0.28)
25-29		0.03 (-0.15, 0.21)
30-34		-0.02 (-0.18, 0.14)
≥35		Reference

Table 4.7: Change in child BMI Z-scores at 5years old per 5kg increment in GWG among full term (≥37 weeks) [1]

Characteristics	Model 1	Model 2
	β (95% CI)	**β (95% CI)**
Main Independent Variable		
Change in child BMI Z-scores per 5kg increment in gestational weight gain		
Control Variables		
Maternal Characteristics		
Race/Ethnicity		
White, Non Hispanic		Reference
Black, Non Hispanic		0.01 (-0.18, 0.20)
Hispanic		0.23 (0.08, 0.38)
Other, Non Hispanic		0.06 (-0.08, 0.20)
Maternal Age		
15-19		0.14 (-0.15, 0.44)
20-24		0.06 (-0.16 , 0.28)
25-29		0.03 (-0.15, 0.21)
30-34		-0.02 (-0.18, 0.14)
≥35		Reference

Table 4.7: Change in child BMI Z-scores at 5years old per 5kg increment in GWG among full term (≥37 weeks) [1]

Characteristics	Model 1	Model 2
	β (95% CI)	**β (95% CI)**
Maternal Education		
≤ 12th grade		0.10 (-0.15, 0.36)
High School Diploma/Equivalent		0.14 (-0.00, 0.28)
Vocational/ Technical or Some College		0.05 (-0.11, 0.21)
Bachelor's Degree or Higher		Reference
Pre-pregnancy BMI		0.04 (0.04, 0.05)
Smoking status in last three months of pregnancy		
Yes		0.09 (-0.11, 0.28)
No		Reference

Source: US Department of Education, National Center for Education Statistics, Early Childhood Longitudinal Birth Cohort, United States, 2001-2007

[1]All estimates are per 5kg GWG, unweighted sample size (n=5,400)

Model 1: Unadjusted

Model 2: Adjusted for maternal characteristics (maternal race/ethnicity, age, pre-pregnancy BMI and smoking status in the last three months of pregnancy)

Table 4.8: Association between GWG and the risk of obesity in the offspring at 5years old per 5kg increment in GWG among full term (≥37 weeks)[1]

Characteristics	Model 1	Model 2
	OR (95% CI)	**OR (95% CI)**
Main Independent Variable		
Risk of obesity in offspring per 5kg increment in total GWG	1.10 (1.00, 1.21)	1.19 (1.08, 1.30)
Control Variables		
Maternal characteristics		
Race/Ethnicity		
White, Non Hispanic		Reference
Black, Non Hispanic		1.37 (0.97, 1.93)
Hispanic		1.92 (1.37, 2.69)
Other, Non Hispanic		1.36 (0.87, 2.12)
Maternal Age		
15-19		1.00 (0.50, 1.99)
20-24		0.94 (0.60, 1.46)
25-29		1.07 (0.71, 1.60)
30-34		0.93 (0.63, 1.36)
≥35		Reference

Table 4.8: Association between GWG and the risk of obesity in the offspring at 5years old per 5kg increment in GWG among full term (≥37 weeks)[1]

Characteristics	Model 1	Model 2
	OR (95% CI)	**OR (95% CI)**
Maternal Education		
≤ 12th grade		1.46 (0.87, 2.42)
High School Diploma/Equivalent		1.57 (1.09, 2.16)
Vocational /Tech or Some College		1.21 (0.81, 1.81)
Bachelor's Degree or Higher		Reference
Pre- pregnancy BMI		1.08 (1.05, 1.10)
Smoking status in last three months of pregnancy		
Yes		1.35 (0.91, 2.00)
No		Reference

Source: US Department of Education, National Center for Education Statistics, Early Childhood Longitudinal Birth Cohort, United States, 2001-2007

[1]All estimates are per 5kg GWG, unweighted sample size (n=5,400)

