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Infant and child outcomes associated with maternal nutritional status:
Examination of maternal prepregnancy body mass index and gestational weight gain

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An abstract of

A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in Graduate Division of Biological and Biomedical Sciences

Nutrition and Health Sciences

2012

ABSTRACT

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Approximately a third of women of reproductive age in the United States are obese. Obesity puts substantial burden on individuals and society. Among women of reproductive age, obesity increases the risk of obstetric complications for mothers and their children. Gestational weight gain (GWG) is a potential mediator of many of the associations with prepregnancy obesity. The 2009 Institute of Medicine GWG recommendations were limited due to a lack of data by obesity severity and on the long-term outcomes of GWG. This dissertation address important research gaps related to infant and child outcomes associated with maternal nutritional status.

The Pregnancy Nutrition Surveillance System was used to examine trends in prepregnancy obesity among low-income women from 1999-2008 and examine the associations between GWG and fetal growth by obesity severity. We observed an overall increase in the prevalence of prepregnancy obesity with substantial variation in trends by maternal race-ethnicity. Associations between GWG and fetal growth differed by obesity severity. Among class I obese mothers, weight loss increased the odds of a growth restricted infant; however, among class II and III obese mothers, limited weight loss, compared to GWG within recommendations, was associated with more favorable birthweights.

The nationally representative Early Childhood Longitudinal Study-Birth Cohort was used to examine long-term outcomes of maternal nutritional status. Associations between GWG and child adiposity at 5 years of age by maternal prepregnancy body mass index (BMI) status were examined. No harm or benefit of low GWG was observed among all mothers. Among normal weight and overweight mothers only, GWG above recommendations was associated with an increase in child BMI z-score. The association between prepregnancy BMI and child neurodevelopment at 2 years of age was examined. Prepregnancy underweight and severe obesity were associated with poor child cognitive development. No association was observed between prepregnancy BMI and child motor development.

The findings of this dissertation address critical data gaps related to infant and child outcomes of maternal nutrition status. While findings related to fetal growth suggest that GWG recommendations may be differentially lowered for obese mothers, data related to long-term outcomes is still limited due to inconsistencies the literature.

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ACKNOWLEDGMENTS

I want to start by thanking the Centers for Disease Control and Prevention and Emory University for the financial support of this research. I have many current and former mentors, friends, and family members to thank to for their support throughout my academic career. I am sincerely grateful to my advisor, Dr. Andrea Sharma, for her never-ending commitment, guidance and support. I have grown academically and personally from her mentoring. I want to thank my entire committee, Drs. Usha Ramakrishnan, Aryeh Stein, Laura Schieve, and Deanne Swan. I am thankful for the time and commitment that they all invested into this project, as well as their continual support and direction. I also want to thank my former mentor Dr. Abhijit Datta, as I would have never ended up at Emory if it weren't for his encouragement and support. I couldn't have completed the last four years without the friendship and emotional support of Leanne Henderson and my fellow NHS students, especially Ruth Grossmann, Silvia Eufinger, and Lisa Staimez. I want to thank my parents for their continual guidance, support and love, for which I certainly could not have gotten here without, and my sister Lauren for being my best friend and always being there for me. Finally, I want to thank my husband, Austin, for his never-ending encouragement, commitment, patience, support, and most importantly love; words cannot adequately express my gratitude and love for you.

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CHAPTER 1

INTRODUCTION

Approximately a third of women of reproductive age in the United States are obese (1). While, the most recent national estimates suggest that there has been little increase over the last few years, the prevalence of obesity remains high. Obesity puts substantial burden on individuals and society through an increased risk of comorbidities, medical complications, social stigma and health care costs (2, 3). Specifically, obesity during pregnancy increases the risk of complications for both the mother and the child. Women who are obese prior to pregnancy have an increased risk of developing diabetes and hypertension during pregnancy, requiring a cesarean delivery, developing postpartum hemorrhage and having a delayed recovery, all leading to increased health care costs (4-8). Infants of obese mothers are more likely to be born large-for-gestational-age (LGA) or macrosomic (9), which can have long-term implications for the child's health and can lead to an intergenerational cycle of obesity (10, 11).

Gestational weight gain (GWG) is a potential mediator of the association between prepregnancy obesity and maternal and child outcomes. In 1990, the Institute of Medicine (IOM) released the first GWG recommendations that were specific to a woman's prepregnancy body mass index (BMI) status (12). In developing these recommendations the IOM placed an emphasis on birthweight as the main outcome due to the substantial amount of available research and the associated morbidity with both low and high birthweight. Although it is generally well accepted that SGA has greater adverse consequences for the child, LGA is associated with adverse outcomes for both the mother

and the child. Therefore establishing GWG recommendations requires a complex balancing of the effects of low and high GWG. Because at the time of the report there was limited research examining GWG among obese mothers, the IOM did not specify a defined range of GWG for obese mothers, but rather recommended a target weight gain of at least 15 lb. However, the obesity epidemic continued to worsen during the 1990s, specifically the prepregnancy obesity prevalence increased by approximately 70% from 1992-93 to 2002-03 (13). During this time period the health risks of prepregnancy obesity for mothers and infants became a greater concern and the 1990 recommendations were questioned for their appropriateness given the risks of excessive GWG and the obesity epidemic (14-16). In 2009, the IOM released updated GWG recommendations, which addressed the obesity epidemic from multiple angles (17).

The 2009 IOM GWG recommendations are very similar to the 1990 recommendations with three main differences (12, 17). The 1990 and 2009 IOM recommendations are shown in Table 1.1. First, the new recommendations are based on the World Health Organization (WHO) BMI criteria that define underweight, normal weight, overweight, and obesity, as opposed to the Metropolitan Insurance Life tables that were used in 1990. This change was in accordance with the widespread adoption of the WHO categories. Second, the new 2009 IOM GWG recommendations provided a defined range of weight gain (11-20 lbs) for obese women. Last, the 2009 recommendations were novel in that for the first time they considered the health of the mother, not just the infant, and they were based not only short-term outcomes, but also considered the long-term impact of GWG, to the best that the available literature allowed.

Although the new recommendations were innovative and based on a plethora of data, many data gaps were identified in the 2009 report (17). First, much of the data used in the specification of the defined range for obese mothers was based on data from mothers who were at the lower end of the obesity range. Therefore, it is unclear if this new defined range of 11-20 lbs should be generalizable to women of all obesity levels. Furthermore, although the IOM stated in the report that they considered long-term outcomes in the new recommendations, the data regarding many of the long-term child outcomes were limited. Specifically, it was noted that there was insufficient evidence regarding child obesity and neurodevelopment.

This dissertation addresses important data gaps identified by the IOM in the 2009 report related to maternal obesity and GWG. First, we were interested in examining if the recommendations should be different for women with different levels of obesity severity. To address this question we examine heterogeneity in the association between GWG and fetal growth by obesity severity. We chose to examine the association with fetal growth because is the most proximal time point available for studying GWG and is the least likely to be affected by residual confounding; furthermore, there is the greatest amount of data available on fetal growth at other prepregnancy BMI levels. We also address data gaps related to long-term child outcomes of GWG. Because there is more limited data on these outcomes, they are addressed among women of all prepregnancy BMI categories. We examine the associations between GWG and child adiposity, while considering lifestyle factors that may confound this association. Another long-term outcome of interest is child neurodevelopment. However, because this is a much understudied area and there is little research on the effect of maternal prepregnancy BMI and child

neurodevelopment, we begin by studying the association with prepregnancy BMI as opposed to GWG.

To address these research questions we utilize two existing data sources; the Pregnancy Nutrition Surveillance System (PNSS) and the Early Childhood Longitudinal Study-Birth Cohort (ECLS-B). Each of these data sources has unique attributes that allow for the examination of our study questions. The PNSS is a voluntary surveillance system maintained by the Centers for Disease Control and Prevention, which provides census data for all women utilizing the Special Supplemental Nutrition Program for Women (WIC) during pregnancy, among the participating states, territories and Indian Tribal Organizations (18). Because low-income women have an elevated risk of prepregnancy obesity and adverse birth outcomes, the PNSS provides a high risk study population with adequate sample size among each of the obesity classes and outcomes of interest (19, 20). The ECLS-B was used for analyses related to long-term child outcomes. The Department of Education sponsored the ECLS-B, which is nationally representative longitudinal study of children born in 2001 (21). Pregnancy related data are available from the child's birth certificate and children were followed from 9-months of age until kindergarten entry, at approximately 5 years of age. A myriad of data on the participating children were available, including measured outcome data on the children for our outcomes of interest, making the ECLS-B an ideal data source.

The subsequent chapters of this dissertation discuss the overall background related to maternal obesity, GWG and our outcomes of interest, as well as our findings and their public health implications. Chapter 3 describes the study populations in detail

and overall methodological issues related to the study questions and the type of data utilized. Chapters 4 through 8 are standalone manuscripts written for the intent of publication in peer review journals. Chapters 4 and 5 utilized the PNSS. Chapter 4 examines the prepregnancy obesity trends from 1999-2008 among low-income women and identifies disparities in the prevalence. Chapter 5 examines the associations between GWG and fetal growth by prepregnancy obesity severity. Chapters 6 through 8 utilize the ECLS-B. Chapter 6 is a reliability study comparing maternal-report of GWG at approximately 10 months postpartum to GWG recorded on the child's birth certificate. This study was used to inform our selection of the GWG measure used in chapter 7 and can also be used inform bias analyses for non-ECLS-B studies that use recalled GWG. Chapter 7 examines the association between GWG and child adiposity at 5 years of age, while controlling for lifestyle factors and assessing mediation by birthweight and breastfeeding. Chapter 8 examines the association between prepregnancy BMI and child neurodevelopment at 2 years of age. Finally, Chapter 9 summarizes all of the findings of the manuscripts and their public health implications. The findings of this dissertation will contribute to the field of nutrition in that they can be used in redefining recommendations for obese mothers and further specifying recommendations for all women in the context of long-term child health.

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Table 1.1: Comparison of the 1990 and 2009 Institute of Medicine prepregnancy body mass index categories and gestational weight gain recommendations

Pregnancy BMI Category	<u>1990</u>		<u>2009</u>	
	BMI Definition (kg/m ²)	GWG Recommendation (lbs)	BMI Definition (kg/m ²)	GWG Recommendation (lbs)
Underweight	<19.8	28-40	<18.5	28-40
Normal	19.8-25.9	25-35	18.5-24.9	25-35
Overweight	26.0-28.9	15-25	25.0-29.9	15-25
Obese	≥29.0	>15	≥30.0	11-20

Abbreviations: BMI, body mass index; GWG, gestational weight gain; lbs, pounds

CHAPTER 2

LITERATURE REVIEW

Maternal Nutritional Status

Optimal maternal nutritional status before and throughout pregnancy is important for fetal growth and development. Maternal nutritional status is comprised of the pre-gravid energy and micronutrient stores and the caloric and micronutrient intake throughout gestation, via foods and supplements. Ideally, maternal nutritional status would be studied via examination of specific biomarkers and detailed measurement of dietary intake. While clearly an oversimplification of complex physiological needs, studying maternal constitutional factors, such as prepregnancy BMI and GWG, is more ideal and feasible for epidemiologic, public health and clinical purposes. In general, maternal prepregnancy BMI provides a proxy for the available energy stores and the metabolic state of the mother. Similarly, total GWG provides a proxy for energy intake throughout pregnancy, although it is also determined by the energy expenditure and basal metabolic rate of the mother. Although adequate micronutrients status is critical for fetal growth and development, this dissertation focuses on maternal prepregnancy BMI and GWG, and therefore, we will not review the literature surrounding specific micronutrients. In the following section we describe the epidemiology and the biological factors associated with prepregnancy obesity and GWG.

Prepregnancy Obesity

Epidemiology

Obesity (BMI ≥ 30 kg/m²) among non-pregnant women of reproductive age (aged 20-39) increased substantially in the latter half of the 20th century. Specifically, in the United States, the prevalence increased from 9.3% in 1960-61 to 28.4% in 1999-2000 (1). The most recent results from the National Health and Nutrition Examination Survey (NHANES) indicate that the prevalence of obesity changed little in the last decade; in 2009-10 the prevalence was estimated at 31.9% (2). Less data is available on the prevalence of obesity among women who become pregnant. Currently, no nationally representative repeated surveys exist to monitor trends of prepregnancy obesity. The Pregnancy Risk Assessment Monitoring System (PRAMS) is a state-based, annual surveillance system that provides the greatest ability to monitor prepregnancy obesity trends in the United States; however, not all states participate. Trend estimates using the PRAMS have not been completed since 2002 and these were not performed using the WHO BMI categorization (3) and therefore are not directly comparable to the trend estimates of non-pregnant women of reproductive age, as described above. In 2004-05 the prepregnancy obesity prevalence using the WHO BMI categorization was estimated at 18.7% based on 26 states that participated in the PRAMS (4).

The estimates of the prevalence of obesity differ considerably between pregnant women in the PRAMS and non-pregnant women in the NHANES. It is unclear if the discrepancy is due to a true difference between women who become pregnant and those who do not, or if the difference is due to methodological inconsistencies between

surveys. While obesity is associated with infertility and miscarriage, potentially leading to fewer obese women becoming pregnant, obesity is also associated with a decrease in the effectiveness of oral contraception (5), potentially increasing the number of obese women who become pregnant. Further, BMI distributions may differ between women who become pregnant and those women who do not. Prepregnancy BMI data obtained from the PRAMS is based on maternal-report postpartum of prepregnancy weight and height. Comparatively, BMI data from the NHANES is based on measured height and weight. Because most women tend to underreport their weight (6), obesity estimates from the PRAMS may be underestimated. Further, the age and race-ethnicity distribution may differ between the two surveys due to the specific states selected, as we know that obesity prevalence varies by state (4). Regardless of the discrepancies in the current surveillance data related to prepregnancy obesity and obesity among women of reproductive age, the obesity prevalence remains at a critically high level given the adverse effects on pregnancy outcomes.

Metabolic consequences

Obesity is associated with many complex metabolic and endocrine changes. A full review of this process is beyond the scope of this paper; however, there are a few critical points that should be noted. Adipose tissue is metabolically active and produces an array of adipokines and inflammatory cytokines causing low-grade systemic inflammation (7). By altering complex signaling pathways, the overproduction of these factors has wide-reaching metabolic consequences, including glucose intolerance and insulin resistance. In a non-pregnant state, obese individuals are more likely to develop other chronic conditions

and co-morbidities than non-obese individuals (8). Pregnant women are not exempt from this reality and are under additional stressors due to the physiological changes associated with pregnancy. Pregnancy in general is associated with an increased inflammatory state; however, when combined with prepregnancy obesity, the inflammatory state of the mother is exacerbated (9) and levels of inflammatory cytokines (e.g. TNF- α , IL-6 and IL-8) are further increased (10). The metabolic and inflammatory state of the mother before and during pregnancy can have adverse consequences for both the mother and the fetus (11). Obese women are more likely to develop gestational diabetes as well as preeclampsia. Further, the inflammatory milieu has been associated with altered fetal growth (12) and is hypothesized to program offspring to develop obesity later in life and to delay neurodevelopment (discussed further below).

Gestational Weight Gain

Epidemiology

Prepregnancy BMI establishes the baseline metabolic profile of mothers and the amount of energy stores available. While prepregnancy BMI is a strong predictor of pregnancy outcomes, GWG has been shown to mediate the effects of prepregnancy BMI (13). Studies have clearly shown an inverse relationship between prepregnancy BMI and necessary GWG, such that obese mothers require the least amount of weight gain during pregnancy. Furthermore, although the reason and consequences are not well established, population based studies have shown that obese mothers may even lose weight during pregnancy (14).

The variation in the required amount of GWG by prepregnancy BMI has been supported in recommendations since 1990. However, due to a lack of data, an upper limit for the recommendation for obese mothers was not specified in 1990. As the prevalence of prepregnancy obesity increased throughout the 1990s, additional research became available, and in 2009, the IOM updated GWG recommendations (Table 2.1). Obese women were recommended to gain between 11-20 lbs. However, because of a paucity of research, recommendations specific to prepregnancy obesity class were not specified. Further, much of the research used in defining the recommendation for obese mothers was based on women in the lowest obesity category, Class I (BMI 30.0-34.9 kg/m²), which represents approximately only half of the obese mothers (2). Furthermore, this report called for additional research related to special populations and long-term outcomes of GWG, including child adiposity and neurodevelopment.

It is estimated that less than half of all pregnant women gain within the IOM recommendations; however no nationally representative estimates are available. The most recent estimates available from 8 states participating in the PRAMS in 2002-03 found that the proportion of women who gained within recommendations was 49.9%, 41.1%, 26.8% and 30.2% among underweight, normal weight, overweight and obese women, respectively (13). Data obtained from the Pregnancy Nutrition Surveillance System (PNSS), which consists primarily of low-income women, suggests a similar, but more dramatic pattern; for example in 2002, only 28.5% of normal weight women in the PNSS gained within recommendations (13). While, these differences may be due to the specific states used in the analyses, they may represent true differences in the pattern of GWG among low-income women compared to women of all socioeconomic statuses. A

previous examination of maternal characteristics that predict absolute GWG suggests that, in addition to prepregnancy BMI, GWG varies by maternal age, race-ethnicity, parity, and schooling (15).

Metabolic consequences

GWG below the amount required for the products of conception (e.g. plasma volume expansion, uterine, placental, mammary and fetal tissue) is hypothesized to cause ketosis in the mother (16). The greatest understanding of the mechanism of ketosis comes from studies of non-gravid individuals. Ketone bodies are byproducts of the breakdown of adipose tissue during prolonged fasting (17, 18). Briefly, as the body transitions from the fed state to a fasting state, hormone levels respond to allow for a cascade of events, which ultimately breaks down adipose tissue into free fatty acids and glycerol. These products are released into the circulation and transported to peripheral tissues for oxidation; however, not all tissues have the ability to utilize fatty acids, specifically the brain, due to the inability of the fatty acids to cross the blood brain barrier. Therefore, during prolonged fasting, at a rate proportional to the overall breakdown of adipose tissue, the liver breaks down fatty acids into ketone bodies, acetoacetate and 3-hydroxybutyrate. These metabolites are water-soluble and can be used by all peripheral tissues, but most importantly, they are used by the brain to spare glucose during the fasted state.

The production of ketone bodies is heightened during pregnancy as pregnant women are more sensitive to fasting than non-pregnant women and enter the fasted state

earlier, due to the increase in hormones, changes in the basal metabolic rate and increased utilization of glucose by the fetus (19). In addition, late in pregnancy, hormone sensitivity increases and therefore the breakdown of adipose tissue is increased and subsequently ketone levels increase (20). Ketone bodies freely cross the placenta by passive diffusion and can be used as an energy source by the fetus (19). The potential consequences for the fetus of exposure to ketone bodies are discussed in subsequent sections.

Similar to the metabolic effects of obesity previously discussed, excessive GWG is hypothesized to be associated with a greater inflammatory milieu. While there is sustainably less evidence relating GWG to the production of inflammatory factors, previous cross-sectional studies suggest an association (21-23). Further there is a strong correlation between GWG and fat mass deposited during pregnancy (24), which also supports the link between excessive GWG and increased inflammation. However, it should also be noted that there is the potential for reverse causality with these studies (13). More research is needed to substantiate these theories.

Infant and Child Outcomes Associated with Maternal Nutritional Status

Fetal Growth

Epidemiology and prior studies

Fetal weight at birth is a phenotypic indicator of the complex process of fetal growth that occurs throughout gestation, and it is the most commonly used indicator of fetal growth. Gestation length-, sex-, and sometimes race-ethnicity-specific birthweight curves are used as a reference to classify fetal growth. The standard definitions for small

and large-for-gestational age (SGA and LGA) are a birthweight <10th or >90th percentile, respectively (13). However, more restrictive definitions have been used in the literature, such as a birthweight <2 standard deviations below the mean for gestational age or an absolute birthweight >4,500 grams (i.e., macrosomia). It should be noted, that the birthweight reference (25-27) and definition of gestational age (28) used across studies can have a small impact on the classification of infants and that the choice of outcome will have implications for the clinical relevance and precision of estimates. Specifically, these more restrictive definitions of inadequate and excessive fetal growth have been shown to be associated with the greatest degree of infant morbidity and mortality (29-33).

Trends in fetal growth estimates are often difficult to interpret due to biological and non-biological factors, as well as methodical factors that can affect the estimates. For example, changes in maternal prepregnancy BMI, GWG, height, diabetes, and smoking during pregnancy can affect fetal growth (34). Further, changes in cesarean delivery practices can impact trends (34). The method of assessment used for the determination of gestational age can also bias trends, for example last menstrual period trends to overestimate gestational age in comparison to the clinical estimate (28). Fetal growth trends in the United States were previously estimated between 1985 and 1998 (34). The findings of this study suggested that the mean birthweight increased during the study period, as well as the proportion of infants born LGA, while the portion of infants born SGA decreased. This is in contrary to the trends reported in the IOM report, which suggested that SGA has increased from 1990 to 2005, while LGA has decreased (13). Although the estimates were noted to vary greatly by race-ethnicity, the trends were similar across within groups.

Fetal growth is the most commonly studied outcome of GWG and was extensively reviewed in the 1990 and 2009 IOM reports (13, 35). Prior studies suggest a strong association between GWG and fetal growth, such that low GWG is associated with SGA and high GWG with LGA. This relationship is stronger among women with a lower or healthy prepregnancy BMI and weaker among those with a higher prepregnancy BMI. As such, GWG recommendations are specific to a woman's prepregnancy BMI. While prevention of SGA was the main focus of the recommendations in 1990, the 2009 recommendations were developed on a broader approach balancing SGA and LGA, in addition to other short- and long-term maternal and child outcomes.

