THE EFFECTS OF MATERNAL PREPREGNANCY BODY MASS INDEX AND GESTATIONAL WEIGHT GAIN ON OFFSPRING ANTHROPOMETRIC OUTCOMES

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ABSTRACT

ANDREA LAUREN DEIERLEIN: The Effects of Maternal Prepregnancy Body Mass Index and Gestational Weight Gain on Offspring Anthropometric Outcomes (Under the direction of Dr. Anna Maria Siega-Riz)

Rates of childhood overweight and obesity have increased over the past several decades. Numerous studies show that obesity during childhood is strongly associated with obesity in adolescence and adulthood, as well as the development of chronic conditions. Maternal prepregnancy body mass index (BMI) and gestational weight gain (GWG) represent modifiable behavioral factors that may influence the development of offspring body composition later in life; however, there are relatively few studies that examine these associations, especially for GWG.

We used data from a recent prospective, longitudinal pregnancy cohort, the Pregnancy, Infection, and Nutrition Study (2001-2008), to examine the effects of prepregnancy BMI and GWG according to the 2009 Institute of Medicine (IOM) recommendations on offspring anthropometric outcomes within the first 3 years of life. Using multivariable regression analysis we found that the relative body size of infants at 6 months differs by maternal exposure. While both prepregnancy BMI and GWG were positively associated with weight-for-age z-scores (WAZ), only GWG was associated with length-for-age z-scores (LAZ). Prepregnancy overweight/obesity and excessive GWG≥200% of the IOM recommendations were associated with higher weight-for-length z-scores (WLZ). At 3 years, children of overweight/obese mothers had

significantly higher BMI z-scores and increased risk of overweight and obesity (≥85th percentile and ≥95th percentile, respectively). Children of mothers with excessive GWG also had significantly higher BMI z-scores but only GWG≥200% of the IOM recommendations was associated with an increased risk of obesity. Results from longitudinal analysis between birth and 3 years were consistent with these findings and revealed higher rates of change in WAZ and WLZ associated with prepregnancy obesity and higher rates of change in WAZ and LAZ with GWG≥200% of the IOM recommendations. Children of overweight/obese women and women with GWG≥200% of the IOM recommendations had distinctly higher predicted mean values of WAZ and WLZ that persisted across the study period compared to women in the lower prepregnancy BMI and GWG categories, respectively.

These findings suggest a need for intervention efforts that reach women during their reproductive years, prior to becoming pregnant, to decrease fetal exposure to maternal overweight/obesity and excessive GWG.

DEDICATION

To my family.

In loving memory of my dad and grandpa.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
IOM	Institute of Medicine
GDM	Gestational Diabetes Mellitus
IGT	Impaired Glucose Tolerance
CDC	Centers for Disease Control
NHANES	National Health and Nutrition Examination Surveys
PIN	Pregnancy, Infection, and Nutrition
UNC	The University of North Carolina at Chapel Hill
IRR	Incidence Risk Ratio

CHAPTER I

INTRODUCTION

Background

Rates of childhood overweight and obesity have dramatically increased over the past several decades. Numerous studies show that obesity during childhood is strongly associated with obesity in adolescence and adulthood, as well as the development of chronic conditions, such as hypertension, type II diabetes mellitus, and dyslipidemia. Thus, identification of modifiable risk factors for the development of overweight and obesity in infants and children is of great importance. Maternal prepregnancy body mass index (BMI) and gestational weight gain represent modifiable behavioral factors that have also increased over the past several decades. Over half of women of child bearing ages are overweight or obese and the majority of women have gestational weight gains in excess of the recommended amounts. Results from animal models suggest that maternal overnutrition, both prior to and during gestation, influences the development of offspring metabolic and appetite regulating systems leading to increased adiposity later in life.

Although previous cross-sectional and observational studies demonstrate that parental BMI, particularly maternal BMI, is positively associated with adiposity (usually assessed by BMI) in children, some of these studies did not evaluate maternal BMI prior to pregnancy. Furthermore, while a substantial literature links gestational weight gain to both maternal and birth outcomes, a recent systematic review identified infant and

childhood weight outcomes as an understudied research area. Of the studies that examined childhood weight outcomes, several have done so using historical cohorts that are not reflective of the current high prevalence of excessive gestational weight gains and maternal and pediatric obesity. These studies used varying definitions of gestational weight gain and failed to include adjustment for potential confounders or explore the interaction between prepregnancy BMI status and gestational weight gain. Currently, there are few studies that examine the association between gestational weight gain and rapid infant weight gain; utilize longitudinal data; or examine infant anthropometric outcomes, especially length outcomes.

This dissertation used data from a recent prospective, longitudinal pregnancy cohort, the Pregnancy, Infection, and Nutrition Study (2001-2008), to determine how maternal prepregnancy BMI and gestational weight gain, based on the 2009 IOM recommendations, related to early offspring anthropometric outcomes.

Research Aims

The specific aims of this research were to:

1. Determine the association between the selected modifiable prenatal maternal factors and early infant anthropometric outcomes: weight-for-age (WAZ), length-for-age (LAZ), weight-for-length z-scores (WLZ) at 6 months, and rapid infant weight gain in the first 6 months of life.

a. How does prepregnancy BMI relate to WAZ, LAZ, and WLZ at 6 months, and/or rapid infant weight gain between birth and 6 months?

b. How does gestational weight gain relate to WAZ, LAZ, and WLZ at 6 months, and/or rapid infant weight gain between birth and 6 months?

2. Determine the association between the selected modifiable prenatal maternal factors and childhood BMI at 3 years of age (defined as BMI z-scores and BMI percentile cut-points of ≥85th and ≥95th).

a. How does prepregnancy BMI relate to child BMI z-score and risk of overweight/obesity at 3 years?
b. How does gestational weight gain relate to child BMI z-score and risk of overweight/obesity at 3 years?

3. Determine the association between the selected modifiable prenatal maternal factors and WAZ, LAZ, and WLZ from birth to 3 years using longitudinal models.

a. How does prepregnancy BMI relate to WAZ, LAZ, and WLZ from birth to 3 years and do the relationships change over time?
b. How does gestational weight gain relate to WAZ, LAZ, and WLZ from birth to 3 years and do the relationships change over time?