Model 1: Unadjusted

Model 2: Adjusted for maternal characteristics (maternal race/ethnicity, age, pre-pregnancy BMI and smoking status in the last three months of pregnancy)

Table 4.9 Summary of the associations of gestational weight gain with the risk of obesity in the offspring and BMI z-scores

	Obesity (BMI≥ 95th percentile) Odds Ratio (95% CI)	**BMI z-score Beta coefficient (95% CI)**
Rate of weekly GWG per kg increment (kg/week)		
Adjusted estimate[1]	2.31 (1.51, 3.54)	0.37 (0.14, 0.61)
Weight gain per 2009 Institute Of Medicine recommendations		
Adjusted estimate[1]		
Inadequate	0.94 (0.67, 1.33)	-0.03 (-0.16, 0.11)
Adequate	Reference	Reference
Excessive	1.32 (0.98, 1.77)	0.14 (0.01, 0.26)
Total Gestational weight gain per 5kg increment among full term (≥37 weeks)		
Adjusted estimate[1]	1.19 (1.08, 1.30)	0.07 (0.02, 0.12)

Source: US Department of Education, National Center for Education Statistics, Early Childhood Longitudinal Birth Cohort, United States, 2001-2007

[1]All estimates adjusted for maternal race/ethnicity, age, pre-pregnancy BMI and smoking status in the last three months of pregnancy

Table 4.10 Estimates of direct and indirect effects (mediated through birth weight- for- gestational -age z-score) of the association between GWG and BMI z-scores in the offspring and the proportion of gestational weight gain that is mediated through birth weight: Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2007

	Change in BMI Z-scores (95% confidence interval)[1]						**Proportion**
Measures of gestational weight gain	**Natural direct effect (NDE)**		**Natural indirect effect (NIE)**		**Total effect**		**mediated through Birth weight (%)**
	β_{NDE}	**95% CI**	**β_{NIE}**	**95% CI**	**β**	**95% CI**	
Rate of gestational weight gain in the second and third trimester	0.065	0.042, 0.088	0.035	0.028, 0.041	0.099	0.076, 0.122	35.553
Adequacy of gestational weight gain ratio							

Table 4.10 Estimates of direct and indirect effects (mediated through birth weight- for- gestational -age z-score) of the association between GWG and BMI z-scores in the offspring and the proportion of gestational weight gain that is mediated through birth weight: Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2007

Measures of gestational weight gain	Change in BMI Z-scores (95% confidence interval)[1]						Proportion mediated through Birth weight (%)
	Natural direct effect (NDE)		Natural indirect effect (NIE)		Total effect		
	β_{NDE}	95% CI	β_{NIE}	95% CI	β	95% CI	
Inadequate vs adequate weight gain	0.124	0.048, 0.200	0.074	0.057, 0.092	0.199	0.121, 0.276	37.186
Excessive vs. adequate weight gain	0.062	0.024, 0.100	0.037	0.028, 0.046	0.099	0.061, 0.138	37.374

Table 4.10 Estimates of direct and indirect effects (mediated through birth weight- for- gestational -age z-score) of the association between GWG and BMI z-scores in the offspring and the proportion of gestational weight gain that is mediated through birth weight: Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2007

Measures of gestational weight gain	**Change in BMI Z-scores (95% confidence interval)[1]**						**Proportion mediated through Birth weight (%)**
	Natural direct effect (NDE)		**Natural indirect effect (NIE)**		**Total effect**		
	β_{NDE}	**95% CI**	**β_{NIE}**	**95% CI**	**β**	**95% CI**	
Total gestational weight gain among those with infants born full term	0.092	0.045, 0.136	0.051	0.040, 0.062	0.143	0.098, 0.186	35.664

[1]Risk ratios were adjusted for maternal race, maternal age, mother's education, pre pregnancy BMI, smoking during the last three months of pregnancy and birth weight- for- gestational -age z-score

Proportion mediated through birth weight were estimated for continuous outcomes as [(β_{NIE} / Total effects), where β_{NIE} refers to the estimates for natural indirect effect.