At the time of the 2009 IOM report, only one study had examined GWG by obesity class. In their study, Kiel and colleagues examined associations between GWG and four outcomes including, SGA (<10th percentile), LGA (>90th percentile), preeclampsia and cesarean delivery (36). The authors concluded that the lowest risk of poor fetal growth, and other adverse outcomes, corresponded to a weight gain of 10-25 lbs for class I obese mothers, a weight gain 0-9 lbs for class II obese mothers, and a weight loss of 0-9 lbs for class III obese mothers. This was the first large population-based study to examine outcomes of GWG by obesity class and to indicate that weight loss among severely obese mothers may be acceptable.

Other studies examined all obesity classes together as one group and reported optimal GWG ranging from weight loss (37,38) to weight gain of 22 lbs or less (39-41). The IOM took a conservative approach when establishing the recommendation for obese mothers and did not specify recommendations by obesity class due to the limited data.

They recommended 11 lbs as the lower limit of GWG for obese mothers due to concerns of adverse long-term neurodevelopmental outcomes associated with weight gain below that required for the products of conception (16) and called for further research examining outcomes among severely obese mothers (13).

Mechanism

Fetal growth is a complex non-linear process that occurs throughout the entire duration of gestation (42). While there is strong observational data supporting an association between both prepregnancy nutritional status and weight gain during pregnancy (13), experimental studies have been less consistent. The fetal growth process can be interrupted by various maternal and environmental factors, and requires coordination between the maternal metabolic and hormonal state, the placenta, and the fetus (43). Protein, glucose, and fatty acids transporters within the placenta can be up- or down-regulated throughout gestation in response to the fetal growth state, helping to ensure adequate nutrient transfer between the mother and the fetus (44).

Many studies have examined the effect of supplementation of protein or specific micronutrients during pregnancy on fetal growth. Findings have varied considerably across studies, with the greatest effect observed among study samples of severely undernourished mothers (44). Higher prepregnancy BMI and GWG are associated with greater fetal growth. Evidence suggests that this association may be in part due to increased glucose levels, which at a certain point, cause increased levels of fetal insulin, which are more poorly regulated (45). Yet, there appears to also be an independent effect

of maternal prepregnancy BMI and GWG on fetal growth (46). Studies aimed at altering maternal weight gain via lifestyle interventions have had mixed success both on weight gain and fetal growth (13). Therefore although there is strong observational evidence, the specific mechanisms and causality of the association between GWG and fetal growth has yet to be fully elucidated, likely due to the many factors and regulatory systems involved.

Child adiposity

Epidemiology and prior studies

In 2009, when the IOM updated GWG recommendations they noted inconsistencies in the literature regarding the association with long-term offspring outcomes, specifically child adiposity. Further understanding the association between GWG and child adiposity is important given that in the United States, approximately one-fifth of children ages 2-5 are overweight or obese (47). Overweight children tend to continue on a trajectory towards becoming overweight as adults, (48) and they develop serious morbidities during adulthood, including type 2 diabetes, metabolic syndrome, high blood pressure and cancer (49). In addition, adolescents who are overweight or obese have a high risk for depression and low self-esteem (50). Thus, prevention of child overweight and obesity is a current priority in the United States (51).

GWG has been previously hypothesized to act on offspring adiposity through both an indirect and direct mechanism. Given that GWG is positively associated with birthweight and birthweight is positively associated BMI later in life (52), there is a clear, indirect mechanism for the association between GWG and child adiposity mediated through birthweight. In addition, GWG may be directly associated with an unfavorable

intrauterine metabolic milieu (21, 23), which may program offspring for an increased risk for later obesity (53-55). This biological hypothesis is supported by animal studies, but in studies of humans, it has yet to be determined if the direct effect is present and large enough to be meaningful. In addition, maternal lifestyle is related to both GWG (56-58) and child lifestyle (59, 60), thus human studies assessing the association between GWG and child adiposity may be confounded by lifestyle, a topic discussed further below.

GWG has been associated with offspring anthropometric measures during infancy (61), childhood (62-69), and adulthood (70-72); however, due to inconsistencies and limitations of previous analyses, the presence and degree of mediation by birthweight remains unclear. Two studies have utilized sibling analyses that control for shared lifestyle and genetics between mother and child (68, 72), yet results indicated no association (68) or the presence of a direct intrauterine effect only in overweight and obese women (72). Two additional studies controlled for select child lifestyle factors (62, 64), albeit no maternal factors, and found a positive association between GWG and child obesity with minimal mediation by birthweight. Most other studies have not controlled for shared lifestyle and, therefore, may be biased. In addition, many of the prior are based on historic cohorts (63, 67, 68, 70-72) and may have limited external generalizability given the dramatic increase in both maternal and child obesity (73, 74) and changes in lifestyles (75, 76) since the data were collected.

Mechanism

Many factors may play a role in the development of child obesity, and it is important to consider the plausible biological mechanisms behind the association between GWG and child adiposity. In healthy adults, energy intake is regulated via the arcuate nucleus within the hypothalamus (17). Briefly, the neurons within this system contain receptors, which are sensitive to overall energy balance and regulated by insulin and leptin. Previous research using animal models aimed at understanding how this system is affected by maternal under- and overnutrition found the pre- and postnatal periods to be critical (55). Offspring of mothers with undernutrition during pregnancy had increased expression of receptors involved in the promotion of food intake; however, offspring of mothers with overnutrition during pregnancy had decreased levels of leptin receptors, which help to signal that the body has a positive energy balance. They also found that the animals also had an ability to potentially restore the function of these pathways with changes during the neonatal period. Additional hypotheses have been also been discussed. Children of mothers who gain excessive weight may have altered appetites due to programming during the fetal period caused by overnutrition, preference for specific types of food (54, 55), and increased adipocytes, which appear to have their overall levels set during early infancy (54). Based on the mechanisms outlined above, it is plausible that there is a direct mechanism between GWG and child obesity.

Confounding by lifestyle

It is well known that lifestyle habits influence weight gain among non-pregnant individuals. Therefore given that dietary habits change little once pregnant (77), it is not surprising that lifestyle factors, such as a poor diet and sedentary behaviors during pregnancy are risk factors for excessive GWG (56). This is further supported by data showing that dietary quality during pregnancy is inversely related to prepregnancy BMI (78). This finding compliments more recent findings, indicating that prepregnancy BMI is associated with psychosocial factors and dietary restraint, which are also risk factors for excessive GWG among normal, overweight, and obese women and inadequate GWG among underweight women (79). These findings likely represent prior unhealthy eating behaviors. If mothers' eating habits and lifestyles continue after pregnancy, it is likely that their habits will influence eating behaviors of their children. It has been previously shown that an infant's dietary quality after weaning is strongly related to their mother's dietary quality (80). In addition, a recent study found that approximately 30% of the variation in children's diet at age 3 is explained by their mother's diet (81). Given the strong relationship between maternal and child diet, it is crucial to control for family lifestyle when assessing the impact of GWG on child outcomes. Other factors that are known to be related to child obesity include reduced physical activity, increased television and computer use, lack of available healthy foods, socioeconomic status and race-ethnicity (50). Also, maternal smoking during pregnancy, as well as after pregnancy, is a strong risk factor for child obesity (82). Lastly, it should be noted that some mothers may have a genetic propensity to become obese and this risk may be passed onto their

children and therefore studies examining maternal and child obesity may have residual confounding due to genetics (83).

Child Neurodevelopment

Epidemiology and prior studies

Altered child neurodevelopment is an important area of research due to the potential for lifelong health consequences and social impacts (84). Developmental disabilities are common among children in the United States. In 2006-08, approximately 15% of children had a developmental disability, of which, approximately half were classified by parent-report as having a learning disability (85). Only a small proportion of children had an intellectual disability (<1%), however, approximately 4% had an unknown type of delay. Infants and toddlers with a developmental delay, or risk factors that put them at a higher probability of developing a delay, are eligible to receive state Early Intervention services (86). Thus, better understanding the biological factors that can affect a child's development is important for public health and policy.

At the time of the 2009 IOM report on GWG, there was limited research available on the impact of maternal prepregnancy BMI and GWG on long-term child neurodevelopment. Most of the prior studies were over 30 years old, based on small samples, did not adequately control for confounding, and yielded inconsistent results (87-90). However, these studies did establish the concern that there may be adverse consequences to low GWG, as a result of ketosis (88, 90). Furthermore, few mothers were obese at the time of these studies and thus provide little inference regarding the effect of low GWG among overweight and obese mothers. Due to the lack of research

related to GWG and neurodevelopment, the IOM reviewed the literature related to SGA and child neurodevelopment, and based their inferences on the well-established association between GWG and SGA (13). Considering, there are many causes of SGA, studies specifically studying the association between GWG and neurodevelopment are critical. Never the less, the committee expressed concern that low GWG may have long-term implications for child neurodevelopment (13) and thus took a conservative approach to the recommendations for obese mothers.

Additional insight into the effect of maternal nutritional status on child neurodevelopment can be obtained from studies of women exposed to famine during pregnancy. These studies suggest that exposure to severe famine at the time of conception may have lasting effects on offspring cognitive function and mental health (91, 92); however, the generalizability of these studies to current western populations may be limited.

The association between prepregnancy BMI and child neurodevelopment has recently received greater attention (93). Results from two prior studies suggest that prepregnancy underweight and obesity may be associated with lower child general cognitive ability (94, 95); however, these findings were not replicated in a study from two other large cohorts (96). These studies were based on data ranging from 1966 to 2006, and were limited in that they were based on a small sample (94), utilized different measures of child neurodevelopment (i.e., degree of delay based on disability diagnosis (95) or maternal report (96)), or had limited data to examine all maternal prepregnancy BMI categories (95, 96). Therefore the evidence relating prepregnancy BMI status to

child neurodevelopment is still limited and further research is needed given the obesity epidemic.

Mechanism

The majority of brain development occurs during the perinatal period. Neurogenesis is a sophisticated process that includes neuron production, migration, differentiation, and programmed cell death (97). These processes can be disrupted by various maternal and environmental factors (98). Maternal prepregnancy BMI status is hypothesized to effect offspring development. This relationship may be directly due to the baseline nutritional status or the intrauterine environment, mediated by GWG or breastfeeding behaviors, or a combination of all of the above.

Both under- and overnutrition may be associated with altered neurodevelopment. Inadequate levels of energy stores prior to or during pregnancy may impact fetal growth (99), and thus impair development (100-102). In addition, insufficient levels of micronutrients stores or intakes during pregnancy, such as iron, iodine, zinc and essential fatty acids, can impact fetal brain development by affecting hormone production, enzyme cofactors and the physical structure (103-108). These conditions may be present among women of all prepregnancy BMI statuses, but are most likely in either underweight or obese mothers. Underweight women likely lack adequate energy stores and therefore require greater amounts of weight gain to compensate, however, they also have the highest risk of inadequate GWG (13). Obese mothers may be at risk due to poor

micronutrient status prior to pregnancy or weight loss during pregnancy, which is most common among obese mothers (13, 109).

Weight loss during pregnancy is also a risk factor for poor fetal neurodevelopment due to the increased potential of developing ketosis. While this is theoretically problematic among mothers of all pregnancy BMI categories, obese mothers are the most likely to lose weight during pregnancy (13). As previously discussed, ketone bodies are a by product of the breakdown of adipose tissue, which can freely cross the placenta by passive diffusion and can further be used as an energy source for the fetal brain (19). Although the fetal consequences of increased circulating ketones have not been definitively shown in humans, previous animal studies have found that ketones inhibit both purine and pyrimidine synthesis in the fetal brain, which may limit brain growth and development, as studies have also associated ketosis with decreased brain weights (20, 110, 111).

It is important to note that there are two reasons that of ketosis that can occur during pregnancy. The first, as described above, is due to fasting or decreased energy intake. The second is due to a pathological response to diabetes. Women with gestational diabetes (GDM) have decreased peripheral insulin sensitivity compared to non-GDM pregnant women (112). Therefore, women with GDM tend to have increased ketone levels, which do not appear to necessarily correlate with the fasting state, as they would with non-GDM pregnant women (113). Some studies suggest that children born to diabetic mothers have altered cognitive development (114). Any developmental effects seen in infants born to mothers with diabetes may be due to the elevated ketosis, as well

as rapid alterations in maternal blood glucose and therefore studies of mothers with GDM may not be a good indicator of the effect of ketone bodies on fetal development.

Children of obese mothers may also have an elevated risk of adverse neurodevelopment due to maternal overnutrition. As previously discussed, prepregnancy obesity is characterized by an inflammatory intrauterine environment, which may be exacerbated with excessive GWG (21-23). Inflammation during pregnancy may hinder neurodevelopment by damaging brain cells and white matter or by reducing oxygen uptake (98, 115, 116)

While the majority of neurodevelopment occurs during the prenatal period, the postnatal period is also critical. Proliferation, migration, and cell death continues into the postnatal period, along with synapse pruning (97). At this point additional input from the external environment is essential for the neurosystem as it matures. Breastfeeding may contribute to the association between maternal prepregnancy BMI and neurodevelopment. Breastfeeding initiation and duration are reduced among obese mothers (117). While this may be due to decreased intention to breastfeed due to social or cultural behaviors, there may also be a biological component involved. None-the-less, this may contribute to the association with child neurodevelopment, as studies continue to suggest that breastfeeding has beneficial effects on child neurodevelopment, regardless of the mechanism (118, 119).

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Table 2.1: Institute of Medicine gestational weight gain recommendations based on prepregnancy body mass index status, 2009

Prepregnancy Body Mass Index Category	(kg/m ²)	Total Gestational Weight Gain (lbs)
Underweight	<18.5	28-40
Normal weight	18.5-24.9	25-35
Overweight	25.0-29.9	15-25
Obese	≥30.0	11-20
Class I	30.0-34.9	
Class II	35.0-39.9	
Class III	≥40.0	

CHAPTER 3

EXPANDED METHODS

Based on the research gaps identified in the previous chapter, the aims of this dissertation were to: 1) examine the prevalence of prepregnancy obesity among low-income US women; 2) examine the associations between gestational weight gain (GWG) and fetal growth among obese mothers; 3) examine the reliability of maternal-report of GWG in comparison to the birth certificate; 4) examine the association between GWG and child adiposity; and 5) examine the association between prepregnancy body mass index (BMI) and child neurodevelopment. Because each of these aims is addressed in a standalone manuscript, the specifics of the analytic plan for each aim are described in their respective chapter. In this chapter, we provided additional details on the statistical methods and intricacies of the data sources used.

Data Sources

Pregnancy Nutrition Surveillance System

Study Design

The Pregnancy Nutrition Surveillance System (PNSS), which is coordinated by the Centers for Disease Control and Prevention (CDC), is a voluntary state-based surveillance system that monitors the nutritional status of women participating in federally-funded maternal and child health programs, specifically the Supplemental Nutrition Program for Women, Infants, and Children (WIC) (1). In general, WIC enrollment is limited to women with a gross income $\leq 185\%$ of the United States Poverty

Income Guidelines (2). Contributors of the PNSS include states, United States territories and Indian Tribal Organizations. Because the PNSS is voluntary, the specific contributors who participate each year can vary, for example the number of contributors has ranged from 27 in 1999 to 35 in 2008.

The PNSS includes data on maternal demographics, health and behaviors, as well as infant health. Data are collected at the clinic, compiled by the contributors, and submitted to the CDC for analysis. Maternal demographic, health and behavioral data are collected from women when they enrolled in WIC, which they can do at any time during pregnancy or the postpartum period. Because we were specifically interested in pregnancy related events, we limited our studies to only those women who initially enrolled during pregnancy. After pregnancy, women return to the WIC clinic to receive additional benefits. At this time, maternal GWG, health, and behavioral data, and infant health data are collected.

Main Variables

Prepregnancy body mass index. At WIC enrollment, women reported their weight prior to becoming pregnant (to the nearest pound) and were measured without shoes to obtain current height (to the nearest eighth of an inch or tenth of a centimeter) based on a standardized protocol. We calculated BMI (kg/m^2) and categorized women as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), or obese (BMI \geq 30.0) according to the well-adopted World Health Organization cut-off points (3). We further categorized those in the obese category as class I obese (BMI 30.0–34.9), class II obese (BMI 35.0–39.9), or class III obese (BMI \geq 40.0).

Gestational weight gain. At the postpartum visit maternal self-reported weight gain during pregnancy was collected based on the following suggested wording, “How much weight did you gain during this pregnancy?” The absolute number of whole lbs gained or lost was recorded, along with a separate variable indicating if it was positive or negative. Unlike many other data sources for GWG, weight loss data was maintained in the data file and was not truncated at 0 lbs. The PNSS considers any weight gain or loss <-30 or >97 lbs as biologically implausible.

Fetal growth. Infant’s birthweight was collected at the WIC postpartum visit from hospital records, the child’s birth certificate or maternal-report. Gestational age was calculated based on the infant’s date of birth and the mother’s report of the date of her last menstrual period (LMP). Race-ethnicity and sex-specific birthweight-for-gestational-age percentiles were calculated using birthweights from the 2004 United States Natality File as a referent. We used two definitions of restrictive and excessive fetal growth, one based on the more commonly used definition (4) and the other a stricter definition that has been shown to be a better indicator of later morbidity and mortality (5-7). Restricted fetal growth was defined as small-for-gestational age (SGA) using two cut-off points; <10th percentile and <-2 standard deviations (<3rd percentile). Excessive fetal growth was defined as large-for-gestational-age (LGA), using >90th percentile as the cut-off point, and macrosomia defined as an absolute birthweight >4,500 grams. Conclusions drawn from this data were based on the more restrictive definitions of fetal growth, although results based on the less restrictive definitions are also provided for comparisons with other studies.

Statistical considerations

Correlated data. In general correlated data refers to any repeat observation on a member of a cluster. Individual observations within a cluster cannot be considered independent. If not properly adjusted, standard errors based on correlated data are underestimated.

Within the PNSS there are clusters of women with data on multiple pregnancies. As long as women continue to meet all eligibility criteria they can enroll in WIC for each of their pregnancies. Our analysis of GWG and fetal growth (see chapter 5), was limited to PNSS data from 2004-06. Approximately 3% of the women meeting the eligibility criteria for this analysis had more than 1 birth outcome during the study period. Therefore, for this analysis we used general estimate equations (GEE) to account for the correlated data *within* mothers. GEE can be used to correctly estimate standard errors whenever there are fixed effect parameters. We used PROC GENMOD in SAS (SAS Institute Inc., Cary, NC) to perform logistic regression using an exchangeable correlation structure. An exchangeable correlation specifies that the correlations between each of the births to an individual mother are equal.

We also used the PNSS data to examine the prepregnancy obesity trends between 1999 and 2008. The purpose of the analysis was to estimate the overall prevalence of prepregnancy obesity among the women who enrolled in WIC during each of the study years. Therefore correlated data within mothers was not a statistical concern in this analysis. Because of the changing demographics of mothers across the study period, we

used direct standardization to adjust all trend estimates for changes in maternal age and race-ethnicity from 1999 to 2008. For this analysis we used 1999 as the referent so that all estimated trends were in reference to the baseline level estimated in 1999.

Early Childhood Longitudinal Study-Birth Cohort

Study Design

The Early Childhood Longitudinal Study-Birth Cohort (ECLS-B) is a United States nationally representative cohort of children born in 2001 (8). The primary sponsor of the ECLS-B was the National Center for Education Statistics (NCES) within the Department of Education (DOE). The ECLS-B is a restricted-use dataset that was obtained through a memorandum of understanding between the DOE and the CDC. As required by the DOE, we report sample sizes rounded to the nearest 50 and present all percentages as weighted population estimates.

The ECLS-B was designed to be representative of the 3,997,200 children born in 2001, with the exception of children born to mothers younger than 15 years of age or those who died or were adopted prior to 9 months of age. The sample frame for the ECLS-B was drawn from birth certificates maintained by the National Center for Health Statistics (NCHS) Vital Statistics System. Investigators divided the country into primary sampling units (PSUs) based on size and other select characteristics. After oversampling low and very low birth weight infants, twins, American Indian/Alaskan Native, Chinese and other Asian/Pacific Islander infants, a total of 14,000 infants were selected to participate. At the first wave of the ECLS-B, when the children were approximately 9

months of age, data were collected on 10,700 infants and their parents who agreed to participate. Children were followed-up at subsequent waves when they were approximately 2, 4, 5, and 6 years of age. Eligibility for the last wave was determined by the children's kindergarten entry year. Most children enrolled in kindergarten in 2006-07, corresponding with the 5-year wave. Only those children who waited until the 2007-08 school year to enroll in kindergarten, or those who repeated kindergarten, were eligible for the 6-year wave. Thus the last wave in which the entire cohort was eligible was the 5-year wave. All analyses were weighted to account for sample attrition and unequal probability of selection to maintain a sample with demographics representative of the target population.

Main Variables

Prepregnancy body mass index. At the 9-month wave interview, mothers were asked their current height and to recall their prepregnancy weight. We calculated prepregnancy BMI (kg/m^2) and categorized mothers according to the WHO cut-off points as underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), obese (BMI \geq 30.0) (3). Due to a sample size limitations, we were unable to further categorize obese mothers into the standard obesity class categories and instead categorized them into two categories; class I obese (BMI 30.0-34.9) and class II and III obese (BMI \geq 35.0) for select analyses.

Gestational weight gain. This data is available in the ECLS-B from two sources, the birth certificate and mother's self-report at the first wave of data collection. These two data sources of GWG are described and compared in detail in chapter 6.