CHAPTER II

LITERATURE REVIEW

Scope of the Problem

Data from the National Health and Nutrition Examination Survey (2007-2008) show that the prevalence of childhood obesity (age- and sex-specific BMI ≥95th percentile of the US growth reference) is not declining; 10.4% of 2-5 year olds and 19.6% of 6-11 year olds were obese.[1] Estimates were similar for the prevalence of overweight (age- and sex-specific BMI ≥85th-<95th percentile) in these age groups, 10.8% among 2-5 year olds and 15.9% among 6-11 year olds.[1] Among infants and toddlers from birth to 2 years, the prevalence of sex-specific weight-for-recumbent length ≥95th percentile was 9.5%.[1] Numerous studies report that obesity during childhood is strongly associated with overweight or obesity later in life.[2-5] Similarly, rapid growth and longitudinal growth (or growth patterns) measured within the first several years of life also increase the likelihood of obesity in adolescence and adulthood.[6-10]

Obesity during childhood is associated with the development of chronic health conditions similar to those found in association with obesity during adulthood. The incidence rate of type II diabetes, a condition that was previously rarely thought to exist among children and adolescents, is rising.[11] Obese preschoolers have approximately three times the risk of hypertension and twice the risk of low high-density lipoprotein cholesterol levels as compared to their normal weight counterparts.[12] In addition to

assessing age-specific obesity, growth rates and trajectories are also informative for predicting health outcomes. Accelerated growth in early life is associated with endothelial dysfunction,[13] insulin resistance,[14] and hypertension in adolescents[15] as well as systolic blood pressure at three years.[16] Rapid infant weight gain between birth and six months is associated with metabolic risk factors in young adults.[17] Considering the high prevalence of obesity among children, particularly during the preschool years, and the major current and future health implications associated with increased childhood weight gain, the identification of modifiable risk factors for the development of obesity in infants and children is of great importance.

Maternal prepregnancy BMI and gestational weight gain represent modifiable behavioral factors that are associated with offspring weight status. In the United States, over half of women of reproductive ages are overweight or obese.[18,19] Several observational studies demonstrate that maternal BMI is linked to offspring adiposity during infancy,[20-24] childhood,[25-3425-28,35] adolescence,[36,37] and adulthood.[38,39] However, not all studies have measured maternal BMI prior to pregnancy.[31,34] Gestational weight gain is associated with fetal and neonatal weight-related outcomes including birthweight, macrosomia, and large-for-gestational-age [40] but its influence on infant and early childhood weight outcomes remains understudied.

Over the past several decades, the recommended amount of gestational weight gain has nearly doubled in an effort to improve infant birthweight and growth outcomes, culminating with the 1990 IOM gestational weight gain guidelines,[41] which were recently updated in 2009.[42] Despite these liberal weight gain thresholds, studies show that a high percentage of women, ranging over forty percent, are gaining in excess of them [43-48] and

the majority of overweight and obese women tend to exceed their respective recommended ranges of gestational weight gain.[47,49,50] A key determinant for these inappropriate weight gains may be women's inability to properly adjust their dietary patterns.

Maternal Diet and Gestational Weight Gain

Popularity of the term "eating for two" and the relaxing of women's normal eating habits, both in quantity and quality, may contribute to the problem of excessive weight gain during pregnancy. Excessive gestational weight gain is positively associated with total calories and inversely associated with walking and vigorous physical activity.[51] Using data from the Pregnancy, Infection, and Nutrition Study, adequacy of gestational weight gain ratios increased across quartiles of dietary energy density (defined as the number of calories/gram of food and caloric beverages consumed); women consuming diets with energy density values in the third and highest quartiles gained a significant excess of over 1 kg compared to those in the first quartile. Women with high gestational weight gains (>18 kg for normal weight women and >12 kg for overweight or obese women) are more likely to eat more sweets early in pregnancy and drink more milk, as well as consume more food, in late pregnancy compared to women with suboptimal (<12.1 kg for normal weight women and <7.1 kg for overweight and obese women) and optimal (12.1-18.0 kg for normal weight women and 7.1-12 kg for overweight and obese women) gestational weight gains.[52] Results from the Stockholm Pregnancy and Weight Development Study[53] showed that women who expressed an increased interest in sweets during pregnancy experienced 1-2 kg greater weight gains than did the other women in

the study. The results from these studies suggest that women with weight gains above the recommended range have increased energy intakes and decreased energy expenditure and choose foods of poor nutrient quality, such as sweets, all of which may have important implications for the developing fetus and the "programming" of obesity later in life.

Biological Mechanisms Linking Prepregnancy BMI and Gestational Weight Gain to Offspring Anthropometric Outcomes

Throughout gestation the mother sends information about her physical environment and health status via the placenta to the developing fetus. Maternal environmental exposures, nutrient status/intakes, and hormone concentrations, and the adaptive fetal responses to the mother can all influence fetal organogenesis and the development of physiologic and metabolic homeostatic set points, possibly resulting in long-term disease risk.[54] Over the past few decades, there has been a great deal of research attention focused on the fetal environment and the impact of in utero exposures on health outcomes later in life. With the rise of obesity, researchers have started to examine the effects of maternal overnutrition (both prior to and during gestation) on the programming of appetite and body weight regulation systems in the fetus that may lead to obesity and its related co-morbidities during the postnatal period.

Relatively few experimental studies have differentiated between maternal overnutrition prior to pregnancy (prepregnancy overweight/obesity) and overnutrition during pregnancy (increased fat/energy intakes); however, overnutrition during these time points may function through a similar pathway and there is evidence to suggest an interaction between them.[28,55] A proposed pathway for the association between maternal

overnutrition and the development of childhood (and adulthood) obesity is displayed in Figure 1 (adapted from McMillen et.al.[56]). Fetal exposures to glucose, insulin, and leptin and their influence on the developing neuroendocrine system are thought to play important roles.