Table 4.11 Estimates of direct and indirect effects (mediated through birth weight- for- gestational -age z-score) of the association between GWG and the risk of obesity in the offspring and the proportion of gestational weight gain that is mediated through birth weight Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2007

Measures of gestational weight gain	Adjusted odds ratio (95% confidence interval)[1]						Proportion mediated through Birth weight (%)
	Natural direct effect (NDE)		Natural indirect effect (NIE)		Total effect		
	OR_{NDE}	95% CI	OR_{NIE}	95% CI	OR	95% CI	
Rate of gestational weight gain in the second and third trimester	1.131	1.067, 1.198	1.038	1.027, 1.050	1.174	1.109, 1.244	24.703

Table 4.11 Estimates of direct and indirect effects (mediated through birth weight- for- gestational -age z-score)of the association between GWG and the risk of obesity in the offspring and the proportion of gestational weight gain that is mediated through birth weight Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2007

Measures of Gestational weight gain	Adjusted odds ratio (95% confidence interval)[1]						Proportion mediated through Birth weight
	Natural direct effect (NDE)		Natural indirect effect (NIE)		Total effect		
	OR_{NDE}	95% CI	OR_{NIE}	95% CI	OR	95% CI	
Adequacy of gestational weight gain ratio							
Inadequate weight gain vs adequate weight gain	1.174	0.985, 1.400	1.088	1.059, 1.118	1.279	1.073, 1.52	37.254

Table 4.11 Estimates of direct and indirect effects (mediated through birth weight- for- gestational -age z-score) of the association between GWG and the risk of obesity in the offspring and the proportion of gestational weight gain that is mediated through birth weight Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2007

Measures of gestational weight gain	Adjusted odds ratio (95% confidence interval)[1]						Proportion mediated through Birth weight (%)
	Natural direct effect (NDE)		Natural indirect effect (NIE)		Total effect		
	OR_{NDE}	95% CI	OR_{NIE}	95% CI	OR	95% CI	
Excessive vs. adequate weight gain	1.084	0.992, 1.183	1.043	1.029, 1.058	1.131	1.036, 1.234	35.687
Total gestational weight gain among those with infants born full term	1.289	1.174, 1.412	1.059	1.038, 1.079	1.365	1.244, 1.498	20.833

[1]Risk ratios were adjusted for maternal race, maternal age, mother's education, pre pregnancy BMI, smoking during the last three months of pregnancy and birth weight- for- gestational -age z-score

Proportion mediated through birth weight were estimated as [(OR_{NDE} * (OR_{NIE}-1) / (OR_{NDE} * OR_{NIE} -1)), where OR_{NDE} and OR_{NIE} refer to the corresponding risk ratios for natural direct effect and natural indirect effect, respectively for binary outcomes.

CHAPTER 5

DISCUSSION

5.1 Association between rate of GWG and child's weight status before age 5

This study evaluated the association between GWG and the risk of obesity among preschool children. We measured GWG in three different ways (the rate of GWG in the second and third trimesters, adequacy of GWG per IOM recommendations and total GWG). We found that the rate of GWG in the second and third trimester was associated with nearly 2 times higher odds of obesity in preschoolers after adjusting for maternal characteristics. In addition, each 1 kg increase of GWG in the second and third trimester was significantly associated with a 0.24 unit increase in child BMI z-score. This association was not modified by maternal prepregnancy BMI.