Child adiposity. Child anthropometry was measured at each wave of the ECLS-B by trained field workers according to a standardized protocol. At the 9-month wave, infants were held by their mothers on a tarred digital scale to obtain current weight. At all subsequent waves, the children were weighed on a digital scale with their shoes and heavy outerwear removed. At the 9-month wave, infant length was measured using a standard pediatric measure mat. At all other waves, child height was measured using a portable stadiometer. All measurements were obtained at least twice and averaged for all calculations.

For our analysis of the association between GWG and child adiposity we used the 5-year data as our endpoint. The CDC's 2000 Growth Charts were used to calculate age- and sex-specific BMI percentiles and z-scores from the measured heights and weights (9), as a validated indicator of child body fatness (10). The correlation between the two weight and height measurements at the 5-year wave were both 1.000 (11). The 5-year wave was chosen as the outcome for this analysis because it was the last wave of data collected on the entire cohort and allowed us to better utilize the longitudinal nature of the data.

Child neurodevelopment. The ECLS-B measured child cognitive and motor development at each of the waves. At the 9-month and 2-year waves, a shortened version of the Bayley Scales of Infant Development-II (BSID-II) was used to obtain cognitive

and motor development scores. At the 4- and 5-year waves, no single standard assessment tool was determined by the NCES to provide a broad measure of children's development. Therefore components of various assessment tools were combined to provide measures of each child's reading and mathematics skills and their fine and gross motor development.

For our analysis of the association between prepregnancy BMI and child neurodevelopment, we used neurodevelopment data obtained at the 2-year wave as our endpoint. The 2-year wave data was chosen for multiple reasons. First, the BSID-II is a standard and widely used assessment tool and substantial data are available regarding its reliability and predictive validity (12). The wide use of the BSID-II will allow our study results to be easily compared with other studies. Also, the BSID-II was recently recommended as the best available tool for child neurodevelopment assessment for a large scale epidemiologic study (13). Further, using an earlier wave of the ECLS-B may help to reduce residual confounding, as there are usually less external inputs at the earlier time points. This decision to use the BSID-II as the measure of child neurodevelopment, left us with the choice to use both the 9-month and 2-year assessment or only one of the waves. Because the predictive validity of the BSID-II before 18 months of age has been questioned (12) and 2-years is the suggested age at which "corrected ages" are no longer required for assessment of children born premature (14), we chose to utilize only the 2-year cognitive and motor developmental assessment.

Cognitive and motor development was assessed at the 2-year wave by trained fieldworkers using the Bayley Short Form-Research Edition (BSF-R), a shortened version of the BSID-II. The BSF-R was developed for the ECLS-B by the NCES to make

the BSID-II, which is generally used in the clinical setting, more compatible for a large national survey. The BSF-R was calibrated to the BSID-II using item response theory and has been determined to have good reliability and discrimination parameters (15). The BSF-R provides a mental development index (MDI) representing early childhood language and cognitive abilities and a psychomotor development index (PDI) representing fine and gross motor skills. Age-standardized T-scores (mean 50, standard deviation 10) normalized to the ECLS-B population provide an overall measure of the child's cognitive and motor abilities relative to other children of the same age. Typically, scores <-2 and <-1 standard deviations on the BSID-II represent severe and mild delay, respectively (16). Both scores are considered clinically relevant as they can be used to identify children who may require additional monitoring and referral for services (17). We analyzed MDI and PDI scores as a continuous and a dichotomous measure. Due to sample size limitations we used <-1 standard deviation as the cut-off point for our dichotomous measure.

Statistical considerations

Complex Survey Data. The ECLS-B was designed to be representative of all births that occurred in 2001 (with the three exceptions discussed previously). The sampling frame for the ECLS-B was drawn from birth certificates collected by the NCHS. Although a simple random sample (SRS) based on the sampling frame would have been ideal, to reduce field costs and ensure desired sample sizes of select minority groups, the sampling frame was broken into 90 primary sampling units (PSUs), which were selectively broken into secondary sampling units (SSUs). Consequently, the sample

obtained is less variable than a sample that would have been obtained from an SRS and without adjustments standard errors would be underestimated. Therefore, all analyses were weighted to account for loss to follow-up and unequal probability of selection, and standard errors were estimated with Taylor Series approximations to account for the multistage, stratified, cluster design of the ECLS-B. When using complex survey data it is important that all variance estimates are based on the entire population. However, in our analyses, we were only interested in generalizing our data to only a subgroup of the population (i.e., singleton infants). Thus we required the use of a domain analysis. The statistical software used, correctly estimates the variance of a group based on the entire sample of the data using an indicator (e.g., dummy variable) for the subpopulation. Correct adjustments to standard errors and point estimates based on a complex survey design were estimated for multiple regression analyses in SAS using the survey procedures (e.g., PROC SURVEYLOGISTIC).

We performed measured variable path analysis (MVPA) for a subset of our analyses. MVPA analyses were completed using Mplus. While Mplus can easily account for the complex survey design in standard analyses through specification of the stratification and cluster variables, we were limited in that we could not perform a domain specific analysis in conjunction with a multi-group analysis (18). A multi-group analysis would have allowed us to estimate if specific paths were invariant across groups (i.e., prepregnancy BMI categories). Therefore we were limited in that we could not perform multi-group analysis in Mplus. We addressed this limitation by examining the models for a statistical multiplicative interaction by prepregnancy BMI category using a

multiple linear regression model in SAS and used Mplus to perform the MVPA among each of the prepregnancy BMI groups separately.

Statistical Methods

For much of the analyses presented in this dissertation, standard linear and logistic regression was utilized to obtain adjusted associations between the exposures and outcomes of interest. Specific details of the statistical analyses used are described in the respective chapters. While most analyses are interested solely in the total effect of the exposure on the outcome, examination of the direct and indirect effects can help inform researchers of the mechanism by which an association occurs. Adjusting models for mediating variables is a common method for obtaining the direct effect. However, this method has been criticized and has the potential to yield biased results if confounding between the mediator-outcome relationships is not addressed (19, 20). Further, this method does not allow for the identification of specific indirect effects. For our analysis of the associations between GWG and child adiposity, we were interested in decomposing the total effect into direct and indirect effects. This was accomplished using MVPA, from the SEM family.

SEM is a common methodology used in the social sciences and is slowly being adapted and accepted in the epidemiology community (21, 22). As with any observational study, using SEM does not allow for causal conclusions. SEM does, however, allow for estimation of indirect effects and requires greater a priori assumptions of the conceptual model (23). SEM simultaneously estimates multiple linear equations, is

primarily based on estimations of the covariance structure, and can include latent variables (23). A latent variable represents a hypothetical construct (e.g. lifestyle or socioeconomic status), is based on multiple measured/observed variables, and is defined using confirmatory factor analysis (CFA). In general SEM is based on two phases, a measurement phase and a structural phase. In the measurement phase, CFA is used to specify multiple latent variables, which are all assumed to correlate with each other. Once the latent variables are determined to be properly defined the structural phase is imposed on the model. In this phase, theory-based directional relations are imposed on the latent variables. MVP is a subset of the SEM family that does not include latent variables and only includes the structural phase. MVP is used when only one measured variable is available for the constructs in the model.

For SEM it is important to determine if the overall specified model fits the data; MVP and CFA model fit are determined by considering multiple goodness-of-fit indices. We used the following indices to determine model fit: the model chi-square, the root mean square error of approximation (RMSEA), the comparative fit index (CFI), the Tucker Lewis index (TLI) and the Akaike Information Criteria (AIC) (AIC was not used for CFA model fit as it is used for comparing fit between models) (23). The null hypothesis for the model chi-square informs the researcher that the over-identified model fits the data. The RMSEA favors a more parsimonious model; in general any value under 0.05 is indicative of adequate fit. The CFI and TLI compare the researcher's model to the baseline independence model; values above 0.95 are indicative of good data-model fit. The AIC compares fit across models, with lower AIC indicating better model fit. Due to

the differing utility of each index (24), we reported and simultaneously considered each index when examining fit of the various models.

We utilized components of SEM to examine the direct and indirect effects of the associations between GWG and child adiposity. We used CFA to define a latent factor based on the hypothetical construct of an unhealthy family lifestyle. We based this factor on multiple measured indicators including maternal smoking in the last 3 months of pregnancy, maternal exercise habits when children were approximately 4 years of age, maternal weight change from prepregnancy to approximately 5 years postpartum, child weekday television habits at 4 year of age, and fast-food and sugar sweetened beverage consumption at 4 years of age. These indicators were determined by the availability of variables in the ECLS-B and also based on prior literature. Lifestyle was the only construct in our conceptual model that was based on multiple indicators; all others were based on only one measured variable.

The combination of constructs based on multiple-indicators and a single-indicator presented a challenge to our analysis plan. Single-indicators of a latent construct can be used if assumptions about the measurement error are made (23). However, identification of the model was not possible with the other complexities included in our model.

Therefore we opted to use CFA in a separate model to define the lifestyle construct and output the factor score for each record. Although this choice prevented us from benefiting from some of the main advantages of SEM, error free measurement of constructs, we were still able to utilize MVPA for the measurement of indirect effects. This choice also allowed us to adjust for lifestyle in our standard linear regression models

by including the factor scores as an additional covariate in our models. Another limitation that we were presented with was that MVPA requires that endogenous variables are linear and not categorical variables. However, our analyses using standard regression techniques suggested that the relationship between GWG and child adiposity is non-linear. We therefore used a first and second order polynomial (GWG and GWG^2) to estimate all paths associated with GWG. Although we could sum the estimates to obtain the total for combined GWG, we could not obtain the overall standard error for GWG due to additional limitations placed on the analysis by also employing complex survey design data. We addressed this limitation by estimating the total effect in SAS where we used the partial F-test to estimate the overall p-value for the total effect of GWG and presented p-values and standard errors for each GWG term separately for the related direct and indirect effects. All CFA and MVPA modeling was performed using Mplus version 6.1 (Muthén & Muthén, Los Angeles, CA)

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CHAPTER 4
PREPREGNANCY OBESITY TRENDS AMONG LOW-INCOME WOMEN,
UNITED STATES, 1999-2009

Published in the Maternal and Child Health Journal, 2011

<http://www.springerlink.com/content/q86723444398w125/>

CHAPTER 5
GESTATIONAL WEIGHT GAIN IN OBESE MOTHERS AND ASSOCIATIONS
WITH FETAL GROWTH

Published in the American Journal of Clinical Nutrition, 2010

<http://www.ajcn.org/content/92/3/644.long>

CHAPTER 6

RELIABILITY OF GESTATIONAL WEIGHT GAIN REPORTED

POSTPARTUM: A COMPARISON TO THE BIRTH CERTIFICATE

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Acknowledgments:

This research was performed under an appointment to the Centers for Disease Control and Prevention, administered by the Oak Ridge Institute for Science and Education under contract number DE-AC05-06OR23100 between the U.S. Department of Energy and Oak Ridge Associated Universities.

Disclaimer:

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abstract

Gestational weight gain (GWG) is an important predictor of short- and long-term adverse maternal and child outcomes. As interest in long-term outcomes increases, utilization of maternal postpartum report is likely to also increase. There is little data available examining the reliability and identifying predictors of bias in GWG recalled by mothers postpartum. We used data from the Early Childhood Longitudinal Study-Birth Cohort, a national study of U.S. children born in 2001, to compare GWG recalled by mothers approximately 10 months postpartum to GWG recorded on the birth certificate among 5,650 records. On average, the postpartum estimates were 2.1 lbs higher (standard error, 0.2 lbs.) than the birth certificate report; 54.7% were within 5 lbs, 27.2% were overreported by more than 5 lbs, and 18.2% were underreported by more than 5 lbs. The difference between the two sources increased with GWG reported postpartum and was significantly greater among mothers who were obese prior to pregnancy, had inadequate prenatal care, or were multiparous. Bias also differed by birth outcome indicating the potential for recall bias. When categorized by adequacy of the 2009 Institute of Medicine GWG recommendations, 70% of women were similarly categorized and associations between GWG adequacy and small- and large-birthweight-for-gestational-age did not differ meaningfully by source of GWG data. These results suggest that for future studies mothers' estimates of their GWG, obtained within the approximately the first year postpartum, may be a reliable substitute when birth certificate GWG data are unavailable.

Introduction

Gestational weight gain (GWG) recommendations were recently revised in 2009. To better define appropriate GWG, the Institute of Medicine (IOM) called for further research on special populations and the associations between GWG and long-term outcomes (1). Because in studies of long-term outcomes, GWG often must be estimated on the basis of maternal report, it is important to identify potential biases in recalled data and how this may impact epidemiologic measures.

Measured maternal weights abstracted from clinical records are considered the gold standard for GWG estimates (1). However, clinical records are not commonly available for large-scale epidemiologic analyses, and thus Vital Statistics data are commonly used (2, 3). Although comparisons of GWG estimates based on birth certificate and maternal clinical records suggest that birth certificate records provide a reliable estimate of GWG (4-7), the use of birth certificate GWG data can be limited. Maternal prepregnancy body mass index (BMI) is not available on many states' birth certificates and GWG recommendations are specific to prepregnancy BMI status. Also obtaining birth certificate data usually requires complex probability based linkages with cohort data that have the potential to lead to bias (8). Therefore women are often asked to recall their prepregnancy weight and GWG at study or program enrollment (9-13) and this practice is likely to increase due to growing interest in long-term outcomes of GWG (1). However, limited data are available regarding the reliability of recalled GWG estimates (14-16). Results of one hospital-based study found that mothers who reported their GWG 4-12 years postpartum tended to overestimate their actual weight gain and

that this reporting bias differed by several characteristics (15), while a small study among adolescents found that when recalled approximately 6 months postpartum, bias in GWG estimates was relatively low (16).

In our study, we used GWG and prepregnancy BMI from the nationally representative Early Childhood Longitudinal Study-Birth Cohort (ECLS-B) to assess the reliability of GWG reported by mothers approximately 10 months postpartum, relative to GWG reported on their child's birth certificate. We identified factors associated with bias and assessed the impact of using GWG from different sources on the association between GWG and infant birthweight-for-gestational-age, one of the most commonly studied outcomes of GWG (1).

Methods

Data source

The ECLS-B is a longitudinal study of a nationally representative cohort of children born in 2001 (17). The ECLS-B sample frame was drawn from birth certificate data collected by the National Center for Health Statistics and select variables from birth certificate were maintained on the ECLS-B data file. In 2001 all states were using the 1989 Certificate of Live Birth. For the present analysis we used birth certificate data and data collected at the first study wave of the ECLS-B, when children in our sample were on average 10 months of age. As required by the Department of Education, which sponsored the ECLS-B, we rounded sample sizes to the nearest 50 and present all percentages as weighted population estimates.

The ECLS-B enrolled 10,700 infants (Figure 6.1). Birth certificate data was unavailable for a small number of records (n=100) and California did not report GWG on the birth certificate in 2001. Therefore we restricted this analysis to records with birth certificate data and from states other than California (n=9,000). We further limited our analysis to records of singleton infants (n=7,500). We performed a complete-subject analysis and excluded records missing data for any of the relevant study variables (discussed below) (n=1,000). The final analytic sample consisted of 5,650 women (Figure 6.1, primary sample) representative of 2,591,454 women who gave birth to singleton infants in the United States in 2001, excluding California.

Variables

Although the protocol for ascertaining birth certificate GWG (GWG_{BC}) varies by state and birth hospital (7, 18-20), in 2001 the birth certificate queried GWG using the following fill in the blank format, “Weight gained during pregnancy ___ (lbs)” (21). If a woman reported losing weight during pregnancy it was coded as zero gain and any gains >98 lbs were coded as 98 lbs by the National Center for Health Statistics. We excluded any records with 98 lbs recorded on the birth certificate as these values were rare (n<50) and represent an unknown range of true values. Postpartum estimate of GWG (GWG_{PP}) was ascertained at approximately 10 months postpartum via an in-home computer assisted interview (17). Biological mothers were asked, “How much weight did you gain during your pregnancy?” We converted any weight gains reported in kg to lbs (1% of records). To be consistent with the birth certificate data cleaning, we coded weight loss as zero gain and excluded any records with $GWG_{PP} \geq 98$ lbs (n=100). Not all records included GWG from both sources. Because we were interested in comparing maternal

report of GWG from the two sources, we excluded records missing either GWG value ($n=850$) (Figure 6.1). The difference between GWG estimates were calculated as GWG_{PP} minus GWG_{BC} and were assessed continuously and categorically (overreported by 5 lbs, within 5 lbs, or underreported by 5 lbs).

At the parent interview, mothers were asked their current height and to their prepregnancy weight. We calculated prepregnancy BMI (kg/m^2) and categorized women as underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), or obese (BMI ≥ 30.0) (22). Using prepregnancy BMI and each source of GWG, we assessed GWG adequacy on the basis of the 2009 Institute of Medicine GWG recommendations (1): 28-40 lbs (BMI <18.5); 25-35 lbs (BMI 18.5-24.9); 15-25 lbs (BMI 25.0-29.9); and 11-20 lbs (BMI ≥ 30.0). We compared the distribution of GWG adequacy by each source. In addition, we examined the potential for digit preference in GWG estimates by computing the proportion of records in which GWG ended in a 0 or a 5; on average, only 10% should have ended in a 0 or 5 if there was no rounding.

We used data from the birth certificate to categorize women by the following characteristics: maternal age, race/ethnicity; marital status; schooling; parity; adequacy of prenatal care utilization (23); diabetes before or during pregnancy; cesarean delivery; preterm birth; and birthweight-for-gestational-age based on age- and sex-specific percentiles (24) [small-for-gestational-age (SGA), $<10^{\text{th}}$ percentile; appropriate, 10^{th} - 90^{th} percentile; large-for-gestational-age (LGA), $>90^{\text{th}}$ percentile]. Women were also categorized based on data collected at the parent interview as having participated in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) during pregnancy; and having smoked during the last 3 months of pregnancy. Mothers were

weighed twice during the interview and the average was used to calculate postpartum weight retention (PPWR, average current weight minus prepregnancy weight).

Statistical Analyses

For univariate analyses we calculated weighted proportions and means with standard errors (SEs) and for bivariate analyses we assessed differences across groups using chi-square statistics and analysis of variance. We assessed correlations between GWG sources using Pearson correlation coefficients and assessed agreement of adequacy categorization by computing a kappa statistic. To identify predictors of the bias between GWG sources we used a multivariable linear regression model adjusted for all covariates of interest including GWG_{PP} .

We assessed the impact of using GWG from the two sources on estimates of the association between GWG and birthweight-for-gestational-age. These analyses were further limited to the 4,400 records of mothers without diabetes who delivered full-term (37- 44 weeks of gestation) (Figure 6.1, secondary sample). We excluded mothers with diabetes because diabetes may affect GWG (25) and also fetal growth (26). We also excluded mothers of preterm infants because evidence suggests that fetal growth is different in preterm than term infants (27). Using logistic regression, we estimated adjusted odds ratios (aORs) and 95% confidence intervals (CIs), using adequate GWG as the referent, to compare the independent associations between GWG adequacy and birthweight-for-gestational-age by each GWG data source. These models were adjusted for the following covariates chosen a priori: maternal age, race-ethnicity, marital status,

parity, schooling, smoking status during pregnancy, participation in WIC during pregnancy, adequacy of prenatal care utilization, height, and prepregnancy BMI.

For all study analyses we considered P-values <0.05 to be significant for main effects. All analyses were performed with use of Statistical Analysis Software (SAS) version 9.2 (SAS Institute Inc., Cary, NC) with Taylor series approximations for standard error calculations to account for the complex design of the ECLS-B. This study was reviewed by a human subjects coordinator at the CDC and determined not involving human subjects in accordance with the federal human subject's protection regulations and CDC's Guidelines for Defining Public Health Research and Public Health Non-Research.

Results

Compared with women in the primary study sample, those excluded from the sample due to missing or invalid data were more likely to be Hispanic; to be unmarried; to have not completed high school; to have received inadequate prenatal care; and to have given birth to a preterm, SGA, or LGA infant. There were no meaningful differences between the primary study sample and those excluded in regard to GWG or in the bias between the two reports of GWG (data not shown).

Among study participants, mean GWG_{BC} was 30.8 lbs (SE, 0.2 lbs), and mean GWG_{PP} was 32.9 lbs (SE, 0.3 lbs), a difference of 2.1 lbs (SE, 0.2 lbs). The correlation between the two estimates was 0.68. GWG_{PP} was within 5 lbs of GWG_{BC} for 54.7% of respondents (including 15.2% for whom the estimates exactly agreed), underreported by

more than 5 lbs for 18.2% of respondents, and overreported by more than 5 lbs for 27.2% of respondents (Figure 6.2). Among women whose GWG_{PP} estimates were underreported by more than 5 lbs the mean difference in estimates was 12.9 lbs (SE, 0.3 lbs) and among those whose GWG_{PP} estimates were overreported by more than 5 lbs the mean difference was 15.9 lbs (SE, 0.3 lbs).

The median age of infants at the postpartum interview was 9.9 months (interquartile range 9.2, 11.1 months); we found no significant differences between the two sets of GWG estimates when we stratified by the time between giving birth and the ECLS-B parent interview (data not shown). The bias between estimates differed significantly by several characteristics, but not by maternal parity, maternal diabetes status, infant gestational age status or infant birthweight-for-gestational-age status (Table 6.1).

GWG from both sources ended in a zero more often than expected by chance, although it was more likely on the GWG_{PP} (41.1%) than the GWG_{BC} (30.5%) ($P < 0.0001$). Similarly, yet less pronounced, GWG ended in a five more often than expected and it was more likely on the GWG_{PP} (25.5%) than GWG_{BC} (17.1%) ($P < 0.0001$).