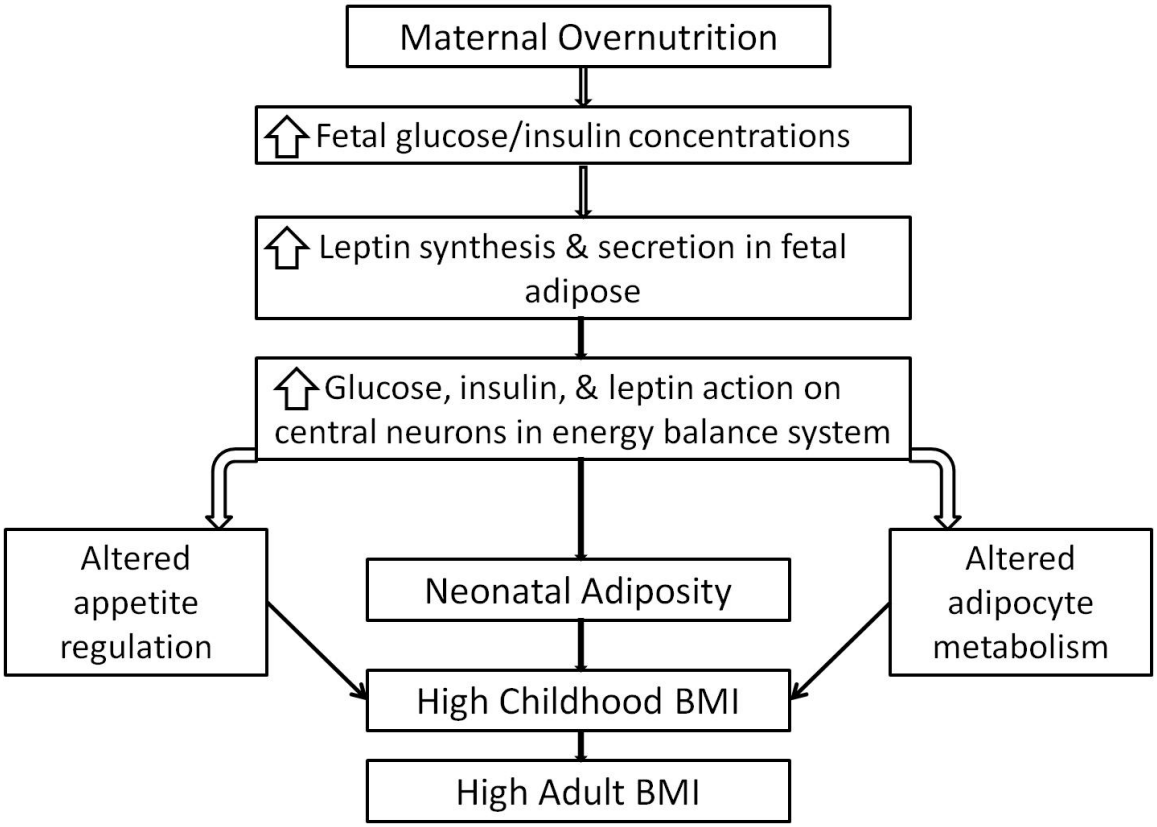


Figure 1. Proposed biological pathway explaining the relationship between maternal overnutrition and adult obesity (adapted from model developed by McMillen et.al.[56]).

Results from rodent models suggest that exposure to maternal overnutrition, both prior to and during gestation, influences the programming of offspring brain appetite and fuel-sensing regulators [57] and leads to an upregulation of placental nutrient transfer isoforms that increase transport of glucose and amino acids, which are positively associated with fetal growth.[58] Exposure to a maternal high fat diet (supplied to dams 4

weeks prior to gestation and maintained throughout gestation) is associated with greater length and decreased insulin sensitivity in first and second generation mice, supporting an epigenetic heritability mechanism.[59] Studies limited to overnutrition during gestation show similar results.

Using a rodent model, Howie et.al.[60] found that adult offspring of dams fed a moderate high fat diet from weaning through lactation, as well as those of dams fed a moderate high fat diet for gestation and lactation only, have increased adiposity, hyperleptinemia, and hyperinsulinemia compared to those of control mothers (fed standard chow diets from weaning throughout lactation). Transient hyperglycemia, induced by glucose injections during early pregnancy in rats (gestational day 10), stimulate fetal growth as a consequence of greater placental weights and increased placenta nutrient transfer.[61] In sheep, an increase in maternal nutrient intakes during late gestation results in increased fat deposition during the postnatal period and changes in the expression of the leptin receptor, as well as appetite regulators neuropeptide Y (NPY) and agouti-related protein (AGRP) (orexigenic regulators) and propiomelanocortin (POMC) and cocaine-and-amphetamine-regulated transcript (anorexigenic regulators) within the hypothalamus.[62] Although similar experiments have not been done in humans, there is evidence to support an association between prenatal nutrition and fetal growth.

In studies of pregnant women, leptin is detectable in amniotic fluid and its levels in venous cord blood are positively correlated with birthweight (and neonatal adiposity).[63-65] Maternal dietary glycemic index is positively associated with biomarkers of maternal carbohydrate metabolism (glycosylated hemoglobin and plasma glucose) as well as fetal growth.[66] Pregnant women consuming a mixed diet from low glycemic

carbohydrate sources have better insulin sensitivity and constant blood glucose levels compared to a 190% increase in blood glucose levels among women consuming high glycemic carbohydrate sources.[67] Additionally, women consuming low glycemic diets have lower gestational weight gains[68] and infants with lower birthweights compared to those consuming high glycemic diets.[66,68] Maternal hyperglycemia, as a result of impaired glucose tolerance or gestational diabetes, is associated with increased fetal plasma glucose and insulin levels[69,70] and infant body fat[70-72]; higher rates of fetal macrosomia[73-78] and LGA[79]; and later risk of obesity in the offspring,[69,70] compared to normal maternal glucose tolerance. Lastly, maternal insulin resistance during late 2nd/early 3rd trimester of pregnancy is associated with greater infant weight gain between birth and 12 months and sum of skin fold thickness at 12 months.[80]

Taken collectively, evidence from animal and human studies suggests that maternal overnutrition prior to as well as during gestation, via increased intakes of energy and high glycemic food sources, leads to an increase in fetal energy supply and hormonal imbalances. This results in an increase in fetal growth and adiposity and may act to program the body weight regulation systems for obesity. The purpose of the current research was to determine how prepregnancy BMI (overnutrition prior to pregnancy) and gestational weight gain (overnutrition during gestation) relate to infant and early childhood anthropometric outcomes.

Observational Studies Linking Prepregnancy BMI and Gestational Weight Gain to Offspring Anthropometric Outcomes

Observational studies demonstrate that prepregnancy BMI is linked to offspring adiposity (or BMI) during infancy[20-24,81], childhood and adolescence[25,27-34,36,37,82,83], and adulthood.[38,39] Several studies have focused on outcomes during infancy and early childhood. Ay et.al.[22] found that prepregnancy BMI was associated with increased peripheral fat mass in infants at 6 months. A linear relationship between child BMI at 3 years and maternal BMI during the first trimester was reported by Olson et.al.,[28] with each one-unit increase in prepregnancy BMI corresponding to an 11% increase in odds of overweight at age 3 years (Adjusted odds ratio (OR):1.11, p=0.003). Among a population of low income preschool children ages 2-4 years, Whitaker[27] found significantly higher odds of child obesity ($\geq 95^{th}$ percentile), ranging from approximately 1.4-4.3, across maternal BMI (measured during the first trimester) categories of overweight (25-29.9 kg/m^2), obese (30-39.9 kg/m^2), and morbidly obese (≥ 40 kg/m^2) compared to normal weight (18.5-24.9 kg/m^2). Finally, using data from the National Longitudinal Survey of Youth's Child-Mother file, Salsberry and Reagan[25] estimated the odds of child overweight ($\geq 95^{th}$ percentile) at three time points between ages 2 and 7 years. Compared to children of mothers with normal prepregnancy BMI (18.5-24.9 kg/m^2), those of mothers with obese prepregnancy BMI (≥ 30 kg/m^2) were 1.37 (95%CI: 1.02-1.84) times more likely to be overweight at 2-3 years. The influence of maternal prepregnancy obesity on child overweight continued across the study time points.