These results are consistent with one previous study that found a significant association.[53] Anderson et al.[53] found that average weekly GWG was positively associated with the child's BMI status at age 7 years during the first (BMI Z-score 0.049; 95% CI = 0.030, 0.067) and second (BMI Z-score 0.059; 95% CI = 0.041, 0.077). However, Anderson et al.[53] did not find an association in the third trimester of pregnancy. Anderson et al.[53] analyzed data which mainly included Caucasian participants from the Danish National Birth Cohort of participants. Therefore, generalizability of the findings to other populations is questionable. Our findings are also different from another study in which Margerison-Zilko et al.[2] did not find a significant association between the rate of GWG in the second and third trimester and child weight status. Margerison-Zilko et al.[2]

found that a 1-kilogram increase in GWG in the first trimester was associated with a 5% higher odds of overweight (BMI $\geq 85^{th}$ percentile) at age 5 years (OR = 1.05; 95% CI =1.02, 1.09). [2] A main difference between our study and Margerison-Zilko et al. is the study population. Margerison-Zilko et al.[2] analyzed data from the Child Health and Development studies, a longitudinal birth cohort of women in California, USA who accessed prenatal care between 1956 and 1967, when lifestyle and environmental exposures might be different from those experienced by people nowadays. We analyzed used data from a more recent, nationally representative cohort to evaluate the association and find the magnitude of the association is far larger than Margerison-Zilko et al.[2]

5.2 Association between adequacy of GWG and child's weight status before age 5

We found that gaining weight exceeding the 2009 IOM recommendations (or excessive GWG) was positively associated with a 0.14 unit increase in child BMI Z-scores at age 4-5 years compared to adequate weight gain There was no significant association between inadequate weight gain and child BMI Z-scores. Also, adequacy of weight gain was not significantly associated with odds of obesity at age 5. Our results are consistent with other studies that found a positive association between excessive GWG GWG and child weight status.[7,10] Oken et al.[10] found that at age 3, children of mothers with excessive GWG had 0.52 unit increase in z-scores (95% CI= 0.44- 0.61) compared to children of mothers with inadequate GWG. Wrotniak et al.[7] found that compared to children born by mothers who gained weight within the IOM recommendations, children born to mothers who gained excessive weight gain had 48% higher odds of overweight at age 7.

5.3. Association between total GWG and child's weight status before age 5 among children who were delivered full term In a subsample of preschool children born full term, we found that a 5kg increase in GWG was associated with 0.07 higher child BMI Z-scores and 19% higher odds of childhood obesity at age 4-5 years. The findings from our study are consistent with the majority of studies that have found a positive association between total GWG and the risk of overweight or obesity in the offspring. [2,4,7,10,12,17] A few studies evaluated this association in preschool children[2,16,17] and children at age 3. [4,10,90] Oken et al. [10] observed that a 5kg increase in additional GWG was associated with 52% higher odds of obesity (BMI ≥ 95th percentile in the offspring (OR=1.52, 95% CI: 1.19, 1.94) in participants in the Project Viva cohort study. Also, Oken et al. [10] found that there was a 0.13 unit increase in child BMI z-scores for every additional 5kg increase in GWG association after adjusting for potential confounders (95% CI: 0.08, 0.19). Wrotniak et al.[7] found that every 1kg increase in GWG was associated with 3% higher odds of overweight (BMI ≥ 85th percentile) in the offspring at 7 years old.

Hinkle et al. [17] found that a 1-kilogram increase in total GWG was associated with 0.008 unit increase in BMI Z-scores in children at age 5 years who were born to mothers with normal weight from the ECLS-B study. Hinkle et al. restricted their study sample to children born full term (≥37weeks gestation age, n=3600) [17] In addition, Hinkle et al. also found that an 1-kilogram increase in total GWG was associated with 0.06 unit increase in BMI Z-scores in children at age 5 years who were born to overweight mothers.[17] However, in our study by combining the data from both Wave III and Wave IV (i.e. children aged 4 and 5 at interview) (n=6400), we increased our sample size greatly and we did not observe any significant interactions between any measures of

GWG and mother's pre-pregnancy BMI. Our findings of the positive association between GWG and child BMI Z-scores are in the same direction as the study by Hinkle et al.[17]

Our significant findings are consistent with evidence from previous studies conducted in animal models. These studies indicate that mother's over nutrition during pregnancy leads to enhanced fat mass, changes in the expression of genes in the adipose tissue, and modifications in appetite centers of the brain in offspring.[46,47]