When categorized by adequacy of GWG, 70% of women were similarly categorized between the birth certificate and maternal postpartum report ($\kappa = 0.53$) (Table 6.2). The overall distributions of adequacy of GWG were similar between sources, as approximately 35% were categorized as gaining adequately regardless of the source of

the GWG estimate. The highest agreement was among those who were categorized as gaining excessively.

Several maternal and child characteristics significantly predicted the bias between GWG reports based on the unadjusted model; however, many were attenuated in the adjusted model (Table 6.3). The most influential predictor of the bias was GWG_{PP} , such that reporting low GWG_{PP} was associated with an underestimate of GWG_{BC} , while reporting high GWG_{PP} was associated with an overestimate of GWG_{BC} . The other significant predictors of the bias included parity, adequacy of prenatal care utilization, prepregnancy BMI, preterm birth and birthweight-for-gestational-age.

Associations between GWG adequacy and infants' birthweight-for-gestational-age classification did not differ meaningfully by source of GWG estimate (Table 6.4).

Discussion

When asked to estimate their GWG approximately 10 months postpartum, 55% of the women in our study estimated their GWG to be within 5 lbs of GWG recorded on their child's birth certificate, leading to a similar adequacy of GWG classification among 70% of women. This percentage of agreement was higher than that found in a previous study in which women were asked to estimate their GWG 4-12 years postpartum (15). Similarly, both studies found that when discordant, the postpartum report tended to be an overestimate. Although bias between data sources was apparent, our findings indicate that associations between GWG and fetal growth differ little by the source of GWG data.

Similar to previous studies (15, 28), we found that the bias between GWG estimates varied by several maternal characteristics. Our study builds on these prior studies by utilizing a multivariable model to identify predictors of bias independent of the amount of GWG reported postpartum, as it was the strongest predictor of the bias. Within this model the additional characteristics that significantly predicted the bias were prenatal care utilization, parity, prepregnancy BMI, and the birth outcome. It is plausible that among women with inadequate prenatal care, the accuracy of the birth certificate may be limited as GWG estimates may be derived from sparse medical records likely leading to an overestimate of GWG. Our finding that women who were obese prior to pregnancy were more likely to overestimate their recalled GWG is consistent with previous studies showing that, when asked during pregnancy, heavier women are more likely to overestimate their target GWG (29-31). We also found that compared to those who gave birth to a full-term infant, women who gave birth to a preterm infant were more likely to overestimate their GWG when asked postpartum, relative to birth certificate report. This finding may be at least in part because women who delivered early may not have been weighed as frequently as those who delivered at term (32) and thus less likely to know their weight at the time of delivery. In addition women who gave birth to an SGA infant were more likely to overestimate, while those who gave birth to an LGA infant were more likely to underestimate their GWG, further indicating the potential for recall bias.

We aimed to assess the impact of the reporting bias by comparing the association between GWG and birthweight-for-gestational age using each of the data sources. We found that the odds ratios varied little by the source of GWG, suggesting that the bias has

little impact on this association when assessed by the adequacy of current recommendations. Therefore for future studies, postpartum estimates of GWG obtained approximately within the first year may be a reliable substitute when birth certificate data are unavailable. Further these results can be used to inform the choice of GWG data for future maternal and child health studies using the ECLS-B, which provides a wide range of high quality data on mothers, fathers and children in the United States (33).

We considered the birth certificate GWG as the referent in our analyses because it was recorded much closer to the time of birth and in many instances may have been abstracted from the gold standard source, maternal medical records (18). The birth certificate protocol for ascertaining data varies across and even within states (7, 18-20), for example, a previous report within one state found that GWG estimates were obtained from the maternal medical record 31% of the time, the prenatal record 56% of the time, and from a birth certificate worksheet completed by the parents prior to discharge 13% of the time (18). Therefore birth certificate GWG in this analysis may not always be based on the maternal medical record; however, overall birth certificates have been shown to provide a reliable estimate compared to maternal medical records (4, 7), although the accuracy of the birth certificate GWG may be diminished when based on maternal report (34). Our choice of the birth certificate as the reference source for our analysis is further supported by the observation that digit preference was considerably less in the birth certificate report than the postpartum report. Also of note, all birth certificate data in the ECLS-B were from the 1989 revision. A new version of the birth certificate has since been approved in 2003 and has slowly been implemented by many states. This new version collects data on maternal height, prepregnancy weight, and

delivery weight (35), which can be used to calculate GWG and prepregnancy BMI. Once this version is implemented by all states and the data are made publically available, vital statistics derived from these data will become a nationally representative source for GWG research.

Possible limitations to our study included the study sample not being completely representative of the population of U.S. women who gave birth to singleton infants in 2001, in part, because of the exclusions previously described; however, as we reported, the distribution of characteristics differed little between participants included in and excluded from our study. In addition, because GWG was not reported on the birth certificate in California, we could not include records of infants born in California in our analysis. Another limitation is that prepregnancy BMI may have been underestimated because it was calculated on the basis of their self-reported prepregnancy weight, and women tend to underestimate their weight (36); although, as performed in our study, adjustment for maternal sociodemographic characteristics has been shown to help to minimize the error in self-reported estimates (36). To distinguish between term and preterm infants, we chose to utilize the National Center for Health Statistics' variable for calculation of gestational age, which preferences the last menstrual period, opposed to the clinical estimate because the clinical estimate may be differentially biased with regard to some of the variables we were interested in utilizing for our analysis (37). Although the chosen variable may overestimate the proportion of preterm infants, we compared our results to those obtained using only the clinical estimate and found no meaningful differences.

Strengths of our study included our use of a multivariable model to examine predictors of the bias between GWG reports. Although results from previous studies have indicated that a large number of sociodemographic variables are related to such differences, we found that many of these differences were attenuated in our diverse sample after adjustments for other factors in the model. Our findings may help future researchers interested in collecting GWG data postpartum to better understand the potential sources of bias in GWG estimates and how their estimates might compare with vital statistics data on GWG. Lastly, we assessed the impact of using postpartum estimates of GWG on epidemiologic measures compared to the birth certificate.

In conclusion, our findings showed that for most women estimates of GWG made approximately 10 months postpartum were within 5 lbs of the GWG reported on their child's birth certificate, and that the mean difference between sources was only 2.1 lbs. These findings suggest that epidemiologic analyses of the relationship between GWG and birth outcomes based on GWG data collected postpartum will likely produce estimates of association similar to those based on GWG data derived from birth certificates.

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Table 6.1. Distribution of gestational weight gain reporting difference by sociodemographic characteristics of study sample, Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2002

Characteristics	%	Gestational Weight Gain Difference % Distribution			p-value
		Underreport >5 lbs	Within 5 lbs	Overreport >5 lbs	
Total		18.2	54.7	27.2	
Age (years)					**
15-19	10.9	20.5	50.3	29.1	
20-24	26.0	19.1	50.0	30.9	
25-29	26.7	18.2	53.7	28.0	
30-34	23.4	16.9	60.4	22.7	
35-50	12.9	16.5	59.3	24.2	
Race-ethnicity					****
White, non-Hispanic	66.9	15.2	59.0	25.8	
Black, non-Hispanic	15.4	25.2	42.0	32.8	
Hispanic	14.3	24.7	48.2	27.0	
Asian/Pacific Islander/ Hawaiian	2.6	16.1	58.4	25.5	
American Indian/Alaskan Native	0.8	22.4	40.5	36.1	
Marital status					****
Married	68.6	17.4	58.1	24.5	
Unmarried	31.4	20.0	47.1	32.9	
Schooling					****
<High school	18.6	23.8	43.3	33.0	
High school	31.5	19.6	50.4	30.0	
Some college	22.8	18.1	55.3	26.6	
College graduate	27.1	12.7	66.9	20.3	
Parity					
Primiparous	41.6	16.9	56.4	26.7	
Multiparous	58.4	19.1	53.5	27.4	
WIC participation during pregnancy					****
Yes	39.3	20.3	47.3	32.4	
No	60.7	16.8	59.4	23.7	
Adequacy of prenatal care utilization ^a					****
Inadequate	9.6	22.4	41.3	36.3	

Intermediate	14.7	17.1	57.5	25.4	
Adequate	45.0	18.0	55.8	26.1	
Intensive	30.6	17.6	55.8	26.6	
Any diabetes during pregnancy					
Yes	2.7	15.9	62.4	21.7	
No	97.3	18.2	54.5	27.3	****
Smoked during pregnancy					
Yes	12.6	17.2	47.4	35.4	
No	87.4	18.3	55.7	26.0	****
Postpartum weight retention (lbs)					
≤0	26.3	19.2	59.5	21.3	
1 to 10	25.2	15.0	61.0	24.0	
11 to 20	19.3	19.6	52.6	27.8	
≥21	29.2	19.0	46.3	34.7	****
Prepregnancy BMI categorization ^b					
Underweight	5.8	13.8	50.7	35.5	
Normal weight	55.2	15.7	57.5	26.8	
Overweight	24.1	20.7	53.0	26.3	
Obese	14.9	25.0	48.5	26.5	****
GWG adequacy ^c based on the postpartum estimate					
Inadequate	18.5	37.5	56.8	5.7	
Adequate	35.2	19.2	64.8	16.0	
Excessive	46.3	9.8	46.1	44.2	*
Cesarean delivery					
Yes	24.9	20.1	50.6	29.3	
No	75.1	17.5	56.0	26.4	
Preterm birth					
Yes	9.8	18.7	50.4	30.9	
No	90.2	18.1	55.1	26.7	
Birthweight-for-gestational-age ^d					
Small	9.5	20.5	54.6	24.9	
Appropriate	80.6	18.5	54.4	27.1	
Large	10.0	13.9	56.7	29.5	

* P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001.

Abbreviations: BMI, body mass index; GWG, gestational weight gain; lbs, pounds; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children

^aAdequacy of prenatal care utilization based on previously recommended definitions (23).

^bPrepregnancy BMI categorization based on the WHO recommendations (22).

^cGestational weight gain adequacy determined according to the 2009 Institute of Medicine Recommendations (1).

^dBirthweight-for-gestational-age based on age-and sex-specific percentiles (24) [small-for-gestational-age (SGA), <10th percentile; appropriate, 10th-90th percentile; large-for-gestational-age (LGA), >90th percentile].

Table 6.2. Agreement between gestational weight gain recorded on the birth certificate and recalled by mothers postpartum when categorized by adequacy according to the 2009 Institute of Medicine Recommendations^a, Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2002

		Postpartum Report of GWG			Total %
		Inadequate %	Adequate %	Excessive %	
Birth Certificate Report of GWG	Inadequate	12.3	5.4	2.7	20.3
	Adequate	4.7	22.6	8.3	35.6
	Excessive	1.5	7.3	35.3	44.1
	Total	18.5	35.2	46.3	100.0

Abbreviations: BMI, body mass index; GWG, gestational weight gain; lbs, pounds.

^a2009 Institute of Medicine Recommendations (1).

Table 6.3. Unadjusted and adjusted difference between gestational weight gain recorded on the birth certificate and recalled by mothers postpartum, Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2002

Characteristics	Unadjusted Bias (lbs)	[95% CI]	Adjusted ^a Bias (lbs)	[95% CI]
Age (years)				
15 - 19	1.3	[0.0, 2.6]	0.4	[-1.4, 2.2]
20 - 24	1.6	[0.5, 2.6]	0.6	[-0.5, 1.7]
25 - 29	1.0	[-0.2, 2.3]	1.0	[0.1, 1.9]
30 - 34	Reference		Reference	
35 - 50	0.6	[-0.6, 1.8]	0.6	[-0.4, 1.6]
Race-ethnicity				
White, non-Hispanic	Reference		Reference	
Black, non-Hispanic	-0.1	[-1.5, 1.2]	0.4	[-0.8, 1.6]
Hispanic	-1.3	[-2.2, -0.3]	-0.4	[-1.3, 0.5]
Asian/Pacific	-0.7	[-1.7, 0.4]	0.9	[-0.1, 1.8]
Islander/Hawaiian				
American Indian/ Alaskan Native	1.5	[-0.7, 3.7]	0.7	[-1.1, 2.4]
Marital status				
Married	Reference		Reference	
Unmarried	1.3	[0.6, 2.0]	0.0	[-0.8, 0.9]
Schooling				
<High school	0.8	[-0.2, 1.8]	-0.2	[-1.5, 1.0]
High school	1.3	[0.3, 2.3]	0.2	[-1.0, 1.2]
Some college	0.6	[-0.5, 1.7]	-0.1	[-1.2, 1.0]
College graduate	Reference		Reference	
Parity				
Primiparous	Reference		Reference	
Multiparous	-0.2	[-1.0, 0.5]	1.4	[0.7, 2.2]
WIC participation during pregnancy				
Yes	1.2	[0.4, 2.0]	0.6	[-0.4, 1.7]
No	Reference		Reference	
Adequacy of prenatal care utilization^b				
Inadequate	2.3	[0.7, 3.6]	2.3	[1.0, 3.6]
Intermediate	0.1	[-0.9, 1.1]	0.1	[-0.8, 0.9]
Adequate	Reference		Reference	
Intensive	0.3	[-0.6, 1.2]	-0.2	[-0.9, 0.6]
Any diabetes during pregnancy				

Yes	-0.2 [-2.1, 1.6]	1.4 [-0.6, 3.4]
No	Reference	Reference
Smoked during pregnancy		
Yes	2.1 [1.0, 3.2]	0.7 [-0.3, 1.8]
No	Reference	Reference
Postpartum weight retention (lbs)		
≤0	Reference	Reference
1- 10	0.8 [-0.3, 1.9]	-0.1 [-1.0, 0.8]
11 – 20	1.0 [-0.4, 2.4]	-1.1 [-2.2, 0.0]
≥21	3.1 [1.8, 4.4]	0.0 [-1.1, 1.1]
Prepregnancy BMI categorization ^c		
Underweight	1.4 [-0.3, 3.0]	0.6 [-0.7, 1.9]
Normal weight	Reference	Reference
Overweight	-1.0 [-1.9, 0.0]	0.1 [-0.8, 1.0]
Obese	-1.5 [-2.7, -0.3]	2.1 [0.8, 3.3]
GWG estimated postpartum (lbs)		
≤ -10	-8.0 [-9.3, -6.6]	-9.3 [-10.8, -7.9]
11- 20	-3.1 [-4.0, -2.3]	-3.6 [-4.4, -2.8]
21 – 30	Reference	Reference
31 – 40	3.1 [2.3, 3.9]	3.5 [2.7, 4.3]
≥41	12.1 [11.4, 12.9]	12.5 [11.7, 13.3]
Cesarean delivery		
Yes	0.1 [-0.7, 0.9]	-0.3 [-1.0, 0.5]
No	Reference	Reference
Preterm birth		
Yes	0.7 [-0.5, 2.0]	2.3 [1.1, 3.4]
No	Reference	Reference
Birthweight-for-gestational-age ^d		
Small	-0.8 [-1.8, 0.3]	0.8 [-0.1, 1.6]
Appropriate	Reference	Reference
Large	1.4 [0.1, 2.8]	-1.4 [-2.6, -0.1]

Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; lbs, pounds; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

^aModel adjusted for all covariates included in table.

^bAdequacy of prenatal care utilization based on previously recommended definitions (23).

^cPrepregnancy BMI categorization based on the WHO recommendations (22).

^dBirthweight-for-gestational-age based on age-and sex-specific percentiles (24) (small-for-gestational-age, <10th percentile; appropriate, 10th-90th percentile; large-for-gestational-age, >90th percentile).

Table 6.4. Adjusted^a associations between gestational weight gain adequacy^b and giving birth to an SGA or LGA infant^c, by source of gestational weight gain estimate, Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2002

Outcome	Data source	Gestational Weight Gain					
		Inadequate		Adequate		Excessive	
		aOR	[95% CI]	aOR	[95% CI]	aOR	[95% CI]
SGA	Birth certificate	2.0	[1.6, 2.5]	Reference		1.0	[0.7, 1.3]
	Postpartum report	2.1	[1.6, 2.7]	Reference		0.8	[0.6, 1.0]
LGA	Birth certificate	0.6	[0.3, 0.9]	Reference		2.1	[1.5, 3.0]
	Postpartum report	0.4	[0.2, 0.7]	Reference		2.0	[1.6, 2.6]

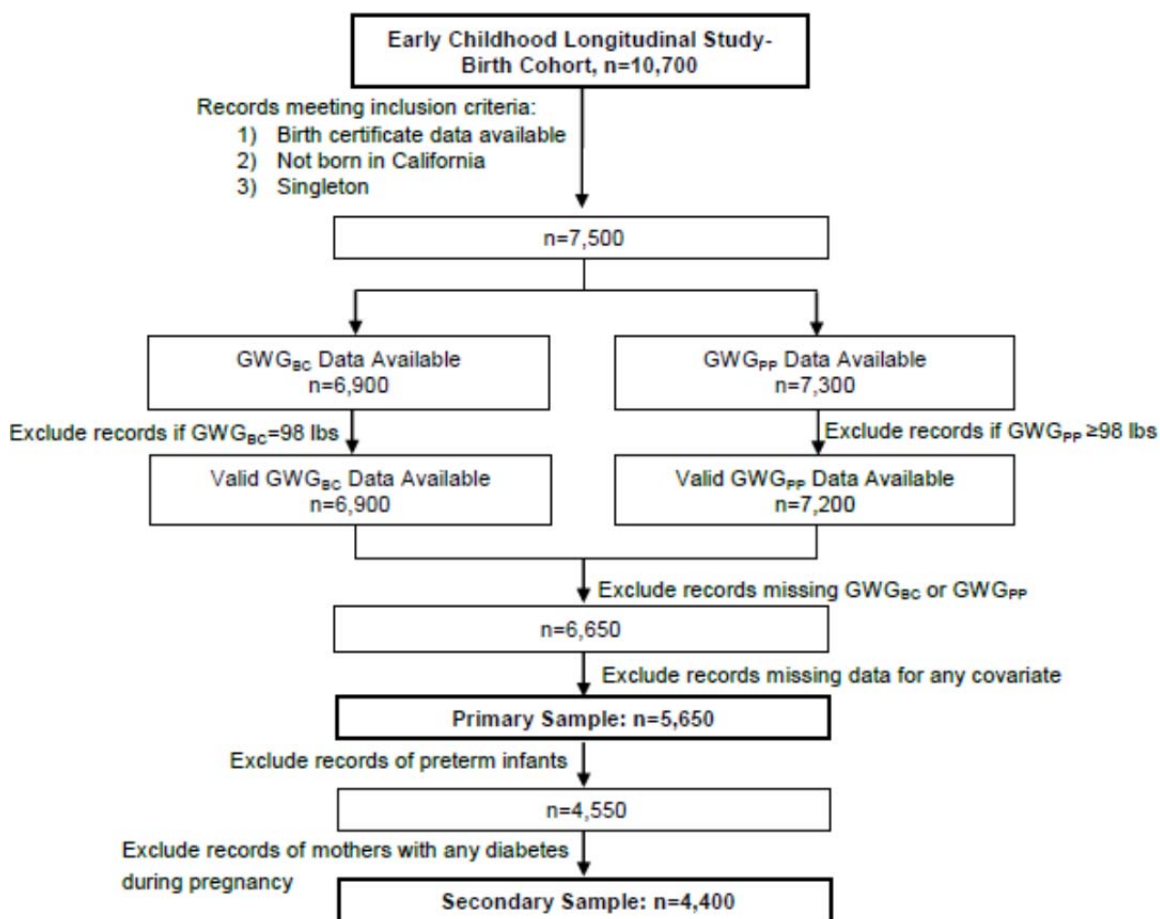
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; LGA, large-for-gestational-age; SGA, small-for-gestational-age

^a Models adjusted for: maternal age, race-ethnicity, marital status, maternal schooling, participation in the Special Supplemental Nutrition Program for Women, Infants, and Children Program during pregnancy, adequacy of prenatal care utilization, parity, smoking during the last 3 months of pregnancy, maternal height, and prepregnancy body mass index.

^b Gestational weight gain adequacy determined according to the 2009 Institute of Medicine Recommendations (1).

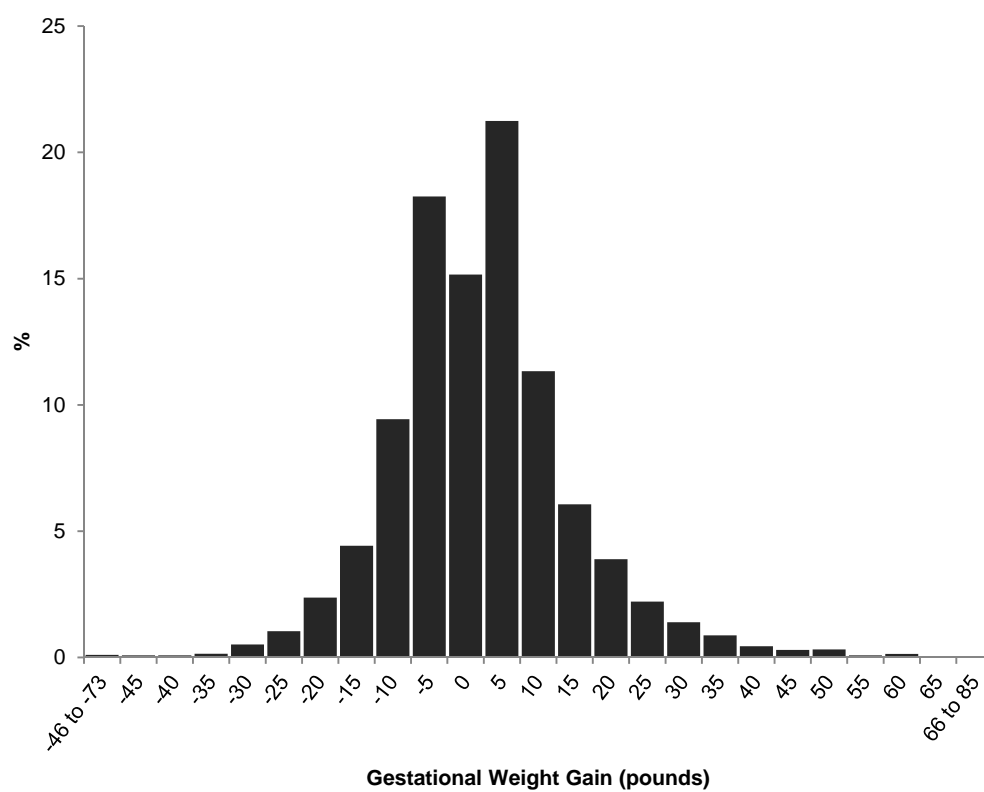
^c birthweight-for-gestational-age based on age-and sex-specific percentiles (24) (SGA, <10th percentile; LGA, >90th percentile).