There are fewer studies and less consistent evidence for an association between gestational weight gain and offspring anthropometric outcomes, especially during infancy

and early childhood. Of the studies that examined offspring weight outcomes, several have done so using historical cohorts that are not reflective of the current trends in gestational weight gain and maternal and pediatric obesity. Furthermore, many of these studies used inconsistent definitions of gestational weight gain and failed to include important pre- and postnatal confounding factors.

Sixteen published studies were identified that reported results for an association between gestational weight gain and child, adolescent, and/or adult weight outcomes, yielding inconsistent conclusions. Positive associations between gestational weight gain and BMI status at 3 years[84], 7 years[55], 6-12 years[85], 9-14 years[86], 18 years[37], 20 years[39], 21 years[87], and 42 years[88] as well as sum of skin fold thicknesses at 3 years[84] were found, with two studies showing a significant interaction between gestational weight gain and maternal prepregnancy BMI.[28,55] Additionally, Li et.al.[26] found an increased risk of early onset overweight developmental trajectory (defined as children with overweight status, $\geq 95^{th}$ percentile, at 2 years that persisted throughout the follow-up period to 12 years of age) associated with gestational weight gain ≥20.43 kg (Adjusted OR: 1.7; 95% Confidence Interval (CI): 1.0-2.9); though there was no association between gestational weight gain and late onset overweight (defined as an initial high probability of overweight status at 2 years, low probability of overweight at 4-6 years, and high probability of overweight after 8 years). In contrast, there were seven studies that found no association between gestational weight gain and infant percent fat mass at 6 months[22]; BMI status at 2-4 years[27]; 4 and 7 years[89]; 4, 8, 10, and 12 years[90]; 6-12 years[83]; fat mass index at 9 years[82]; or sum of skin fold thicknesses at 18.0-22.9 years in an exclusively African-American population.[38]

Research Gaps

As mentioned, the majority of the observational studies suffer from methodological flaws that may undermine the ability to discern the true nature of the association of prepregnancy BMI and gestational weight gain with anthropometric outcomes, some of which are discussed in detail below:

Use of historical cohorts. Several studies[26,37-39,55,86,88-90] used cohort data that are not reflective of current guidelines for gestational weight gain as well as recent trends in excessive gestational weight gain, maternal obesity, and pediatric obesity. Of the studies that provided a mean or median gestational weight gain for the women in the study, there is a clear increase in these values over time; in the 1960s and 1970s median gestational weight gain was 9.5 kg[38,55] and mean weight gain was 10.5 kg[39], in the 1980s mean weight gain was 11.2 kg[86] and 12.0 kg[90], while in the 2000s mean weight gain was 15.6 kg.[84] Among the studies that found a positive association between gestational weight gain and childhood overweight, significant increased risks of childhood overweight were seen for women with the greatest amounts of weight gain. Using data from historical cohorts is therefore problematic because it may lack sufficient variation in prepregnancy BMI and gestational weight gain, as well as have low prevalence of maternal and pediatric obesity and excessive gestational weight gain, thereby limiting the ability to detect associations if they exist. A major strength of the current research is that it utilized prospectively collected data from a recent pregnancy cohort, with all children being born in the years 2001-2005.

Inconsistent categorization of gestational weight gain. Previous studies used varying categories of gestational weight gain: 1 kg, 5 kg, 5 lb, and 10 lb increments; categories based on the weight gain distribution within the population; and categories based on the IOM guidelines. The lack of consistency in categorization makes it difficult to compare results across studies or to determine appropriate ranges of gestational weight gain within the context of pediatric obesity development. Considering that the IOM guidelines are used by health care professionals to advise women of appropriate gestational weight gain, it is imperative to examine the IOM recommended ranges with respect to childhood weight outcomes and to identify whether there are corresponding consequences of excessive weight gain.

Lack of consideration for important pre- and postnatal factors. Many of the studies do not consider pre- and postnatal factors that may confound or have an intermediate role in the associations of prepregnancy BMI and gestational weight gain with child anthropometric outcomes including: birth order, maternal glucose tolerance status, smoking during pregnancy, breast feeding, and introduction to solid foods.

- *Birth Order (or Parity).* Birth order may be a predictor for overweight development; however, the evidence is contradictory. First born status is associated with rapid weight gain between birth and 24 months (OR: 2.01; 95% CI: 1.10-3.69)[91] and weight status during childhood[85](OR: 1.8; 95% CI: 1.0-3.4)[31] and young adulthood (OR: 4.0; 95% CI: 1.4-11.2)[38]; while, having a birth order of third or higher is associated with late onset overweight growth trajectories (OR: 2.3; 95% CI: 1.0-5.2).[26] There is also evidence for no

association between birth order and later weight status.[92,93] It is suggested that primiparity may be a marker of an inadequate intrauterine environment.[91] Additionally, there is the possibility of postnatal factors that contribute to this effect, such as differences between multiple- and single child households, but more research is needed.[38]

- *Maternal Glucose Tolerance Status.* Maternal hyperglycemia and gestational diabetes (GDM) are associated with high birthweight outcomes in the offspring.[94-96] GDM may be associated with an increased risk of obesity in the offspring due to prenatal programming of maternal fetal glucose metabolic processes.[97] Previous studies demonstrate both positive[98,99] and null[97,100] findings. In one study, large-for-gestational age (LGA) infants born to mothers with GDM were more likely to have greater weights, skin fold thicknesses, and circumference measurements at 4-7 years compared to average-for-gestational age (AGA) infants born to mothers with GDM, control LGA infants, and control AGA infants; maternal GDM was identified as a significant predictor of this growth pattern.[98] Among a cohort of Pima Indians, offspring of diabetic pregnancies had an average BMI that was 2.6 kg/m^2 higher than a sibling born from a previous non-diabetic pregnancy. GDM has been shown to be associated with obesity (>95^{th} percentile) at 9-14 years; however, this association was no longer significant after adjustment for maternal BMI and birthweight.[97] Mild, diet-treated GDM was not found to increase the risk of childhood overweight at 5 to 10 years.