5.4 Birth weight as a mediator between GWG and offspring's weight status at age 4or 5.

We found that birth weight is a moderate mediator for the association between GWG and offspring's weight status among preschoolers. The proportion of increased risk of obesity in the offspring mediated through birth weight varied somewhat by measures of GWG and childhood obesity. The highest proportion of total effects of GWG mediated through birth weight were observed in the association between adequacy of GWG among children born to mothers with excessive GWG compared to children born to mothers with adequate GWG and child BMI z-scores (37.4%) while the lowest effects mediated through birth weight were observed in the association between total GWG among those with infants born full term and the risk of obesity of obesity in the offspring (20.8%). The risk ratios for the direct effects were stronger than the indirect effects. Therefore, our results indicate that excessive GWG may have a long-term effect on the child's weight status through pathways other than birth weight. [17]

5.5 Strengths and Limitations

There are several strengths of our study. This study used data from a recent prospective cohort study conducted in the United States with a large nationally representative sample. Therefore, the findings of this study may be generalized to mothers and children in the United States. Children's height and weight data came from two objective measurements done by trained ECL-B researchers following the standard protocol, thus enhancing the accuracy of our outcome variables. Our results are also strengthened by the use of measurements obtained from birth certificates which include GWG, child birth weight and gestational age. We had the ability to adjust for several potential confounders. Finally, compared to another published study which used the same data source as ours, we were able to increase our sample size greatly by using data from both wave III and wave IV. Thus, we have more power to assess the interactive effects between GWG, prepregnancy BMI, and the mediator (birthweight). Moreover, we were also able to partition the total effects of GWG into direct and indirect effects and further to determine the percentage of the total effects of GWG obesity mediated by birth weight in the association between GWG and the risk of obesity in the offspring.

Our study has limitations. Information on maternal diet and physical activity during pregnancy was unavailable.[17] The SAS macro used to perform mediation analysis does not incorporate sampling weights /survey design.[82] Therefore, the standard errors in mediation analysis may have been underestimated. Furthermore, due to the small number of women with gestational diabetes, we were not able to examine other pathways which might have mediated the association between GWG and the risk of obesity in the offspring.

5.6 Future research and Conclusions

The significant association between maternal GWG and the risk of obesity in preschoolers indicate that pregnant women should be counseled by health practitioners to maintain a healthy weight during pregnancy. The results from this study also indicate that children born to mothers with excessive GWG compared to children born to mothers with adequate weight gain are at risk of higher child BMI Z-scores. Our findings suggest that identifying populations of women at high risk of gaining GWG more than the recommended IOM guidelines and targeting appropriate interventions and programs to prevent excess GWG during pregnancy may be a useful strategy in the prevention of obesity in children. Programs such as prenatal classes should be in place to help women gain healthy weight during pregnancy. Research suggests that mother's behaviors and health during pregnancy play a significant role in the child's risk of obesity. Hence, the amount of GWG during pregnancy may be an important modifiable risk factor that affects fetal growth and outcomes later in life such as childhood obesity.

The increase in the prevalence of childhood obesity continues to be a major concern in the United States and without effective treatment, prevention is important.[10] In addition to other risk factors to prevent childhood obesity, there is a need to focus on the intrauterine environment which might have programmed individuals to be on the trajectory of having higher BMI. This study adds to the current literature in this area.

In spite of the research we conducted, our findings also suggest that future research is needed to explore factors such as diet and exercise during pregnancy and child BMI outcomes. This could be effective in developing polices useful in preventing excessive GWG. Moreover, more research needs to be done to elucidate the potential mechanisms of the intrauterine environment and the development of childhood obesity.

In conclusion, our study found that maternal GWG was positively associated with the risk of obesity in preschool children at age 5years. Birth weight is a moderate mediator between the association of maternal GWG and offspring's weight status. Targeting maternal GWG may be an approach to prevent childhood obesity.

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