Figure 6.1. Study inclusion and exclusion criteria with sample size, Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2002



Sample sizes reported rounded to the nearest 50 per data agreement with the U.S. Department of Education. GWG_{BC} , gestational weight gain recorded on the birth certificate; GWG_{PP} , gestational weight gain recalled by mothers postpartum; lbs, pounds

Figure 6.2: Distribution of the difference between gestational weight gain recorded on the birth certificate and gestational weight gain recalled by mothers postpartum, Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2002



End categories collapsed due to sample size reporting restrictions per data agreement with the U.S. Department of Education

CHAPTER 7

GESTATIONAL WEIGHT GAIN AND CHILD ADIPOSITY MEASURED AT

5 YEARS OF AGE: EXAMINATION OF DIRECT AND INDIRECT

MECHANISMS

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Acknowledgments:

This research was performed under an appointment to the Centers for Disease Control and Prevention, administered by the Oak Ridge Institute for Science and Education under contract number DE-AC05-06OR23100 between the U.S. Department of Energy and Oak Ridge Associated Universities.

Disclaimer:

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abstract

In 2009, the Institute of Medicine updated recommendations for gestational weight gain (GWG) and noted inconsistencies in the literature regarding the association with long-term child outcomes, specifically child adiposity. GWG has been previously hypothesized to act on child adiposity through both a direct and indirect mechanism, the later mediated through birthweight, however the presence and degree of mediation remains unclear. We analyzed data from 3,600 participants of the nationally representative Early Childhood Longitudinal Study-Birth Cohort. We used multivariable linear regression, controlling for sociodemographics and family lifestyle, to examine associations between GWG and subsequent child adiposity measured at 5 years of age. We further used path analysis to provide a more detailed understanding of the direct and indirect effects. No significant association was observed among underweight mothers. Among normal weight mothers there was no significant association between GWG and child BMI z-score at weight gains below 30 lbs, whereas above 30 lbs, child BMI z-score increased significantly with increases in GWG ($p < 0.001$). Similarly, among overweight mothers there was no association between GWG and child BMI z-score with weight gains below 20 lbs, but increased significantly with GWG above 20 lbs ($p < 0.01$). The addition of birthweight-for-gestational-age to the model slightly attenuated the association among normal weight mothers ($p < 0.01$) and fully attenuated the association among overweight mothers. Path analysis models indicated a positive association between GWG and birthweight-for-gestational-age among all BMI groups, and with the exception of underweight mothers, birthweight-for-gestational-age was positively associated with child BMI z-score. Our findings indicate the presence of an indirect effect

of GWG on child adiposity among normal, overweight and obese mothers, with a direct mechanism among normal weight mothers only. Prevention of excessive GWG may be one among other strategies to prevent childhood obesity.

Introduction

The Institute of Medicine (IOM) recommends that pregnant women gain weight within defined ranges, dependent on their prepregnancy body mass index (BMI), in order to achieve optimal birth outcomes such as birthweight and delivery mode (1). However, it is unclear if the current recommendations are optimal with regard to long-term outcomes as the IOM concluded that there was insufficient evidence on long-term outcomes of gestational weight gain (GWG), including child adiposity. The relationship between GWG and child adiposity is of particular interest given the current obesity epidemic in the United States (2). GWG has been previously hypothesized to act on child adiposity through both an indirect and direct mechanism. Given that GWG is positively associated with birthweight and birthweight is positively associated with BMI later in life (3), there is a clear indirect mechanism for the association between GWG and child adiposity mediated through birthweight. In addition, GWG may be directly associated with an unfavorable intrauterine metabolic milieu (4, 5), which may program children for an increased risk for later obesity (6-8). This biological hypothesis is supported by animal studies, but in studies of humans it has yet to be determined if the direct effect is present and large enough to be meaningful. In addition, maternal lifestyle is related to both GWG (9-11) and child lifestyle (12, 13); consequently human studies assessing the association between GWG and child adiposity may be confounded by lifestyle.

GWG has been associated with child anthropometric measures during infancy (14), childhood (15-22), and adulthood (23-25); however, due to inconsistencies and limitations of previous analyses, the presence and degree of mediation by birthweight

remains unclear. Two studies have utilized sibling analyses to control for shared lifestyle and genetics between mother and child (21, 25) and found either no association (21) or the presence of a direct intrauterine effect only in overweight and obese women (25). Two studies have controlled for select child lifestyle factors (15, 17), albeit no maternal factors, and found a positive association with minimal mediation by birthweight. Most other studies have not controlled for shared lifestyle and therefore may be biased. Many of the prior studies are based on historic cohorts (16, 20, 21, 23-25) and may have limited external generalizability given the dramatic increase in both maternal and child obesity (26, 27) and changes in lifestyles (28, 29) since the data were collected.

We extend previous studies by using measured variable path analysis (MVPA) to provide a more nuanced picture of the relationship between GWG and child adiposity at 5 years of age among a representative sample of children born in the United States in 2001. Although similar to standard regression, MVPA requires specific a priori hypotheses regarding the conceptual framework of the model (Figure 7.1), assesses relations among observed variables based on the covariance structure and can be used to compare nested models. We compare model fit with and without the direct effect of GWG on child adiposity and include unhealthy family lifestyle in the model. We also assess heterogeneity by maternal prepregnancy BMI as it is unclear if associations between GWG and long-term outcomes differ by maternal prepregnancy BMI (1).

Methods

Data source and study population

The Early Childhood Longitudinal Study-Birth Cohort (ECLS-B) is a longitudinal study of a nationally-representative cohort of children born in 2001. Study participants were selected from birth certificates collected by the National Center for Health Statistics' Vital Statistics System. Data from participants and their parents were collected in five waves, at target child ages of 9 months, and 2, 4, 5, and 6 years of age. Wave 4 was the last wave that included the entire cohort since wave 5 was completed only among children who delayed entry into or repeated kindergarten. Therefore we use the children's BMI data measured at wave 4, when children were approximately 5 years of age, as the outcome for the present analysis.

The ECLS-B enrolled 10,700 infants at the first wave of data collection, which included oversampling of select race-ethnic groups, twins and infants born <2,500 g. [As required by the Department of Education, which sponsored the ECLS-B, we report sample sizes rounded to the nearest 50 and present all percentages as weighted population estimates]. Only singleton, full-term (≥ 37 weeks gestational age) infants, born to non-diabetic mothers, were eligible for this analysis ($n=6,700$). We did not include preterm infants because fetal and postnatal growth may differ between full-term and preterm infants (30). In addition we did not include children of mothers with reported diabetes because diabetes may affect GWG (31) and fetal growth may differ among mothers with diabetes (32). This inclusion criterion represents 83% of the weighted ECLS-B population.

Of the eligible sample, 2,400 were lost to follow-up by wave 4; however, all data are weighted to account for non-response in order to maintain a sample with a demographic distribution similar to target population. We performed a complete-subject analysis and excluded any records missing data for any of the study variables (n=700, 16% of the sample meeting the inclusion criteria) leaving a final analytic sample of 3,600 children, weighted to be representative of 2,701,165 children born in 2001.

Maternal prepregnancy body mass index

At the wave 1 ELCS-B parent interview, mothers were asked their current height and their prepregnancy weight. We calculated prepregnancy BMI (kg/m^2) as weight divided by height squared. We categorized mothers as underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), or obese (BMI \geq 30.0).

Gestational weight gain

The ECLS-B includes two sources of GWG, the child's birth certificate and maternal self-report at the wave 1 parent interview. We first used GWG obtained from the birth certificate (81% of records); when unavailable we used GWG reported by mothers at the first parent interview. We compared our final results with those based on a sample using only records with birth certificate GWG and found no meaningful differences (data not shown). The National Center for Health Statistics codes weight loss during pregnancy as zero gain on the birth certificate and codes any gains >98 lbs as 98 lbs; we consistently coded GWG from the parent interview such that records reporting weight loss during pregnancy (n<50) were coded as zero gain and excluded any records with GWG \geq 98 lbs (n<50) as these values were rare and represent an unknown range of

true values. Adequacy of GWG was defined according to the mother's prepregnancy BMI (kg/m^2) status on the basis of the 2009 IOM GWG recommendations (1): 28-40 lbs (BMI <18.5); 25-35 lbs (BMI 18.5-24.9); 15-25 lbs (BMI 25.0-29.9); and 11-20 lbs (BMI ≥ 30.0). Given the IOM's stated interest in examining non-linearity in the associations between GWG and long-term outcomes (1), we included a quadratic term for GWG in all of our continuous models.

Child Adiposity

At wave 4, when the children were approximately 5 years of age, they were weighed and measured twice by trained field workers with shoes and heavy outerwear removed according to a standardized protocol (33). Age- and sex-specific BMI z-scores and percentiles were calculated using the Centers for Disease Control and Prevention's 2000 Growth Charts (34). We categorized children as underweight (BMI $<5^{\text{th}}$ percentile), normal weight (BMI percentile 5^{th} to $<85^{\text{th}}$), overweight (BMI percentile 85^{th} to $<95^{\text{th}}$) or obese (BMI percentile $\geq 95^{\text{th}}$).

Sociodemographic covariates

Maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander/Hawaiian, American Indian/Alaskan Native); age at delivery (in years); parity (primiparous, multiparous); marital status (married, unmarried); and schooling (in years) were obtained from the child's birth certificate. Maternal participation in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) during pregnancy (yes, no) was ascertained during the ECLS-B wave 1 interview.

Family lifestyle variables

We used multiple maternal and child variables to assess overall family lifestyle. Maternal use of tobacco during the last 3 months of pregnancy (yes, no) was ascertained during the wave 1 interview. At the wave 3 interview, mothers were asked how many days in a typical week they exercised for 30 minutes or more. We categorized mothers as non-exercisers if they did not exercise at least once per week (yes, no). At each interview, mothers were weighed at least twice on a digital scale with shoes and heavy outerwear removed. We calculated the mother's change in weight (lbs) from prepregnancy to wave 4, as an indicator of maternal lifestyle (35). If mother's weight at wave 4 was unavailable, we used her weight at either wave 3 (9% of mothers) or wave 5 (<1% of mothers) to calculate weight change from prepregnancy. Children's typical weekly intake of various food groups at approximately 4 years of age was assessed via the wave 3 parent interview. We categorized children as consumers of sugar sweetened beverages (yes, no) (36) and fast-food (yes, no) (37) if they consumed these products at least once a week, based on these products' known associations with child BMI. Children's weekday television viewing habits (38) were assessed at wave 3 by asking parents about the child's typical weekday hours spent watching television and videos/DVDs. We summed the two measures to capture the total weekday television time for each child (hours). Using confirmatory factor analysis (CFA) (39), we defined a latent construct of unhealthy family lifestyle using all of the aforementioned lifestyle related variables. The CFA model was determined to fit well based on multiple goodness-of-fit indices (data not shown) and the factor scores were output for use in regression and MVPA models.

Mediating variables

Using birthweight and gestational age obtained from the child's birth certificate we calculated sex-specific infant birthweight-for-gestational-age z-scores and percentiles according to a national reference (40). Breastfeeding status was assessed at the wave 1 and 2 parent interviews. Duration was censored at the child's age at the wave 2 interview (approximately 2 years of age) if the mother indicated that she was still breastfeeding at that time. We categorized breastfeeding duration for descriptive purposes and natural log-transformed it due to non-normality for models, where it was treated as a continuous variable.

Statistical Analysis

We tested and confirmed a statistical interaction between GWG, GWG^2 and prepregnancy BMI category using a multiple partial F-test with 6 degrees of freedom ($p=0.13$) and therefore stratified all analyses, descriptive and analytic, by maternal prepregnancy BMI category. We computed weighted proportions or means with standard errors (SEs) for all variables and assessed differences across prepregnancy BMI category using chi-square statistics for proportions and analysis of variance (ANOVA) for continuous variables.

For each prepregnancy BMI category, we used ordinary least squares (OLS) regression to estimate the independent association between GWG and child BMI z-score across the entire range of GWG data, with the reference set at the midpoint of the 2009 IOM recommended range for each BMI category. Although the quadratic term for GWG was not significant within all prepregnancy BMI categories, we retained it in all models

for consistency, as the coefficient for this term will approach zero as the underlying association becomes more linear. We present regression coefficients, per 10 lbs GWG, for 4 models. Model A presents the crude association, while Model B is adjusted for sociodemographic covariates only. We additionally adjusted for lifestyle covariates in Model C to demonstrate any independent effect lifestyle has on the estimates. The estimates from this model represent the total effect of GWG on child adiposity and do not differentiate the indirect and direct effects. Last, Model D also includes birthweight-for-gestational-age. The estimates from this model represent the direct effect of GWG, independent of its effect on birthweight.

Based on our a priori conceptual model (Figure 7.1), we used MVPA to further examine how the total effect of GWG on child BMI, as identified by the OLS regression, is decomposed into direct and indirect effects, the latter mediated through birthweight-for-gestational-age. In our conceptual model, we specified a direct effect of GWG on child BMI based on theoretical biological effects; however, because of previously discussed inconsistencies in the literature, we compared model fit with and without the direct effect of GWG on child BMI. All endogenous variables were modeled continuously and we centered and rescaled GWG to stabilize the covariance. As with the OLS regression, we included the quadratic term for GWG and adjusted for all confounders. We stratified MVPA models by prepregnancy BMI and therefore removed all paths associated with prepregnancy BMI from the model. MVPA coefficients are presented as standardized estimates.

MVPA and CFA model fit was determined by considering multiple goodness-of-fit indices, namely the model chi-square, the root mean square error of approximation (RMSEA), the comparative fit index (CFI), the Tucker Lewis index (TLI) and the Akaike Information Criteria (AIC) (39). The null hypothesis for the model chi-square informs the researcher that the over-identified model fits the data. The RMSEA favors a more parsimonious model; in general any value under 0.05 is indicative of adequate fit. The CFI and TLI compare the researcher's model to the baseline independence model; values above 0.95 are indicative of good data-model fit. The AIC compares fit across models, with lower AIC indicating better model fit. Due to the differing utility of each index (41), we report and simultaneously considered each index when examining fit of the various models.

We used Statistical Analysis Software (SAS) version 9.2 (SAS Institute Inc., Cary, NC) for data cleaning, univariate, bivariate and multivariable linear regression analyses. CFA and MVPA were performed using Mplus version 6.1 (Los Angeles, CA). We considered p-values <0.05 significant for main effects and p-values <0.15 significant for multiplicative interactions due to the low power associated with tests of homogeneity (42). All analyses were weighted to account for loss to follow-up and unequal probability of selection, and standard errors were estimated with Taylor Series approximations to account for the multistage, stratified, cluster design of the ECLS-B. This analysis was reviewed by a human subjects coordinator at the CDC and determined not involving human subjects.

Results

We compared records excluded due to missing data with those retained in the analytic sample, and found that the mothers were significantly more likely to be older (mean 27.3 years vs. 26.6 years); to be non-Hispanic white (62.7% vs. 56.6%); to be married (69.7% vs. 62.4%); to be more educated (mean 13.1 vs. 12.0 years); to have not used WIC services during their pregnancy (60.9% vs. 47.0); to have breastfed longer than 6 months (34.8% vs. 25.3%); and to be normal weight prior to pregnancy (57.5% vs. 45.6%); and that the children had a lower BMI z-score at 5 years of age than those excluded (mean 0.67 vs. 0.81). No other significant differences between those excluded due to missing data and those retained in the analytic sample were detected across study variables (data not shown).

In the final sample, 4.7% of mothers were underweight, 57.5% were normal weight, 24.6% were overweight, and 13.2% were obese prior to pregnancy. At wave 4, children were, on average 65 months of age (range 57-74 months), and 1.7% were underweight, 63.9% were normal weight, 18.6% were overweight, and 15.8% were obese. Several participant characteristics differed significantly across maternal prepregnancy BMI categories (Table 7.1). Specifically, as prepregnancy BMI increased, mean GWG significantly decreased and child BMI significantly increased. Less than half of the mothers gained within the IOM GWG recommendations (ranging from 42.3% among underweight to 28.1% among obese mothers).

The associations between GWG and child BMI z-score at 5 years of age stratified by prepregnancy BMI status are presented in Table 7.2. Adjustment for sociodemographic characteristics slightly attenuated the association between GWG and child BMI z-score among normal and overweight mothers. Further adjustment for an unhealthy lifestyle also attenuated the association among overweight mothers only. Regression estimates from Model C are plotted in Figure 2 and represent the overall association between GWG and child BMI z-score. Among underweight mothers, there was no significant association. Among normal weight mothers there was no significant association between GWG and child BMI z-score at weight gains below 30 lbs, whereas above 30 lbs, child BMI z-score increased with further increases in GWG. Among overweight mothers there was no association between GWG and child BMI z-score with weight gains below 20 lbs, but increased with GWG above 20 lbs. Among obese mothers there was no significant overall association. Additional adjustment for birthweight-for-gestational-age in Model D had little impact on the associations with the exception that the model was slightly attenuated and estimates no longer reached statistical significance among overweight mothers (Table 7.2). No significant associations were observed among underweight or obese mothers.

With the exception of obese mothers, where there was little difference between models, MVPA models with the direct effect of GWG on child BMI z-score fit the data best (data not shown, available on request). For consistency we report model parameters with the direct effect of GWG on child BMI z-score for all prepregnancy BMI groups. Table 7.3 presents the parameter estimates for the MVPA model as displayed in Figure 7.3 (sociodemographic parameter estimates were estimated, but are not shown in the table

for simplicity). Unhealthy family lifestyle confounded one or more of the estimated relations in the MVPA model among normal and overweight mothers only, where it was inversely associated with breastfeeding duration among normal and overweight mothers, and positively associated with GWG and child BMI z-score among overweight mothers only. We observed a positive direct effect of GWG on child BMI z-score among normal weight mothers only. Across all prepregnancy BMI categories, there was a positive association between GWG and infant birthweight-for-gestational-age. With the exception of children of underweight mothers, birthweight-for-gestational-age was further positively associated with child BMI z-score, indicating an indirect effect of GWG on child BMI z-score. No significant associations were observed between birthweight-for-gestational-age and breastfeeding duration nor breastfeeding duration and child BMI z-score.

Discussion

We utilized a contemporary, nationally representative cohort to examine the relationship between GWG and child adiposity measured at 5 years of age, and observed heterogeneity by maternal prepregnancy BMI status. Our findings indicate the presence of an indirect effect of GWG mediated through birthweight among normal, overweight, and obese mothers and a direct mechanism among normal weight mothers only. As expected, among all mothers, GWG was positively associated with infant birthweight-for-gestational-age. With the exception of children born to underweight mothers, the association between birthweight-for-gestational-age and child BMI z-score was positive and increased with increasing prepregnancy BMI, indicating a positive indirect effect of

GWG on child adiposity, mediated through birthweight. Heterogeneity by prepregnancy BMI is supported by recent literature examining child anthropometric outcomes and GWG (14, 16, 17, 22, 24, 25) and is consistent with the well documented interaction between GWG and prepregnancy BMI with respect to short-term obstetric outcomes (1).

Our findings are independent of maternal sociodemographics and an unhealthy family lifestyle. Controlling for lifestyle as a confounder is important given that maternal lifestyle is strongly associated with GWG (9, 11) and child lifestyle (12, 13). We utilized various indicators of an unhealthy maternal or child lifestyle to create a factor score for the family's unhealthy lifestyle. We found that the inclusion of unhealthy family lifestyle slightly attenuated the association between GWG and child BMI z-score among overweight mothers, as it was associated with GWG, birthweight-for-gestational-age, breastfeeding duration and child BMI z-score. In addition, by stratifying by prepregnancy BMI status, we partially controlled for shared lifestyle and genetics associated with adiposity (43). We could not, however, control for confounding due to genetic factors related to GWG, but the evidence supporting common genetic factors between excessive GWG and child adiposity is less strong (44, 45).

Our results indicate that a direct effect of GWG on later child adiposity may be present among normal weight mothers only. The significant positive direct effect of GWG, not mediated through birthweight, suggests that excessive GWG among normal weight mothers may have a lasting effect on child adiposity. Excessive GWG is associated with poor dietary quality (10) and an unfavorable intrauterine metabolic environment (4), which may be associated with developmental programming of obesity.

Specific evidence from animal studies suggest that over nutrition during pregnancy is associated with altered fetal adipogenesis, appetite control, and possibly even a preference for high-fat, high-sugar foods (6-8). We hypothesize that the direct effect of GWG was observed only among normal weight mothers, as maternal prepregnancy obesity is also associated with an unfavorable intrauterine metabolic environment (46), and therefore may be masked by the competing risk associated with high prepregnancy BMI.