- *Smoking During Pregnancy.* Smoking during pregnancy may increase the risk of obesity during childhood.[26,28,101-103] A recent meta-analysis[101] based on 84,563 children from 14 observational studies reported that children whose mothers smoked during pregnancy were 1.5 times more likely (pooled adjusted OR: 1.50; 95% CI: 1.36-1.65) to be overweight at ages 3-33 years compared to children of non-smokers. The estimates were similar for the odds of obesity (OR: 1.52; 95% CI: 1.36-1.69). Animal studies have also confirmed a link between prenatal exposure to nicotine and increased adiposity in the offspring[104-106]{{}} but the mechanisms by which prenatal smoking exposure may influence offspring weight are not well understood or defined.
- *Breast Feeding and Formula Feeding.* There is data to suggest that breast feeding exposure elicits a small but protective effect against overweight development later in life[107]; however, a recent critical review found insufficient evidence for a causal association.[108] Breast feeding is associated with slower rates of weight gain and linear growth compared to formula fed infants, with formula fed infants gaining 0.18 kg (95% CI: 0.00-0.35) more than breastfed infants between birth and 6 months.[109] Compared to infants breastfed for greater than 40 weeks, those breastfed for less than 20 weeks gained an excess of 317.4 g (standard error (SE): 43.6) between birth and 1 year.[110] This may be a result of greater energy intakes among formula fed infants. Formula fed and mixed fed (combination of breast milk and formula) infants have been shown to have higher energy intakes and greater body weights, compared to exclusively breastfed infants.[111,112] Greater energy

intakes at 4 months are predictive of higher weight gains between birth and 1, 2, and 3 years of age. An increase in 420 kJ/day (100 kcal/day) in energy intake among formula or mixed fed infants is associated with an increased odds of having a BMI>85th percentile at 3 and 5 years of age (OR: 1.46; 95% CI: 1.20-1.78 and OR: 1.25; 95% CI: 1.00-1.55, respectively).[111] Breast feeding may also represent a marker for health-promoting behaviors that are associated with offspring weight and are difficult to control for in analyses.[113] For example, mothers who breastfeed may be more health conscious and more likely to promote healthy behaviors in their offspring concerning eating patterns and physical activity compared to women who do not breastfeed.[113]

- *Introduction of Solid Foods.* An early age of introduction to solid foods during infancy (between 1 and 4 months) is associated with greater energy intakes at 4 months, which are predictive of greater weight gains and higher BMI between birth and 5 years of age.[111] Infants given solid foods prior to 16 weeks gained 224.2 g (SE: 53.3) more weight from birth to 1 year compared to infants given solid foods at 16 weeks or later.[110] There is some evidence to suggest that infant size is a predictor of age at solid food introduction, with bigger infants being introduced earlier than their smaller counterparts, and does not necessarily lead to greater weight gain after introduction[109,114,115]; however, this is not consistently shown. [110]

The PIN Study collected data on all of these potential covariates of interest and they were considered in statistical analyses for the current research.

Variation in age at measurement of offspring anthropometric outcomes. As mentioned, the ages of the offspring at which anthropometric measurements were ascertained differs across the studies, ranging from infancy through adulthood. The current research examines anthropometric outcomes throughout the first 3 years of life. High growth rates and adiposity during infancy are associated with an increased risk of future overweight/obesity development[7,83,116-118] and high systolic blood pressure at 3 years.[16] Childhood overweight during the preschool years has been shown to track into adolescence and adulthood[119]; children with a BMI≥85th percentile during the preschool years at 24, 36, and 54 months were over five times more likely (OR: 5.4; 95% CI: 2.9-9.9) to have a BMI≥85th percentile at 12 years compared to children who were not overweight (BMI<85th percentile) at all three preschool time points. At 3 years, compared to children with BMI<50th percentile, children who were overweight (85-<95th percentile) and obese (≥95th percentile) were four (OR: 4.0; 95%CI: 2.3-7.1) and ten (OR: 10.0; 95%CI: 3.8-26.7) times more likely to have a BMI≥85th percentile at 12 years, respectively. These values were slightly attenuated but remained significant when the reference group was children with BMI <75th percentile.[120] Thus, identification of risk factors for excess weight development early in life is imperative. Furthermore, the use of a 3 year old child cohort in the current research contributes to the already existing literature among this age group[27,28,84] and allows for a comparison of results with those from the previous studies.

Overall scarcity of research. There are relatively few studies that examine how gestational weight gain relates to infant anthropometric outcomes, rapid infant weight

gain, or longitudinal weight/length development in early childhood. We identified five studies that examined the association between gestational weight gain and childhood overweight[28,84-86] or fat mass.[82] There was one study[26] that examined longitudinal growth (as BMI trajectories) in association with gestational weight gain. The current studies make much needed contributions to the literature with regard to these research questions.

Significance of the Proposed Research

Prepregnancy BMI and gestational weight gain represent modifiable behavioral factors that may have an independent role in the development of childhood overweight via increased fetal growth and fetal programming of the physiologic and hormonal pathways responsible for appetite, metabolism, and body weight regulation, as well as an association with an obesogenic postnatal environment. The current research utilized a contemporary pregnancy cohort to extensively examine and contrast the effects of prepregnancy BMI and gestational weight gain, according to the 2009 IOM recommendations, on weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length z-scores (WLZ) at 6 months; rapid weight gain from birth to 6 months; BMI z-score and risk of overweight/obesity at 3 years; and longitudinal changes in WAZ, LAZ, and WLZ development from birth to 3 years. The information gained from this research is crucial for evaluating the current IOM guidelines and advising future clinical and policy recommendations for preconceptional and pediatric obesity interventions.

References

1. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007-2008. *JAMA*. 2010;303(3):242-249.

2. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of childhood BMI to adult adiposity: The Bogalusa Heart Study. *Pediatrics*. 2005;115(1):22-27.

3. Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, Byers T. Do obese children become obese adults? A review of the literature. *Prev Med*. 1993;22(2):167-177.

4. Guo SS, Chumlea WC. Tracking of body mass index in children in relation to overweight in adulthood. *Am J Clin Nutr*. 1999;70(1):145S-148S.

5. Wright CM, Parker L, Lamont D, Craft AW. Implications of childhood obesity for adult health: Findings from Thousand Families cohort study. *Br Med J*. 2001;323(7324):1280-1284.