We used a quadratic model to allow for the flexibility to detect a J- or U-shaped relationship between GWG and child BMI z-score. We observed no association between low GWG and child BMI z-score, which is contrary to only a few previous findings (18, 24). In the absence of this quadratic term we would have concluded that, among normal weight and overweight mothers, low GWG was associated with a decrease in child BMI z-score.

Only a small proportion (4.8%) of mothers were underweight at the start of their pregnancy. While GWG was positively associated with birthweight-for-gestational-age, there was no association between birthweight-for-gestational-age and child BMI z-score. In addition, we did not observe a significant total or direct effect of GWG on child BMI z-score among underweight mothers; however, it is possible that we did not have a sufficient sample size to detect an effect among underweight women. When measured at 5 years of age, most children (78%) born to mothers who were underweight prior to pregnancy had a healthy, normal weight.

In contrast to children born to underweight mothers, a large proportion of children born to obese mothers were either overweight (20%) or obese (27%) at 5 years of age. Maternal GWG was positively associated with infant birthweight-for-gestational-age, and subsequently child BMI z-score, indicating a small indirect effect through birthweight-for-gestational-age. The lack of an overall association between GWG on child BMI z-score may be in part due to the many factors contributing to childhood obesity among children born to obese mothers (7, 43, 47) or the longitudinal nature of this question, which may cause the total effect to be diminished and only detected when assessed at more proximal time points (48). Our principal finding of no overall association among obese mothers should not be interpreted as suggesting that obese mothers can gain across the entire spectrum of GWG without an increased risk of obesity in their offspring, as we did observe a small indirect effect through birthweight-for-gestational-age; furthermore, excess GWG in obese mothers is strongly associated with adverse short-term obstetric outcomes such as macrosomia and cesarean delivery (1).

This analysis was based on a prospective nationally representative longitudinal cohort. We included data obtained from multiple waves of data collection, which reduces recall bias. Although our analytic sample included a greater proportion of records of mothers who tend to have better obstetric outcomes than those who were excluded due to missing data, we observed no differences in GWG, as well as other sociodemographic variables between the two groups. Therefore we believe that external validity has not been compromised and our results are likely generalizable to all non-diabetic mothers who give birth to a singleton, full-term infant. GWG in this study was obtained from the birth certificate for over 80% of the cohort. The birth certificate has previously been

shown to be a reliable source of GWG (49, 50). Lastly, we utilized MVPA to provide a more nuanced picture of the relationship between GWG and child adiposity at 5 years of age. MVPA allowed us to compare models with and without the direct effect of GWG and to easily include multiple mediators, specifically birthweight-for-gestational-age and breastfeeding duration.

Our study had limitations. We calculated prepregnancy BMI from maternal weight that was self-reported by mothers at the first ECLS-B parent interview, approximately 10 months postpartum. Mothers may differentially underreport their prepregnancy weight (51) and therefore it is possible that they were misclassified. Prior studies have found that although some mothers are misclassified the association with prepregnancy BMI and obstetric outcomes were not meaningfully different (52). It is possible that we lacked adequate power to detect an association between GWG and child adiposity among underweight women (n=250). A limitation of MVPA is that good model fit does not necessarily indicate that the model is properly specified. Our conceptual model was determined a priori based on previously published literature, although as with any observational study, the presence of direct and indirect effects do not necessarily imply causality.

The current IOM GWG recommendations were established primarily for the purpose of optimizing birthweight and other short-term obstetric outcomes. At that time, data were insufficient to support child adiposity as an influential outcome (1). Recently there has been concern that recommendations may be too high, given the current obesity epidemic (53). On the other hand, with respect to child adiposity, our data, in accord

with other studies (14, 16, 17, 23), suggest that there is no benefit of low GWG. In addition excessive GWG was associated with an increase in child adiposity among normal and overweight mothers. We also found that a large proportion of women gained more than the IOM recommended GWG ranges, with gains proportion (61%) among mothers who were already overweight. Our study provides the first nationally representative estimates of the proportion of women who gain excessively during pregnancy. Determining how to prevent excessive GWG is a critical “next step”, given the increased risk for adverse short-term obstetric outcomes (1), and as indicated by our study, the increased risk of adiposity among children born to normal and overweight mothers. Some diet and physical activity trials have been successful in the prevention of excessive GWG (54); however, they have not been powered to examine short- or long-term outcomes.

Our study adds to the literature by supporting the association between GWG and child adiposity, specifically among normal weight and overweight mothers. Although current recommendations were established primarily for short-term outcomes, our data support these recommendations in the context of later child adiposity and do not show any benefit of lowering recommendations. Regardless of maternal prepregnancy BMI, prevention of excessive GWG is important for short-term birth outcomes (1) and may be a strategy in the prevention of childhood obesity.

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Table 7.1: Sample characteristics by maternal prepregnancy BMI status, Early Childhood Longitudinal Study-Birth Cohort, United States, 2001- 2007

	Maternal Prepregnancy BMI Status				p-value
	Underweight n=250 ^a Mean (SE) or %	Normal Weight n=2,150 ^a Mean (SE) or %	Overweight n=750 ^a Mean (SE) or %	Obese n=450 ^a Mean (SE) or %	
Maternal Sociodemographic variables					
Age (years)	25.2 (0.6)	27.2 (0.2)	27.7 (0.3)	27.6 (0.4)	***
Race-ethnicity					***
White, non-Hispanic	62.1	65.0	62.6	52.9	
Black, non-Hispanic	11.8	12.0	12.8	25.3	
Hispanic	15.9	17.8	22.5	19.9	
Asian/Pacific Islander/ Native Hawaiian	9.3	4.5	1.6	0.8	
American Indian /Alaskan Native	0.9	0.6	0.6	1.1	
Marital status					**
Married	62.3	72.0	69.5	63.0	
Unmarried	37.7	28.0	30.5	37.0	
Schooling (years)	12.6 (0.2)	13.3 (0.1)	12.9 (0.1)	12.8 (0.2)	***
Parity					***
Primiparous	52.6	44.8	39.5	30.6	
Multiparous	47.4	55.2	60.5	69.4	
Utilized WIC services during pregnancy					**
Yes	51.7	36.6	40.3	43.6	
No	48.4	63.4	59.7	56.5	
Lifestyle variables					

Smoked during pregnancy						
Yes	23.4	10.3	8.0	13.2		***
No	76.6	89.7	92.0	86.8		
Maternal exercise						
Yes	53.1	59.5	58.7	52.6		
No	46.9	40.5	41.3	47.4		***
Maternal weight change from						
prepregnancy (lbs)	21.3 (2.4)	19.0 (0.7)	23.1 (1.5)	18.4 (2.0)		
Child sugar sweetened beverage consumption						
Yes	73.2	70.4	72.2	75.7		
No	26.8	29.6	27.8	24.3		
Child fast food consumption						
Yes	76.5	75.2	76.4	77.2		
No	23.5	24.8	23.6	22.8		**
Child weekday screen time (hours)						
	3.5 (0.3)	3.6 (0.1)	3.6 (0.1)	4.0 (0.2)		*
Unhealthy family lifestyle (factor score) ^b						
	0.06 (0.05)	-0.03 (0.02)	0.01 (0.03)	0.08 (0.03)		
Mediating variables						
Birthweight-for-gestational age z-score						***
	-0.42 (0.09)	-0.08 (0.03)	0.12 (0.04)	0.13 (0.06)		
Breastfeeding duration (months)						
Never or <1	26.9	26.0	30.1	37.7		*
1-5	42.9	36.1	36.8	35.8		
6-11	18.6	19.7	18.4	13.9		
≥12	11.6	18.1	14.7	12.6		
Maternal exposures						
Gestational weight gain (lbs)	35.2 (1.6)	33.6 (0.3)	30.7 (0.6)	24.4 (0.8)		***
Adequacy by 2009 IOM recommendations						

Inadequate	29.8	21.8	8.7	19.0	***
Adequate	42.3	40.4	30.7	28.1	
Excessive	27.9	37.8	60.7	52.9	
Child outcomes at 5 years of age					
BMI z-score	0.32 (0.09)	0.54 (0.03)	0.82 (0.04)	1.04 (0.05)	***
Underweight	2.4	1.8	1.5	1.0	***
Normal weight	77.7	68.7	56.7	51.7	
Overweight	14.1	16.9	22.5	20.4	
Obese	5.8	12.5	19.3	26.9	

Abbreviations: BMI, body mass index; IOM, Institute of Medicine; SE, standard error; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

^a Sample size rounded to the nearest 50 per data agreement with the Department of Education.

^b Based on confirmatory factor analysis model with maternal smoking during pregnancy, exercise and weight change since prepregnancy and child sugar sweetened beverage and fast-food consumption and screen time.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 7.2: Association between gestational weight gain and child BMI z-score at 5 years of age, by maternal prepregnancy BMI status, Early Childhood Longitudinal Study-Birth Cohort, United States, 2001- 2007

Model ^a	Maternal Prepregnancy BMI Status																			
	Underweight n=250					Normal Weight n=2,150					Overweight n=750				Obese n=450					
	GWG		GWG ²		p	GWG		GWG ²		p	GWG		GWG ²		p	GWG		GWG ²		
	β	(SE)	β	(SE)		β	(SE)	β	(SE)		β	(SE)	β	(SE)		β	(SE)	β	(SE)	p
A	0.31	(0.33)	-0.03	(0.04)		-0.11	(0.07)	0.03	(0.01)	***	-0.10	(0.10)	0.03	(0.02)	**	0.00	(0.08)	0.00	(0.01)	
B	0.38	(0.35)	-0.04	(0.04)		-0.07	(0.07)	0.02	(0.01)	***	-0.07	(0.10)	0.03	(0.01)	*	-0.03	(0.08)	0.00	(0.01)	
C	0.42	(0.34)	-0.05	(0.04)		-0.07	(0.07)	0.02	(0.01)	***	-0.04	(0.10)	0.02	(0.01)	*	-0.02	(0.08)	0.00	(0.01)	
D	0.42	(0.34)	-0.05	(0.04)		-0.08	(0.07)	0.02	(0.01)	**	-0.05	(0.09)	0.02	(0.01)		-0.03	(0.09)	0.00	(0.01)	

Abbreviations: BMI, body mass index; GWG, gestational weight gain; SE, standard error.

Sample size rounded to the nearest 50 per data agreement with the Department of Education.

All estimates are per 10 lbs GWG

^a Model A, unadjusted; Model B, adjusted for sociodemographic characteristics; Model C: adjusted for sociodemographic characteristics and unhealthy family lifestyle; Model D: adjusted for sociodemographic characteristics, unhealthy family lifestyle, and birthweight-for-gestational-age z-score.

* p<0.05, ** p<0.01, *** p<0.001.

Table 7.3: Standardized estimates for the path model examining the association between gestational weight gain and child BMI z-score measured at 5 years of age, by maternal prepregnancy BMI, Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2007

Analyzed Path (Figure 3)	Maternal Prepregnancy BMI Status							
	Underweight ^a n=250		Normal Weight ^b n=2,150		Overweight ^c n=750		Obese ^d n=450	
	β	p	β	p	β	p	β	p
Confounding by family lifestyle								
Path A: Unhealthy family lifestyle ^e → GWG	0.06		0.05		0.00		0.00	
Path B: Unhealthy family lifestyle ^e → GWG ²	0.13		0.04		0.10	*	0.10	
Path C: Unhealthy family lifestyle ^e → Birthweight-for-gestational-age z-score	-0.02		-0.03		-0.10	*	-0.02	
Path D: Unhealthy family lifestyle ^e → ln[breastfeeding duration+1]	-0.01		-0.17	***	-0.16	***	-0.03	
Path E: Unhealthy family lifestyle ^e → Child BMI z-score	0.10		0.01		0.12	*	0.07	
Direct effect of GWG								
Path F: GWG → Child BMI z-score	0.18		0.05		0.09		-0.08	
Path G: GWG ² → Child BMI z-score	-0.15		0.05	*	0.05		-0.01	
Indirect effect of GWG through birthweight-for-gestational-age								
Path H: GWG → Birthweight-for-gestational-age z-score	0.33	***	0.19	***	0.22	***	0.20	***
Path I: GWG ² → Birthweight-for-gestational-age z-score	0.11		0.02		0.05		0.03	
Path J: Birthweight-for-gestational-age z-score → Child BMI z-score	-0.02		0.15	***	0.18	***	0.19	***
Path K: Birthweight-for-gestational-age z-score → ln[breastfeeding duration+1]	0.15		0.04		0.04		0.02	

Path L: ln[breastfeeding duration+1]→ Child BMI	0.16	-0.07	0.03	-0.07
Z-score				

Abbreviations: AIC, Akaike Information Criterion; BMI, body mass index; CFI, comparative fit index; CI, confidence interval; DF, degrees of freedom; GWG, gestational weight gain; ln, natural log; RMSEA, root mean square error approximation; TLI, Tucker Lewis index; χ^2 , chi-square.

Sample size rounded to the nearest 50 per data agreement with the Department of Education.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

^a Underweight model fit: $df = 2$; χ^2 : 2.67 $p = 0.26$; RMSEA (90%CI): 0.038 (<0.001, 0.141); CFI: 0.997; TLI: 0.885; AIC: -23555

^b Normal weight model fit: $df = 2$; χ^2 : 3.19 $p = 0.20$; RMSEA (90%CI): 0.017 (<0.001, 0.049); CFI: 0.999; TLI: 0.964; AIC: 20876

^c Overweight model fit: $df = 2$; χ^2 : 4.35 $p = 0.11$; RMSEA (90%CI): 0.039 (<0.001, 0.090); CFI: 0.994; TLI: 0.780; AIC: -4722

^d Obese model fit: $df = 2$; χ^2 : 2.24 $p = 0.33$; RMSEA (90%CI): 0.016 (<0.001, 0.097); CFI: 0.998; TLI: 0.920; AIC: -11669

^f Based on confirmatory factor analysis model with maternal smoking during pregnancy, exercise and weight change since prepregnancy and child sugar sweetened beverage and fast-food consumption and screen time.

Figure 7.1: Conceptual framework for the relationships between gestational weight gain and child adiposity measured at 5 years of age

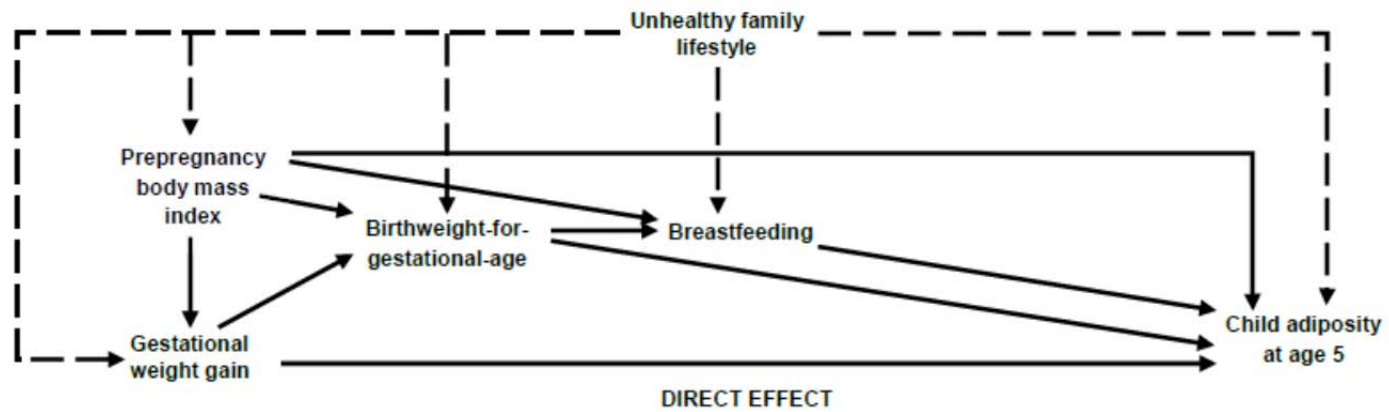
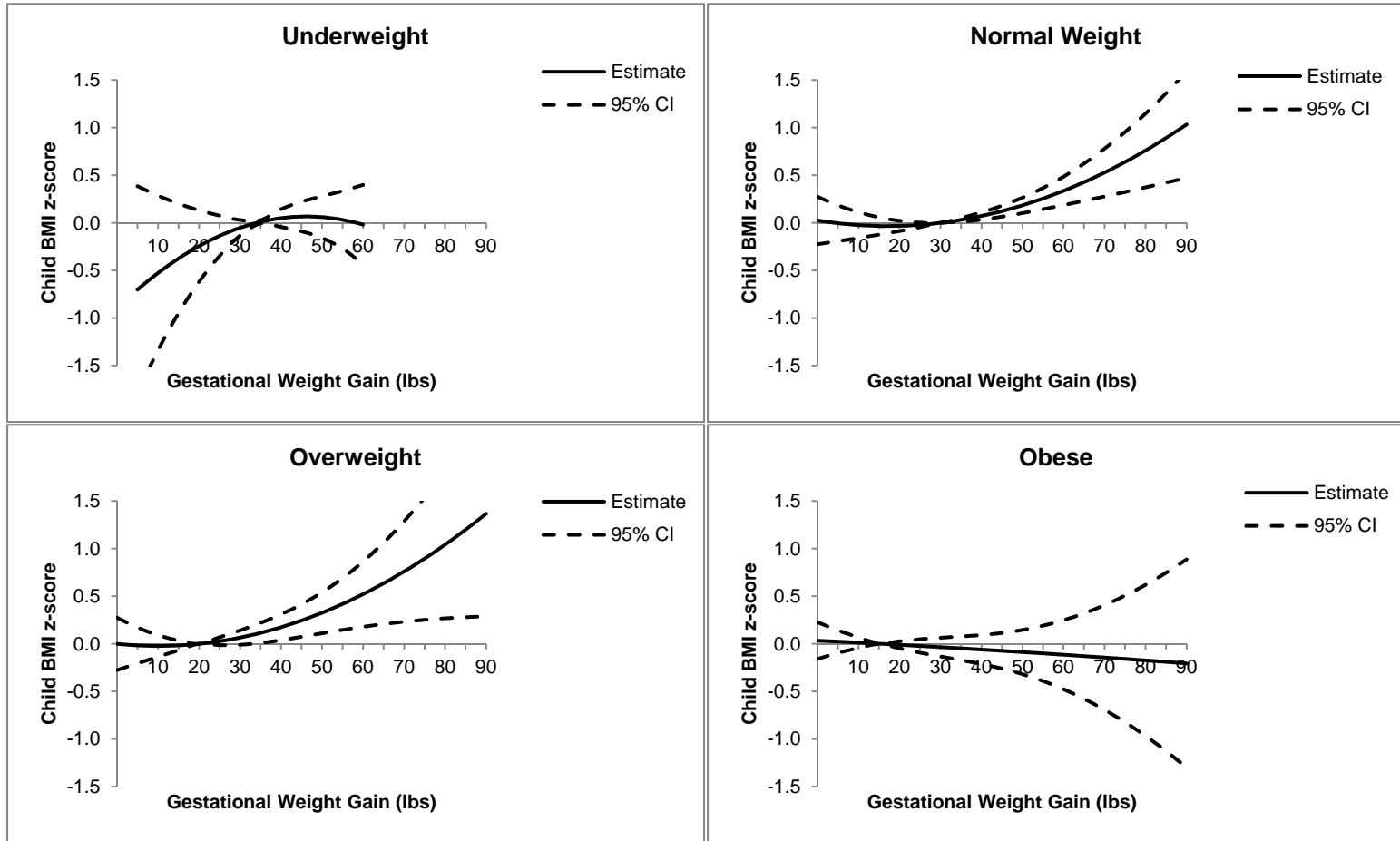


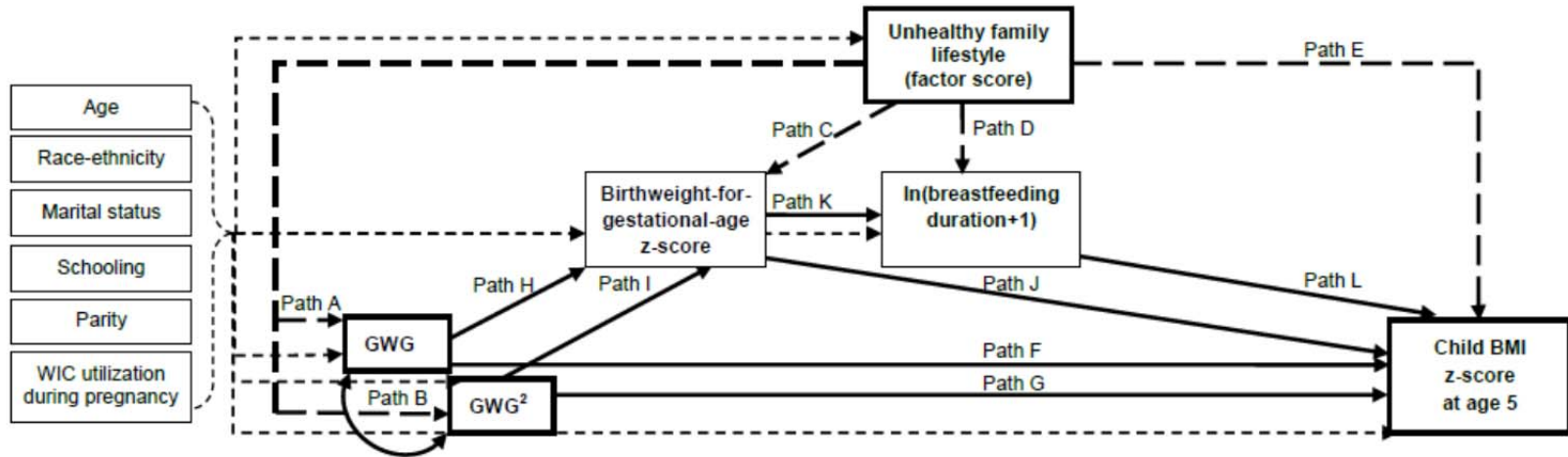
Figure 7.2: Adjusted^a association between gestational weight gain and child BMI z-score at 5 years of age, by maternal prepregnancy BMI status, Early Childhood Longitudinal Study-Birth Cohort, United States, 2001-2007



Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; lbs, pounds

^aModels adjusted for sociodemographic characteristics and unhealthy family lifestyle.

Figure 7.3: Measured variable path analysis model for the relationships between gestational weight gain and child adiposity measured at 5 years of age, by maternal prepregnancy body mass index status



Abbreviations: BMI, body mass index; GWG, Gestational weight gain; ln, natural log; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

CHAPTER 8**ASSOCIATIONS BETWEEN MATERNAL PREPREGNANCY BODY MASS****INDEX AND CHILD NEURODEVELOPMENT AT 2 YEARS OF AGE**

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Acknowledgments:

This research was performed under an appointment to the Centers for Disease Control and Prevention, administered by the Oak Ridge Institute for Science and Education under contract number DE-AC05-06OR23100 between the U.S. Department of Energy and Oak Ridge Associated Universities.

Disclaimer:

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abstract

Animal studies suggest that the inflammatory and hormonal intrauterine environment associated with maternal obesity can have long-term impacts on offspring neurodevelopment; however, there has been little epidemiologic research examining the impact of maternal obesity on child neurodevelopment. We examined sociodemographic-adjusted associations between maternal prepregnancy body mass index (BMI) and child development among 6,850 children from the nationally representative Early Childhood Longitudinal Study-Birth Cohort. Certified interviewers used a validated shortened version of the Bayley Scales of Infant Development-II to obtain the childrens' age-adjusted mental (MDI) and psychomotor (PDI) development T-scores (mean 50, SD 10) at approximately 2 years-of-age. Scores were analyzed continuously and dichotomously (<1 SD). Prepregnancy BMI (kg/m^2) was reported by mothers 9-months postpartum and analyzed categorically. MDI distributions were shifted to the left among all prepregnancy BMI categories relative to normal weight mothers (BMI 18.5-24.9), with the greatest difference among children of severely obese (BMI ≥ 35.0) mothers [-2.13 (95% CI -3.32, -0.93)]. The odds of low MDI were increased among children of underweight (BMI <18.5) [adjusted odds ratio (AOR) 1.48 (95% 1.05, 2.10)] and severely obese [AOR 1.50 (95% CI 1.04, 2.18)] mothers, relative to children of normal weight mothers. No associations were observed with PDI. In conclusion, prepregnancy BMI follows a U-shaped dose-response association with child cognitive development. These findings have notable public health implications at the population level. If the obesity epidemic continues on the current trajectory, a larger proportion of children may be classified as

having a cognitive disability, which can have lifelong consequences for the individual and society as a whole.

Introduction

As obesity prevalence has increased among women of reproductive age (1), awareness of the impact that maternal obesity has on child outcomes has also increased. Infants of obese mothers are more likely to be born by cesarean delivery and be large-for-gestational-age or macrosomic at birth (2). In addition, children of obese mothers are more likely to be obese adults (2). It is hypothesized that the inflammatory and hormonal intrauterine environment associated with maternal obesity may program infants to become obese in adulthood (3). Similarly, maternal obesity is hypothesized to have long-term impacts on offspring neurodevelopment (4). Animal studies suggest that the metabolic and hormonal environment associated with maternal obesity can cause altered brain development impacting offspring cognitive and behavioral function (5, 6). There has been little epidemiologic research examining the impact of maternal obesity on child neurodevelopment (4).

Results from two studies suggest that prepregnancy obesity may be associated with lower child general cognitive ability (7, 8), however, these findings were not replicated in a study from two other large cohorts (9). These studies are based on data ranging from 1966 to 2006 and were limited in that they either used a small sample (7), different measures of child neurodevelopment (i.e., degree of delay determined by disability diagnosis (8) or maternal report(9)) or had limited data to examine all maternal prepregnancy body mass index (BMI) categories (8, 9).

We examined the associations between maternal prepregnancy BMI and standardized measures of child mental and motor development measured at 2 years of age in a large nationally representative cohort of children born in the United States.

Methods

Study population

The Early Childhood Longitudinal Study-Birth Cohort (ECLS-B) is a longitudinal study of a nationally-representative cohort of children born in 2001 (10). The Department of Education was the primary sponsor of the ECLS-B. The ECLS-B was designed to inform research and policy related to children's early life experiences from infancy to kindergarten entry. Study participants were drawn from birth certificates provided by National Center for Health Statistics' Vital Statistics System's. For this analysis, we utilize data collected on children and their parents at the first two waves, the 9-month wave and the 2-year wave.

The ECLS-B enrolled 10,700 infants and oversampled selected race-ethnic groups, twins, and infants born weighing <2,500 g. As required by the Department of Education, we report sample sizes rounded to the nearest 50 and present all percentages as weighted population estimates. Only singleton infants without major structural or genetic congenital anomalies, as reported on the birth certificate, were eligible for this analysis (n=8,850). This inclusion criterion represents 97% of the weighted ECLS-B population.

At the 2-year wave 750 children were lost to follow-up and an additional 750 children did not complete the child assessment; however, all data are weighted to account for non-response, to maintain a sample representative of the target population. We performed a complete-subject analysis and excluded records missing data for any of the relevant study variables ($n=500$), leaving a final analytic sample of 6,850 children, weighted to be representative of 3,563,508 children born in 2001.

Maternal prepregnancy body mass index

At the 9-month wave, mothers were asked their current height and their prepregnancy weight. Prepregnancy BMI (kg/m^2) was calculated and categorized according to WHO guidelines (11): underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), obese class I (BMI 30.0–34.9), obese class II (BMI 35.0-39.9) and obese class III (BMI ≥ 40.0). Due to sample size limitations, we grouped obese class II and III into one category, denoted as severely obese.

Child neurodevelopment

Child mental and motor development was assessed at the 2-year wave (age range 20- 38 months; interquartile range 24-25 months) by trained fieldworkers using the Bayley Short Form-Research Edition (BSF-R), a shortened version of the Bayley Scales of Infant Development-II (BSID-II). The BSF-R was developed for the ECLS-B to make the BSID-II, which is generally used in the clinical setting, more compatible for a large national survey. The BSF-R was calibrated to the BSID-II and determined to have good reliability and discrimination parameters (12). Age-standardized T-scores [mean 50, standard deviation (SD) 10] normalized to the ELCS-B population provide an overall

measure of the child's mental and motor abilities relative to other children of the same age. The mental development index (MDI) represents early childhood language and cognitive abilities and the psychomotor development index (PDI) represents fine and gross motor skills (13). We analyzed MDI and PDI as continuous and dichotomous measures. Scores <-2 SD represent severe delay, while scores from ≥-2 to <-1 SD represent mild delay (14). Due to sample size limitations we were unable to study severe delay and therefore used a cutoff of <-1 SD to represent children with mild and severe delay who may require closer monitoring and referral for additional services (15). We analyzed MDI and PDI as continuous and dichotomous measures (<-1 SD vs. ≥-1 SD).

Covariates

Maternal race/ethnicity, age at child's delivery, parity, marital status and schooling, and child sex were obtained from the child's birth certificate. Household poverty status was determined by maternal report of household income and size at the 2-year wave interview and dichotomized as $<185\%$ and $\geq 185\%$ of the federal poverty limit (13).

Statistical analysis

We used analysis of variance (ANOVA) to examine the weighted mean (SE) MDI and PDI across sample characteristics. Sociodemographic and pregnancy related covariates were chosen a priori. Because associations related to child development have been shown to vary across socioeconomic indicators, we examined a multiplicative statistical heterogeneity by household poverty status. We used linear and logistic

regression models to estimate the associations of MDI and PDI with prepregnancy BMI category. All results are presented relative to normal weight mothers.

Because it is unclear if adult cutpoints for BMI categorization should be applied to pregnant adolescents and WHO cutpoints overestimate overweight and obesity among adolescents (16), we performed a sensitivity analysis comparing our final results to those obtained among mothers >18 years of age only. Similarly, because prematurity status is a strong risk factor for delayed development (17), we examined associations between prepregnancy BMI and developmental outcomes among a sample limited to children born full-term (gestational age ≥ 37 weeks).

We used Statistical Analysis Software (SAS) version 9.2 (Cary, NC) and considered p-values <0.05 significant for main effects and p-values <0.15 significant for interactions due to the low power associated with tests of heterogeneity (18). All analyses were weighted to account for loss to follow-up and unequal probability of selection, and standard errors were estimated with Taylor Series approximations to account for the multistage, stratified, cluster design of the ECLS-B. This study was reviewed by a human subjects coordinator at the CDC and determined not to involve human subjects.

Results

Compared to those retained in the analytic sample, children excluded due to incomplete data were more likely to have mothers who were Hispanic, unmarried, and less schooling; to live in a low-income household; and to have a lower MDI and PDI (data not shown); however, no differences were observed by maternal age, parity, smoking during pregnancy, prepregnancy BMI or child gender.

Among the analytic sample (n=6,850), 5% of mothers were underweight prior to pregnancy, while 14% were obese. MDI varied across all maternal and child characteristics studied, while PDI differed by all characteristics except maternal age and prepregnancy BMI (Table 8.1). Overall, 14% of children were classified as having low MDI or PDI. Relative to normal weight mothers, the distribution of child MDI is shifted to the left among all other prepregnancy weight categories (Figure 8.1). The proportion of children with a low MDI score among underweight, normal weight, overweight, obese class I, and obese class II and III was 18.8%, 12.4%, 13.8%, 13.0% and 18.7%, respectively (p=0.007). The proportion of children with a low PDI score among underweight, normal weight, overweight, obese class I, and obese class II and III was 15.0%, 14.1%, 14.8%, 14.0% and 16.5%, respectively (p=0.88).

We found no significant multiplicative heterogeneity by poverty status for either outcome and thus present poverty-adjusted opposed to stratified results. Adjustment for covariates slightly attenuated the association between prepregnancy BMI and MDI; however, MDI remained significantly associated with prepregnancy BMI status, with results suggesting an inverse U-shaped relationship (Table 8.2). Compared to children of normal weight mothers, MDI was lower among children of mothers in all other prepregnancy BMI categories, with significantly lower scores among children of obese class II and III mothers. Similar associations were observed with the logistic model examining the odds of having a low MDI, such that compared to children of normal weight mothers, those born to underweight or obese class II and III mothers had significantly higher odds of having a low MDI. No significant associations were observed with child PDI (Table 8.3). Restriction to women >18 y or to children born at term did

not meaningfully change the estimates, but precision was lost due to the smaller sample size (data not shown).

Discussion

Results from this nationally representative cohort of children demonstrate a significant association between maternal prepregnancy BMI and child mental development at 2 years of age. Specifically, results indicate an inverse U-shaped relationship, such that the highest MDI was observed among children of normal weight mothers. We did not observe any association between prepregnancy BMI and child motor development.

The ECLS-B used a shortened version of the BSID-II to assess mental and motor development. The BSID-II had been previously recommended for longitudinal epidemiologic studies assessing the developmental status of young children (19), but pilot testing determined that it was too time consuming. The BSF-R was determined to have good psychometric properties (12). Specifically the mental index of the BSF-R examines memory, expressive and receptive vocabulary, reasoning and problem solving, and concept attainment, while the motor index examines fine and gross motor abilities, perceptual-motor integration and balance (13). Bivariate distributions of the MDI and PDI followed standard patterns (20-22) and varied by most sociodemographic variables, although less variation was observed in the PDI than the MDI.

Severe prepregnancy obesity was associated with a population average decrease of approximately a quarter of a standard deviation in child MDI compared to children of normal weight mothers. Although on the surface this difference seems fairly small at the individual level, it has a notable public health impact at the population level (23). Further approximately 18% of the children born to obese class II and III mothers had a low MDI, while only 12% of those born to normal weight mothers had a low MDI. Given our data are representative of over 3 million births that occurred in 2001, this equates to a non-trivial increase in the number of children that may require social services and referral to early intervention programs, in addition to a potential for lifelong impacts on earning potential and health conditions (24, 25).

Previous research is limited and somewhat difficult to compare because the psychometric test or domains assessed differ across studies as do the maternal BMI distributions and definitions (7-9). Similar to our study, a small study of low-income African-American children at 5 years of age, that utilized standard psychometric tests, suggested that prepregnancy obesity is associated with lower scores for general cognitive ability (IQ), but not gross motor development. Evaluation of the cognitive cluster scores suggested that the finding was driven by an association with non-verbal (i.e., pattern and spatial ability), but not verbal (i.e., receptive language, syntax and concepts) cognitive development. Although that study lacked statistical power among underweight mothers, the authors suggested that there may be a U-shaped relationship between prepregnancy BMI and child cognitive function. In our study, we were unable to examine associations among the separate the cognitive domains. In a study from Northern Finland, utilizing either psychometric tests or medical diagnoses to define mild or severe disability,

maternal underweight was associated with mild cognitive delay among 11 year old children born in 1966, while maternal obesity was associated with mild and severe delay among 11 year old children born in 1985-86 (8). Although the U-shaped relationship was not present at each time period, the authors concluded this relationship may be present. Lastly, results from two other large European cohorts suggest that there is no association between maternal overweight/obesity and child cognition based on maternal-report at about 3 years of age (9). However, this study was limited in that overweight and obesity were combined and the prevalence of overweight/obesity among each cohort (21% and 22%) was much lower than observed in the ECLS-B (39%). Given that we observed the strongest association among severely obese mothers, it is plausible that combining overweight and obesity into one category masked an association.

An association between prepregnancy BMI and child mental development may be attributable to direct and indirect mechanisms. Maternal underweight is most likely related to a lack of energy and micronutrient stores, which can impact fetal growth (26) and impair brain development (27, 28). While the consequences of maternal obesity on offspring cognitive development is a much newer area of study, animal studies suggest that the intrauterine inflammatory environment associated with maternal obesity (29) may have a direct effect by damaging the developing brain (5, 6) and also make it more susceptible to other intrauterine environmental insults by increasing the permeability of the fetal blood brain barrier (30). Indirect mechanisms may also impact child development. First, the association may be mediated by gestational weight gain, which has a strong association with maternal prepregnancy BMI (16). The majority of women gain outside of the Institute of Medicine recommended weight gain ranges (16);

specifically, 24% and 46% of obese mothers gain inadequate or excessive weight, respectively. Inadequate weight gain, particularly below the amount required for the products of conception, has been hypothesized to be associated with delayed development via inadequate fetal growth or maternal ketosis (16). Comparatively, excessive weight gain may exacerbate already elevated inflammatory levels associated with obesity (31, 32), further hindering development. A second potential mediator may be a lack of initiation or a shortened breastfeeding duration associated with maternal underweight and obesity (33). It is plausible that this process may act through biological or behavioral mechanisms. It is important to note that the observed association may be due to residual confounding by maternal lifestyle and the integration of lifestyle into future studies will be important in delineating the underlying mechanism. Studies of older children will be informative in determining if this association becomes strong or weaker as the children age.

We did not observe an association with child motor development at 2 years of age. While previous studies also observed similar null findings (7, 9); this was slightly surprising given the strong relationship between prepregnancy BMI and fetal growth (34), a hypothesized mediator of the association between BMI and motor development. Because there is considerable variation in the age at which healthy children reach motor developmental milestones (35), it has been suggested that detection of motor delay may be difficult using broad-based assessments (34). Therefore it is plausible that our study, in addition to others, has not utilized assessments sensitive enough to detect delay among population-based cohorts.

Our study has several important strengths. To our knowledge, this is the first study reporting differences in associations with child neurodevelopment by obesity severity. Compared to children of normal weight mothers, the largest difference in child MDI was observed among children of severely obese mothers. Given the high prevalence of severe prepregnancy obesity (36), our finding of a dose response with BMI above normal weight is of particular concern. Our results are based on a large diverse population-based sample of children with development measured at 2 years of age by fieldworkers who were rigorously trained (12). Utilizing certified interviewers reduces the potential for maternal response bias in our study. We performed multiple sensitivity analyses to ensure our data were robust. We also examined and ruled-out heterogeneity by poverty status, which has been previously shown to be one of the strongest predictors for cognitive disabilities.

Our study is not without limitations. Prepregnancy BMI was assessed approximately 9 months postpartum. Because women tend to underreport their weight, prepregnancy BMI may have been misclassified (37). However, we adjusted for factors associated with reporting bias and have no reason to believe that reporting would be differential by developmental outcomes. Although the data were weighted to account for attrition and non-response, we restricted the analysis to those with complete data for all covariates and therefore our sample may not be fully representative. Also we cannot rule out the possibility of survival bias as we do not have any data regarding the reason for attrition. In addition the predictive validity has not been studied in the BSF-R and it remains unclear in the BSID-II (38). Therefore studies examining the association between

prepregnancy BMI and neurodevelopment among older children are necessary to fully understand the implications of these findings.

In conclusion, we report that both low and high maternal prepregnancy BMI are significantly associated with low child cognitive development scores at 2 years of age. Children born to underweight and severely obese mothers may require closer monitoring for developmental delays. Given the current obesity epidemic, the greater public health implications of this finding lie in the increased risk of cognitive delay among children of severely obese mothers. While there are barriers and challenges to preconception weight loss (39) and a high proportion of pregnancies are unplanned (40), increasing the proportion of women who conceive at a normal weight is a current public health priority (41). This study adds to the growing body of literature documenting the diverse and long-term adverse child outcomes that are associated with maternal obesity.

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pregnancy									
Yes	6,050	(12)	49.01	(0.41)	<.0001	49.21	(0.46)	0.002	
No	800	(88)	50.48	(0.23)		50.23	(0.24)		
Household poverty at 2-year wave									
<185%	3,150	(45)	47.53	(0.27)	<.0001	49.47	(0.32)	<.0001	
≥185%	3,700	(55)	52.59	(0.20)		50.64	(0.28)		
Child sex									
Male	3,550	(51)	48.63	(0.26)	<.0001	49.38	(0.26)	<.0001	
Female	3,350	(49)	52.08	(0.27)		50.88	(0.30)		
Maternal prepregnancy BMI									
Underweight	500	(5)	49.49	(0.64)	<.0001	48.98	(0.63)	0.13	
Normal weight	3,850	(56)	50.83	(0.24)		50.17	(0.26)		
Overweight	1,550	(25)	50.16	(0.38)		50.19	(0.36)		
Obese class I	600	(8)	49.52	(0.56)		50.32	(0.51)		
Obese class II and III	400	(6)	47.91	(0.67)		49.94	(0.69)		

Abbreviations: BMI, body mass index.

^aPresented an unweighted sample size rounded to the nearest 50 and a weighted % per data agreement with the Department of Education.

Table 8.2: Associations between maternal prepregnancy BMI status and child mental development at approximately 2 years of age, Early Childhood Longitudinal Study-Birth Cohort, 2001-2004

Model	Underweight	Normal Weight	Overweight	Obese class I	Obese class II and III
MDI Score, β (95% CI)					
Unadjusted	-1.34 (-2.71, 0.02)	0.00 (referent)	-0.68 (-1.38, 0.02)	-1.32 (-2.58, -0.06)	-2.92 (-4.19, -1.65)
Adjusted ^a	-0.47 (-1.77, 0.84)	0.00 (referent)	-0.21 (-0.88, 0.46)	-0.57 (-1.63, 0.48)	-2.13 (-3.32, -0.93)
MDI <40 vs. ≥40, OR (95% CI)					
Unadjusted	1.63 (1.14, 2.34)	1.00 (referent)	1.13 (0.93, 1.38)	1.06 (0.77, 1.45)	1.62 (1.16, 2.26)
Adjusted ^a	1.48 (1.05, 2.10)	1.00 (referent)	1.03 (0.84, 1.27)	0.93 (0.68, 1.28)	1.50 (1.04, 2.18)

Abbreviations: BMI, body mass index; CI, confidence interval; MDI, mental development index; OR, odds ratio.

^aAdjusted for all covariates including maternal age (continuous), race-ethnicity, marital status, parity, schooling (continuous), smoking during pregnancy, household poverty status, and child sex.