6. Ong KK, Loos RJF. Rapid infancy weight gain and subsequent obesity: Systematic reviews and hopeful suggestions. *Acta Paediatrica*. 2006;95(8):904-908.

7. Ekelund U, Ong K, Linne Y, et al. Upward weight percentile crossing in infancy and early childhood independently predicts fat mass in young adults: The Stockholm Weight Development Study (SWEDES). *Am J Clin Nutr*. 2006;83(2):324-330.

8. Stettler N, Kumanyika SK, Katz SH, Zemel BS, Stallings VA. Rapid weight gain during infancy and obesity in young adulthood in a cohort of African Americans. *Am J Clin Nutr*. 2003;77(6):1374-1378.

9. Stettler N, Zemel BS, Kumanyika S, Stallings VA. Infant weight gain and childhood overweight status in a multicenter, cohort study. *Pediatrics*. 2002;109(2):194-199.

10. Monteiro POA, Victora CG. Rapid growth in infancy and childhood and obesity in later life-a systematic review. *Obes Rev*. 2005;6(2):143-154.

11. Fagot-Campagna A. Emergence of type 2 diabetes mellitus in children: Epidemiological evidence. *J Pediatr Endocrinol Metab*. 2000;13(Suppl 6):1395-1402.

12. Williams CL, Strobino B, Bollella M, Brotanek J. Body size and cardiovascular risk factors in a preschool population. *Preventive Cardiology*. 2004;7:116-121.

13. Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? *Circulation*. 2004;109(9):1108-1113.

14. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. *The Lancet*. 2003;361(9363):1089-1097.

15. Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: Two cohorts after randomised trials. *The Lancet*. 2001;357(9254):413-419.

16. Belfort MB, Rifas-Shiman SL, Rich-Edwards J, Kleinman KP, Gillman MW. Size at birth, infant growth, and blood pressure at three years of age. *J Pediatr*. 2007;151(6):670-674.

17. Ekelund U, Ong KK, Linne Y, et al. Association of weight gain in infancy and early childhood with metabolic risk in young adults. *Journal of Clinical Endocrinology & Metabolism*. 2007;92(1):98-103.

18. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 2002;288(14):1723-1727.

19. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA*. 2006; 295(13):1549-1555.

20. Hull HR, Dinger MK, Knehans AW, Thompson DM, Fields DA. Impact of maternal body mass index on neonate birthweight and body composition. *Am J Obstet Gynecol*. 2008;198(4):416e1-e6.

21. Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S. Fetuses of obese mothers develop insulin resistance in utero. *Diabetes Care*. 2009;32(6):1076-1080.

22. Ay L, Van Houten VAA, Steegers EAP, et al. Fetal and postnatal growth and body composition at 6 months of age. *J Clin Endocrinol Metab*. 2009;94(6):2023-2030.

23. Silliman K, Kretchmer N. Maternal obesity and body composition of the neonate. *Neonatology*. 1995;68(6):384-393.

24. Sewell MF, Huston-Presley L, Super DM, Catalano P. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. *Obstet Gynecol*. 2006;195(4):1100-1103.

25. Salsberry PJ, Reagan PB. Dynamics of early childhood overweight. *Pediatrics*. 2005;116(6):1329-1338.

26. Li C, Goran MI, Kaur H, Nollen N, Ahluwalia JS. Developmental trajectories of overweight during childhood: Role of early life factors. *Obesity*. 2007;15(3):760-771.

27. Whitaker RC. Predicting preschooler obesity at birth: The role of maternal obesity in early pregnancy. *Pediatrics*. 2004;114(1):e29-e36.

28. Olson CM, Strawderman MS, Dennison BA. Maternal weight gain during pregnancy and child weight at age 3 years. *Matern Child Health J*. 2009;13(6):839-846.

29. Mesman I, Roseboom TJ, Bonsel GJ, Gemke RJ, van der Wal MF, Vrijkotte TGM. Maternal pre-pregnancy body mass index explains infant's weight and BMI at 14 months: Results from a multi-ethnic birth cohort study. *Br Med J*. 2009;94(8):587-595.

30. Reilly JJ, Armstrong J, Dorosty AR, et al. Early life risk factors for obesity in childhood: Cohort study. *Br Med J*. 2005;330(7504):1357.

31. Dubois L, Girard M. Early determinants of overweight at 4.5 years in a population-based longitudinal study. *Int J Obes*. 2006;30(4):610-617.

32. Li R, Jewell S, Grummer-Strawn L. Maternal obesity and breast-feeding practices. *Am J Clin Nutr*. 2003;77(4):931-936.

33. Blair NJ, Thompson J, Black PN, et al. Risk factors for obesity in 7-year-old European children: The Auckland Birthweight Collaborative study. *Br Med J*. 2007;92(10):866-871.

34. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med*. 1997;337(13):869-873.

35. Olson CM, Strawderman MS, Reed RG. Efficacy of an intervention to prevent excessive gestational weight gain. *Obstet Gynecol*. 2004;191(2):530-536.

36. Li C, Kaur H, Choi WS, Huang TT, Lee RE, Ahluwalia JS. Additive interactions of maternal prepregnancy BMI and breast-feeding on childhood overweight. *Obes Res*. 2005;13(2):362-371.

37. Stuebe AM, Forman MR, Michels KB. Maternal-recalled gestational weight gain, pre-pregnancy body mass index, and obesity in the daughter. *Int J Obes*. 2009;33(7):743-752.

38. Stettler N, Tershakovec AM, Zemel BS, et al. Early risk factors for increased adiposity: A cohort study of African American subjects followed from birth to young adulthood. *Am J Clin Nutr*. 2000;72(2):378-383.

39. Terry MB, Wei Y, Esserman D. Maternal, birth, and early-life influences on adult body size in women. *Am J Epidemiol*. 2007;166(1):5-13.

40. Viswanathan M, Siega-Riz AM, Moos MK, et al. Outcomes of maternal weight gain. *Evidence report/technology assessment*. 2008;168:1-223.

41. Institute of Medicine. *Nutrition during Pregnancy. Part I. Weight Gain.* Washington, DC: National Academy Press; 1990.

42. IOM (Institute of Medicine), NRC (National Research Council). *Weight Gain during Pregnancy: Reexamining the Guidelines.* Washington, DC: The National Academies Press; 2009.

43. Schieve LA, Cogswell ME, Scanlon KS. Trends in pregnancy weight gain within and outside ranges recommended by the Institute of Medicine in a WIC population. *Matern Child Health J*. 1998;2(2):111-116.

44. Lederman SA, Paxton A, Heymsfield SB, Wang J, Pierson RN. Body fat and water changes during pregnancy in women with different body weight and weight gain. *Obstet Gynecol*. 1997;90(4, Part 1):483-488.