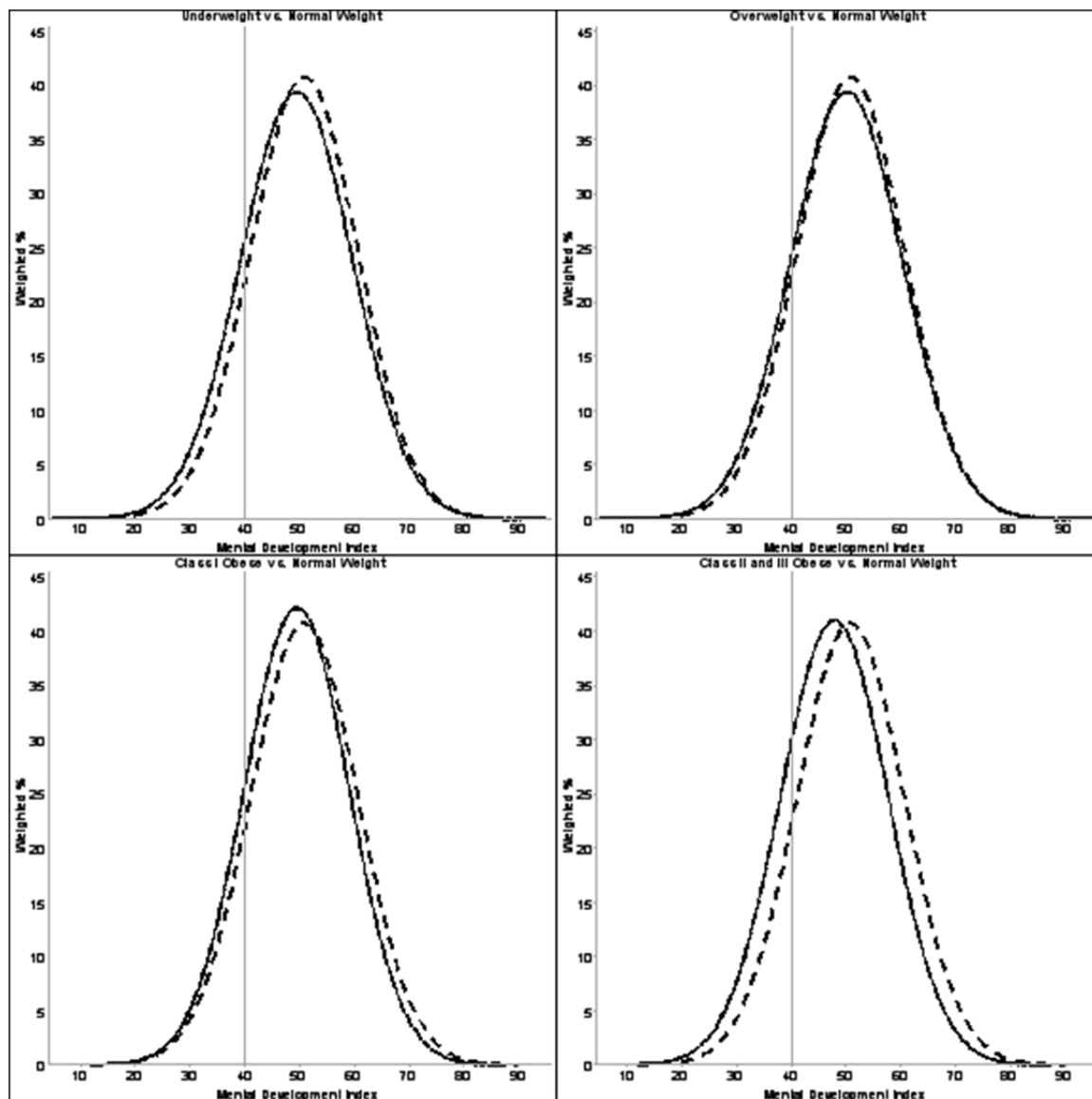
Table 8.3: Associations between maternal prepregnancy BMI status and child motor development at approximately 2 years of age, Early Childhood Longitudinal Study-Birth Cohort, 2001-2004

Model	Underweight		Normal Weight	Overweight		Obese class I		Obese class II and III	
PDI Score, β (95% CI)									
Unadjusted	-1.20	(-2.44, 0.05)	0.00 (referent)	0.02	(-0.61, 0.65)	0.15	(-0.90, 1.20)	-0.24	(-1.61, 1.13)
Adjusted ^a	-0.93	(-2.16, 0.31)	0.00 (referent)	0.13	(-0.52, 0.78)	0.22	(-0.82, 1.26)	-0.30	(-1.69, 1.09)
PDI <40 vs. ≥40, OR (95% CI)									
Unadjusted	1.08	(0.74, 1.58)	1.00 (referent)	1.06	(0.87, 1.29)	0.99	(0.72, 1.36)	1.20	(0.82, 1.76)
Adjusted ^a	1.02	(0.69, 1.51)	1.00 (referent)	1.03	(0.84, 1.27)	0.97	(0.70, 1.34)	1.21	(0.83, 1.78)

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; PDI, psychomotor development index.

^aAdjusted for all covariates including maternal age (continuous), race-ethnicity, marital status, parity, schooling (continuous), smoking during pregnancy, household poverty status, and child sex.

Figure 8.1: Distribution of age-standardized mental development index by prepregnancy BMI status at approximately 2 years of age, Early Childhood Longitudinal Study-Birth Cohort, 2001-2004



Vertical lines indicate mental development index (MDI) scores <40. Dashed lines indicate distribution among children of normal weight mothers.

CHAPTER 9

SUMMARY AND PUBLIC HEALTH IMPLCIATIONS

Main findings

The objective of this research was to better understand the implications of maternal nutritional status on infant and child outcomes, based on critical gaps in the literature related to maternal prepregnancy body mass index (BMI) and gestational weight gain (GWG). The Institute of Medicine (IOM) updated GWG recommendations in 2009 (1); however, there was limited data available on the short-term outcomes of GWG among severely obese mothers and on the long-term outcomes of GWG among mothers of all prepregnancy BMIs levels. The findings presented in this dissertation can be used to inform GWG recommendations for severely obese mothers and to contribute to the growing body of literature documenting the adverse infant and child outcomes associated with maternal obesity.

We identified two existing large data sources capable of addressing our research aims. The Centers for Disease Control and Prevention (CDC) Pregnancy Nutrition Surveillance System (PNSS) is a voluntary, state-based, surveillance system designed to monitor the nutritional status of low-income women participating in the Special Supplemental Program for Women, Infants, and Children (WIC). We used the PNSS to examine prepregnancy obesity trends among low-income women, a previously identified high-risk population (2). Between 1999 and 2008, the prepregnancy obesity prevalence

among women utilizing WIC services steadily increased and varied by maternal race-ethnicity. The greatest increase in the prevalence was among Hispanic mothers (18.9% to 24.6%), followed by Asian/Pacific Islander mothers (6.8% to 10.8%). The prepregnancy obesity prevalence appears to be stabilizing among the most high risk groups, American Indian/Alaskan Native and non-Hispanic black mothers, but none the less, the prevalence remains at a critically high level with more than a third of the mothers entering pregnancy obese. Our data also highlight the rapidly increasing prevalence among low-income Hispanic and Asian/Pacific Islander mothers. While it was recently suggested that in the general population the prevalence of obesity among women is stabilizing (3), it has also been hypothesized that, just as the obesity prevalence varies among subgroups of the population, the trends in stabilization will follow a similar suit (4). Our data support this hypothesis and indicate that prepregnancy obesity may be stabilizing only among select race-ethnic groups of low-income women, specifically those who have had the highest risk over the last decade. Increasing the proportion of women who enter pregnancy at a normal weight is a national priority (5) and our data can be used by obesity prevention programs to better target high-risk low-income women.

We also used the PNSS to examine the association between GWG and fetal growth by obesity severity. Currently the IOM recommends that all obese women gain between 11 and 20 lbs during pregnancy (1). Our data, however, suggest that lower weight gains may be acceptable, in regard to fetal growth, among women of all prepregnancy obesity categories. Specifically, using clinically relevant outcomes of SGA

and macrosomia, we identified the following ranges of GWG to be associated with the most favorable fetal growth outcomes: class I (BMI 30.0-34.9), 0 to 20 lbs; class II (BMI 35.0-39.9), -10 to 10 lbs; and class III (BMI \geq 40.0), -10 to lbs. Our results support obesity class specific recommendations and are similar to those published at the time of the IOM report (6) and have since further been supported by additional research on fetal growth among various populations (7-10). It is important to note that all of the studies, which have reported obesity class specific results, support lowering the recommended amount of GWG, to some degree, among class II and III obese mothers. Although the current recommendations have been criticized for being too high given the obesity epidemic among both mothers and children (11), there is concern that lowering the recommendations may have adverse consequences for child neurodevelopment (12).

To better understand the long-term implications of maternal prepregnancy BMI and GWG on child health we utilized the nationally representative, Early Childhood Longitudinal Study-Birth Cohort (ECLS-B), which followed children from infancy through kindergarten entry. GWG data is available from two sources in the ECLS-B, the birth certificate and maternal report at approximately 10 months postpartum. We compared these two measures in chapter 6, and found that, although maternal report of GWG tended to be higher than the birth certificate report by an average of 2.1 lbs and varied by select sociodemographic and pregnancy related variables, there was no meaningful difference in measures of association with fetal growth by GWG data source. We used this data to inform our studies of GWG in the ECLS-B, yet more importantly

the findings of this study can be used by others to inform bias studies when maternal postpartum reported GWG is utilized (13). This is important as the practice of collecting GWG data retrospectively is likely to increase due to greater interests in long-term outcomes of GWG (1).

We used the ECLS-B to examine the association between GWG and child adiposity at 5 years of age. GWG has previously been hypothesized to act on offspring adiposity through both a direct and indirect mechanism, the later mediated through birthweight; however, the presence and degree of mediation remains unclear (1). In this study we found that among normal and overweight mothers, GWG below IOM recommendations was not associated with changes in child BMI z-score, while GWG above recommendations was associated with a significant increase in child BMI z-score. We observed no association between GWG and changes in child BMI z-score among obese mothers. This study was unique in that we controlled for family lifestyle by developing a factor score based on various maternal and child lifestyle indicators. We examined for mediation by birthweight and breastfeeding using measured variable path analysis. As previously stated, there is concern that the current GWG recommendations may be contributing to the child obesity epidemic (11); however, we did not observe any beneficial (or adverse) effects of GWG lower than the current recommendations, indicating that lowering recommendations for the sake of preventing child obesity may be moot. Furthermore, we found that GWG above recommendations was associated with an

increase in child BMI z-score among children of normal and overweight mothers, suggesting that current recommendations are appropriate.

Lastly, we used the ECLS-B to examine the association between maternal prepregnancy BMI status and child neurodevelopment at 2 years of age. Our findings indicate that the distribution of child cognitive development scores are shifted to the left (i.e., lower scores) among children born to underweight (BMI <18.5) and severely obese (BMI \geq 35.0) mothers, compared to the children of normal weight mothers (BMI 18.5-24.9). When we examined the odds of children having a developmental score below 1 standard deviation from the mean, we found that children of underweight and severely obese mothers had approximately a 1.5 times increase in the odds of cognitive delay compared to the children of normal weight mothers. We did not observe any significant or meaningful associations between prepregnancy BMI and motor development. These findings have notable implications at both the population and individual level. Children with low cognitive scores may require closer monitoring and referral for additional services (14). Further, a shift in the distribution of cognitive scores has implications for society as a whole, as a non-trivial proportion of children have an elevated risk of delay (15), which can put additional burden on public health services and can have lifelong implications on earning potential and health conditions (16, 17). There is limited previous research in this area and due to substantial variability in study design and populations (18-20); while it is difficult to directly compare previous findings with ours, it appears that our findings are supported by two of the prior studies(18, 20). Additional research on

child neurodevelopment with longer follow-up is certainly warranted given the public health implications of these findings.

Strengths and limitations

Although secondary data analysis has the advantage of being more efficient and less financially burdensome than primary data collection, researchers using secondary data are presented with challenges that may impact the internal and external validity of their findings due to data collection methods or study design. We used two large existing data sources to address our research aims; the PNSS and the ECLS-B. While these data provided unique opportunities to address data gaps, they are not without limitations.

The PNSS is maintained by the CDC to monitor the nutritional status of low income women participating in WIC. Data are collected at WIC entry, compiled and reported to the CDC for analysis. Information bias may present in our analyses due to this means of PNSS data collection. Prepregnancy BMI was calculated using maternal height measured at the WIC clinic and self-reported prepregnancy weight. Because women tend to differentially under- or overreport their prepregnancy weight, we may have misclassified women into specific BMI categories (21). The effect of prepregnancy BMI misclassification bias on obstetric outcomes was previously studied in a hospital-based cohort (21). They found that, although measures of association between prepregnancy BMI and obstetric outcomes were slightly biased away from the null, overall conclusions based on the data were not meaningfully altered. The calculation of prepregnancy BMI in

the PNSS is based on measured height and therefore may be less biased than studies of self-reported weight and height.

GWG data in the PNSS was collected based on maternal report at the first postpartum visit. Our data presented in chapter 6 on the bias between self-reported GWG and birth certificate data, indicates that women tend to overreport their GWG when asked postpartum, although we found that in the ECLS-B, the associations with fetal growth were not meaningfully different based on the source of GWG data. The PNSS is a unique source of GWG data in that it provides data on weight gain or loss during pregnancy. Most cohort studies and vital statistics data right censor the GWG data, such that any reported weight loss is truncated at 0 lbs (22). Therefore our study contributes to a critical gap in the literature, as weight loss during pregnancy is understudied among obese mothers.

Birthweight data in the PNSS was obtained from birth certificates, hospital records, or maternal report at the first postpartum visit. Birth certificates are known to provide a reliable estimate of infant birthweight (23-25), although bias can occur due to rounding between grams and ounces (26). Further, prior studies have found that maternal reporting of birthweight in WIC is reliable (27). We used the mother's report of her date of last menstrual period (LMP) to assess gestational age and subsequently calculate small-for-gestational age (SGA). LMP tends to overestimate gestational age; consequently, we may have been more likely to classify normal weight infants as SGA

and thus bias our results towards the null. Lastly, covariates of interest may also have been biased due to reporting error, transcription of data or various other unknown reasons; however, it is important to note that the PNSS has multiple internal quality control checks. These multiple sources of error likely reduced the precision of our estimates and it is unclear in which overall direction the measures of association may be biased.

The PNSS provides a uniquely large sample size of low-income mothers. Therefore, we were able to examine clinically relevant fetal growth outcomes by maternal obesity class. The findings obtained from the PNSS may not be completely generalizable to all low-income pregnant women. First, not all states, Indian tribal organizations or U.S. territories participate in the PNSS, as it is a voluntary surveillance system. For example, our study of prepregnancy obesity trends was based on data from 27 participating states, Indian tribal organizations or U.S. territories that continuously participated from 1999 to 2008. In this analysis we highlighted differences in the prepregnancy obesity prevalence between contributors. This is a concern as our fetal growth PNSS analysis was further limited to only the 6 states that voluntarily reported infant sex, thereby limiting its generalizability. Second, not all eligible women participate in WIC and therefore our data may not truly be representative of all low-income women (28). However, it is important to note that our findings related to GWG and fetal growth among obese mothers are supported by additional studies of women from various populations (6-10, 29).

The ECLS-B was sponsored by the Department of Education to provide comprehensive data on children's early life experiences. The study was designed to be nationally representative of all children born in 2001, with 3 exceptions: children born to mothers who were younger than 15 years of age and those who were adopted or died before 9-months of age were not included. Because we do not have any data on children who died before data collection or on those who died after the first wave, and thus were lost-to-follow-up, we cannot completely rule out survival bias in our estimates. Our studies may also be biased by misclassification related to prepregnancy BMI. Prepregnancy BMI was calculated from maternal report of height and prepregnancy weight at the first wave of data collection, approximately 9-months postpartum. Due to underreporting of prepregnancy weight, women may be misclassified (30). As discussed above, this bias has previously been shown to not meaningfully alter conclusions related to certain obstetric outcomes (21). The bias related to GWG was discussed in detail in chapter 6. The outcomes used in our analyses, adiposity, calculated based on height and weight, and neurodevelopment, were directly measured by certified field workers and have been shown to have good psychometric properties (31, 32).

The ECLS-B was designed to be nationally representative. Sample weights were calculated by the National Center for Education Statistics and all data were weighted to account for non-response in order to maintain a sample with demographic distributions representative of the target population. However, we performed complete-subject analyses and excluded records of missing data for any of the relevant study variables. We

assumed that data were missing at random and were not related to our exposure-outcome relationships of interest.

We were limited in that both the PNSS and the ECLS-B only assessed total GWG and therefore we could not examine associations related to the rate of GWG. Thus, for both of our studies related to outcomes of GWG, we restricted our analyses to infants born at term. Some studies have found that the timing of the rate of GWG is more important than total GWG (1). Further, our results are generalizable only to mothers who carried to term. However, this should not impact the clinical implications of the data as all women should be advised to gain based on the assumption that they will carry the infant to term (at least 37 weeks).

Our analysis on GWG and child adiposity required many assumptions. We aimed to build on the work of previous studies by accounting for confounding due to lifestyle and by providing a more detailed analysis of GWG and child adiposity by examining the direct and indirect effects. We accomplished these aims by utilizing confirmatory factor analysis (CFA) and measured variable path analysis. We used CFA to create a factor score representing the hypothetical construct of an unhealthy family lifestyle using multiple measured variables. The indicators included in the CFA were maternal smoking in the last 3 months of pregnancy, maternal exercise habits when children were approximately 4 years of age, maternal weight change from prepregnancy to 5 years postpartum, child weekday television habits at 4 year of age, and fast-food and sugar

sweetened beverage consumption at 4 years of age. These were selected based on the availability of variables in the ECLS-B and on prior literature. However, it certainly is not an exhaustive list of potential indicators and it is plausible that it did not truly capture an unhealthy lifestyle. Future studies including more detailed data on diet and exercise of the mother and child, as well as lifestyle during pregnancy, will help to further account for residual confounding from lifestyle. In addition because we only had a single measure for the other variables of interest we were limited in that we could only perform measured variable path analysis opposed to structural equation modeling (SEM). Therefore we could not take advantage of some of the benefits of SEM, specifically its ability to account for measurement error (33). Our path analysis models were also limited in that we could not perform a multi-group analysis due to the additional restrictions imposed on the model by the use of complex survey data required by the ECLS-B design. We also could not examine non-linear associations with the mediating paths, such as those through birthweight or breastfeeding duration. MVPA requires that endogenous variables be continuous variables and our ability to interpret the model would have been reduced had we included additional quadratic terms. Last, it is always important to remember that although the family of SEM techniques is commonly known as causal modeling, it does not allow us to make any causal conclusions about the variables in the model. While many of the limitations discussed were related to our data sources, it is unlikely that the questions addressed in this dissertation could have been completed without the use of these data. Although prospective primary data collection would have been ideal, obtaining a sample size large enough to have the power to

examine rare birthweight outcomes by obesity class could not have been performed without the use of the PNSS data. Although there was substantial attrition in the ECLS-B, this is generally unavoidable with longitudinal surveys and is not limited to the ECLS-B. Attrition may have been reduced with a smaller sample size and therefore greater resources to retain participants; however, power and generalizability would likely have been compromised. Our analyses address important gaps in the literature and could not have been performed without reliance on these public data sources, but like all observation studies, they were fraught with limitations and should be considered in the context of findings from other studies.

Public health implications

The findings of these analyses underscore the importance of preconception care supporting a healthy lifestyle as well as counseling during pregnancy to help women gain within the IOM GWG recommendations. Women, who begin their pregnancy at a healthy, normal weight, have repeatedly been shown to have better short-term obstetric outcomes (1). Moreover, our findings suggest that their children also have better long-term outcomes related to weight status and cognitive development.

Preconception care is a broad concept encompassing screenings, health promotion and interventions among women of reproductive age to reduce adverse pregnancy outcomes (34). Increasing the proportion of women at a healthy weight prior to pregnancy is one of the identified goals of preconception care and is a national priority

(5). While there are many public health and individual barriers to achieving this goal, several strategies have been presented, ranging from ensuring that all low-income women of reproductive age have access to health care and utilizing family practice physicians to educate and promote behavioral changes among individuals exceeding a healthy weight (34-37). Our findings from the PNSS trend analyses can be used to better target low-income women of reproductive age at the highest risk of prepregnancy obesity.

In addition to strategies directly targeting individuals of reproductive age, changing many aspects of our built environment will be necessary to achieve this preconception weight goal (38). Obesity among young girls is critically high (39), thus considering these girls are the next generation of mothers, addressing obesity and promoting a healthy lifestyle among young girls may provide long-term beneficial effects. In addition, focusing preconception care related to obesity at a level higher than the individual is also important as many pregnancies are unplanned (40). Also, focusing on interconception care and strategies such as breastfeeding may be beneficial as childbearing is often cited as a reason for weight gain in young women (41). Promotion of GWG within recommendations may help to prevent postpartum weight retention (1) and therefore may also have beneficial effects for future pregnancies.

Studies have clearly shown that GWG is a mediator of many adverse pregnancy outcomes related to prepregnancy BMI. Therefore promotion of GWG within IOM recommendations is also an important strategy to improve obstetric outcomes (1). Our

data provide the first nationally representative estimates of the proportion of women who gain within the IOM recommendations. The IOM recommends that practitioners track individual's weight gain and counsel them on GWG throughout their pregnancy. In addition, the IOM noted that without changes to the environment, many women will be presented with barriers to achieve the appropriate GWG, just as individuals do with achieving a normal weight prior to pregnancy(1). It is unclear if behavioral interventions are successful in increasing appropriate GWG (42); however, there is some suggestion that physical activity interventions may aid in increasing appropriate GWG (43). Additional intervention trials are needed to better understand how to promote appropriate GWG, thereby theoretically improving pregnancy outcomes.

Summary

The findings of this dissertation address critical data gaps related to infant and child health outcomes of maternal nutrition status. In 2009, the IOM updated the GWG recommendation for obese mothers to 11-20 lbs. The lower limit of this range was based on the theoretical weight required for the products of conception (12); however, it has been criticized for being too high (4). Our data suggest that lower GWG does not increase the risk of SGA and may lower the risk of macrosomia for all obese mothers. This finding has been supported by many other studies in various populations (6-10). However, comprehensive data supporting lower recommendations for obese mothers is still limited. To our knowledge, no high quality population based studies have examined

the association between GWG and child neurodevelopment. We found that prepregnancy obesity increased the likelihood that children would have cognitive delay at 2 years of age compared to those of normal weight mothers. This association may act through direct or indirect effects, such as breastfeeding or GWG. Therefore, further examination of the mechanism by which this association functions is critical before GWG recommendations should be lowered. Further, we found no benefit of lower GWG in regard to child adiposity at 5 years of age, therefore reducing the sense of urgency related to lowering recommendations for obese mothers until high quality data related to neurodevelopment are available. In the meantime, focusing on helping obese women of reproductive age achieve a healthy weight may be beneficial to this high risk population.

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