45. Carmichael S, Abrams B, Selvin S. The pattern of maternal weight gain in women with good pregnancy outcomes. *Am J Public Health*. 1997;87(12):1984-1988.

46. Caulfield LE, Witter FR, Stoltzfus RJ. Determinants of gestational weight gain outside the recommended ranges among black and white women. *Obstet Gynecol*. 1996;87:760-766.

47. Kiel DW, Dodson EA, Artal R, Boehmer TK, Leet TL. Gestational weight gain and pregnancy outcomes in obese women: How much is enough? *Obstet Gynecol*. 2007;110(4):752-758.

48. DeVader SR, Neeley HL, Myles TD, Leet TL. Evaluation of gestational weight gain guidelines for women with normal prepregnancy body mass index. *Obstet Gynecol*. 2007; 110(4):745-751.

49. Cogswell ME, Scanlon KS, Fein SB, Schieve LA. Medically advised, mother's personal target, and actual weight gain during pregnancy. *Obstet Gynecol*. 1999; 94(4):616-622.

50. Saldana TM, Siega-Riz AM, Adair LS, Savitz DA, Thorp JM. The association between impaired glucose tolerance and birth weight among black and white women in central North Carolina. *Diabetes Care*. 2003;26(3):656-661.

51. Stuebe AM, Oken E, Gillman MW. Associations of diet and physical activity during pregnancy with risk for excessive gestational weight gain. *Obstet Gynecol*. 2009; 201:58.e1-58.e8.

52. Olafsdottir AS, Skuladottir GV, Thorsdottir I, Hauksson A, Steingrimsdottir L. Maternal diet in early and late pregnancy in relation to weight gain. *Int J Obes*. 2005;30(3):492-499.

53. Öhlin A, Rössner S. Factors related to body weight changes during and after pregnancy: The Stockholm Pregnancy and Weight Development study. *Obes Res*. 1996;4:271-276.

54. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359(1):61-73.

55. Wrotniak BH, Shults J, Butts S, Stettler N. Gestational weight gain and risk of overweight in the offspring at age 7 y in a multicenter, multiethnic cohort study. *Am J Clin Nutr*. 2008;87(6):1818-1824.

56. McMillen IC, Edwards LJ, Duffield J, Muhlhausler BS. Regulation of leptin synthesis and secretion before birth: Implications for the early programming of adult obesity. *Reproduction*. 2006;131(3):415-427.

57. Chen H, Simar D, Lambert K, Mercier J, Morris MJ. Maternal and postnatal overnutrition differentially impact appetite regulators and fuel metabolism. *Endocrinology*. 2008;149(11):5348-5356.

58. Jones HN, Woollett LA, Barbour N, Prasad PD, Powell TL, Jansson T. High-fat diet before and during pregnancy causes marked up-regulation of placental nutrient transport and fetal overgrowth in C57/BL6 mice. *The FASEB Journal*. 2009;23(1):271-278.

59. Dunn GA, Bale TL. Maternal high-fat diet promotes body length increases and insulin insensitivity in second-generation mice. *Endocrinology*. 2009;150:4999-5009.

60. Howie GJ, Sloboda DM, Kamal T, Vickers MH. Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet. *Exp Physiol*. 2009;587(4):905-915.

61. Ericsson A, Säljö K, Sjöstrand E, et al. Brief hyperglycaemia in the early pregnant rat increases fetal weight at term by stimulating placental growth and affecting placental nutrient transport. *J Physiol (Lond)*. 2007;581(3):1323-1332.

62. Muhlhausler BS, Adam CL, Findlay PA, Duffield JA, McMillen IC. Increased maternal nutrition alters development of the appetite-regulating network in the brain. *FASEB J*. 2006;20(8):1257-1259.

63. Schubring C, Kiess W, Englaro P, Rascher W, Blum W. Leptin concentrations in amniotic fluid, venous and arterial cord blood and maternal serum: High leptin synthesis in the fetus and inverse correlation with placental weight. *Eur J Pediatr*. 1996;155(9):830-834.

64. Schubring C, Kiess W, Englaro P, et al. Levels of leptin in maternal serum, amniotic fluid, and arterial and venous cord blood: Relation to neonatal and placental weight. *Journal of Clinical Endocrinology & Metabolism*. 1997;82(5):1480-1483.

65. Harigaya A, Nagashima K, Nako Y, Morikawa A. Relationship between concentration of serum leptin and fetal growth. *Journal of Clinical Endocrinology & Metabolism*. 1997;82(10):3281-3284.

66. Scholl TO, Chen X, Khoo CS, Lenders C. The dietary glycemic index during pregnancy: Influence on infant birth weight, fetal growth, and biomarkers of carbohydrate metabolism. *Am J Epidemiol*. 2004;159(5):467-474.

67. Clapp JF. Effect of dietary carbohydrate on the glucose and insulin response to mixed caloric intake and exercise in both nonpregnant and pregnant women. *Diabetes Care*. 1998;21:107-112.

68. Clapp JF. Maternal carbohydrate intake and pregnancy outcome. *Proc Nutr Soc*. 2007;61(01):45-50.

69. Silverman BL, Rizzo T, Green OC, et al. Long-term prospective evaluation of offspring of diabetic mothers. *Diabetes*. 1991;40 Suppl 2:121-125.

70. Silverman BL, Rizzo TA, Cho NH, Metzger BE. Long-term effects of the intrauterine environment: The Northwestern University diabetes in pregnancy center. *Diabetes Care*. 1998;21:142-149.

71. Catalano PM, Thomas A, Huston-Presley L, Amini SB. Increased fetal adiposity: A very sensitive marker of abnormal in utero development. *Obstet Gynecol*. 2003; 189(6):1698-1704.

72. Plagemann A, Harder T, Kohlhoff R, Rohde W, Dörner G. Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes. *Int J Obes*. 1997;21(6):451-456.

73. Garner P, Okun N, Keely E, et al. A randomized controlled trial of strict glycemic control and tertiary level obstetric care versus routine obstetric care in the management of gestational diabetes: A pilot study. *Obstet Gynecol*. 1997;177(1):190-195.

74. Naylor CD, Sermer M, Chen E, Sykora K. Cesarean delivery in relation to birth weight and gestational glucose tolerance: Pathophysiology or practice style? *JAMA*. 1996;275(15):1165-1170.

75. Lu GC, Rouse D, Dubard M, Cliver S. The impact of lower threshold values for the detection of gestational diabetes mellitus. *Obstet Gynecol*. 2000;95:44.

76. Langer O, Brustman L, Anyaegbunam A, Mazze R. The significance of one abnormal glucose tolerance test value on adverse outcome in pregnancy. *Am J Obstet Gynecol*. 1987;157(3):758-763.

77. Lindsay MK, Graves W, Klein L. The relationship of one abnormal glucose tolerance test value and pregnancy complications. *Obstetrics & Gynecology*. 1989;73(1):103-106.

78. Tan YY, Yeo GSH. Impaired glucose tolerance in pregnancy-is it of consequence? *Australian and New Zealand Journal of Obstetrics and Gynaecology*. 1996;36(3):248-254.

79. Scholl TO, Sowers MF, Chen X, Lenders C. Maternal glucose concentration influences fetal growth, gestation, and pregnancy complications. *Am J Epidemiol*. 2001;154(6):514-520.

80. Hamilton JK, Odrobina E, Yin J, Hanley AJ, Zinman B, Retnakaran R. Maternal insulin sensitivity during pregnancy predicts infant weight gain and adiposity at 1 year of age. *Obesity*. 2010;18(2):340-346.

81. Nohr EA, Timpson NJ, Andersen CS, Davey Smith G, Olsen J, Sørensen TI. Severe obesity in young women and reproductive health: The Danish National Birth cohort. *PLoS One*. 2009;4(12):e8444.

82. Gale CR, Javaid MK, Robinson SM, Law CM, Godfrey KM, Cooper C. Maternal size in pregnancy and body composition in children. *Journal of Clinical Endocrinology & Metabolism*. 2007;92(10):3904-3911.

83. Catalano PM, Farrell K, Thomas A, et al. Perinatal risk factors for childhood obesity and metabolic dysregulation. *Am J Clin Nutr*. 2009;90(5):1303-1313.

84. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. *Obstet Gynecol*. 2007;196(4):322.e1-322.e8.

85. Moreira P, Padez C, Mourao-Carvalhal I, Rosado V. Maternal weigh gain during pregnancy and overweight in Portuguese children. *Int J Obes*. 2007;31(4):608-614.

86. Oken E, Rifas-Shiman SL, Field AE, Frazier AL, Gillman MW. Maternal gestational weight gain and offspring weight in adolescence. *Obstet Gynecol*.2008;112(5):999-1006.

87. Mamun AA, O'Callaghan M, Callaway L, Williams G, Najman J, Lawlor DA. Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: Evidence from a birth cohort study. *Circulation*. 2009; 119(13):1720-1727.

88. Schack-Nielsen L, Michaelsen KF, Gamborg M, Mortensen EL, Sørensen TIA. Gestational weight gain in relation to offspring body mass index and obesity from infancy through adulthood. *Int J Obes*. 2009;34(1):67-74.

89. Fisch RO, Bilek MK, Ulstrom R. Obesity and leanness at birth and their relationship to body habitus in later childhood. *Pediatrics*. 1975;56(4):521-528.

90. Maffeis C, Micciolo R, Must A, Zaffanello M, Pinelli L. Parental and perinatal factors associated with childhood obesity in north-east Italy. *Int J Obes Relat Metab Disord*. 1994;18(5):301-305.

91. Karaolis-Danckert N, Buyken AE, Kulig M, et al. How pre-and postnatal risk factors modify the effect of rapid weight gain in infancy and early childhood on subsequent fat mass development: Results from the Multicenter Allergy Study 90. *Am J Clin Nutr*. 2008;87(5):1356-1364.

92. Baecke JA, Burema J, Frijters JE, Hautvast JG, van der Wiel-Wetzels WA. Obesity in young Dutch adults: I, socio-demographic variables and body mass index. *Int J Obes*. 1983;7(1):1-12.

93. Charney E, Goodman HC, McBride M, Lyon B, Pratt R. Childhood antecedents of adult obesity: Do chubby infants become obese adults? *N Engl J Med*. 1976;295(1):6-9.

94. Jensen DM, Korsholm L, Ovesen P, Beck-Nielsen H, Mølsted-Pedersen L, Damm P. Adverse pregnancy outcome in women with mild glucose intolerance: Is there a clinically meaningful threshold value for glucose? *Acta Obstet Gynecol Scand*. 2008;87(1):59-62.

95. Cheng YW, McLaughlin GB, Esakoff TF, Block-Kurbisch I, Caughey AB. Glucose challenge test: Screening threshold for gestational diabetes mellitus and associated outcomes. *Journal of Maternal-Fetal and Neonatal Medicine*. 2007;20(12):903-908.

96. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;358:1991-2002.

97. Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. *Pediatrics*. 2003;111(3):e221-226.

98. Vohr BR, McGarvey ST, Tucker R. Effects of maternal gestational diabetes on offspring adiposity at 4-7 years of age. *Diabetes Care*. 1999;22(8):1284-1291.

99. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity. *Diabetes*. 2000;49:2208-2211.

100. Whitaker RC, Pepe MS, Seidel KD, Wright JA, Knopp RH. Gestational diabetes and the risk of offspring obesity. *Pediatrics*. 1998;101(2):e9.

101. Oken E, Levitan EB, Gillman MW. Maternal smoking during pregnancy and child overweight: Systematic review and meta-analysis. *Int J Obes*. 2008;32(2):201-210.

102. Huang JS, Lee TA, Lu MC. Prenatal programming of childhood overweight and obesity. *Matern Child Health J*. 2007;11(5):461-473.

103. Leary SD, Smith GD, Rogers IS, Reilly JJ, Wells JCK, Ness AR. Smoking during pregnancy and offspring fat and lean mass in childhood. *Obesity (Silver Spring)*. 2006;14(12):2284-2293.

104. Newman MB, Shytle RD, Sanberg PR. Locomotor behavioral effects of prenatal and postnatal nicotine exposure in rat offspring. *Behav Pharmacol*. 1999;10(6-7):699-706.

105. Williams CM, Kanagasabai T. Maternal adipose tissue response to nicotine administration in the pregnant rat: Effects on fetal body fat and cellularity. *Br J Nutr*. 2007;51(01):7-13.

106. Gao YJ, Holloway AC, Zeng Z, et al. Prenatal exposure to nicotine causes postnatal obesity and altered perivascular adipose tissue function. *Obes Res*. 2005;13(4):687-692.

107. Owen CG, Martin RM, Whincup PH, Davey-Smith G, Gillman MW, Cook DG. The effect of breast feeding on mean body mass index throughout life: A quantitative review of published and unpublished observational evidence. *Am J Clin Nutr*. 2005;82(6):1298-1307.

108. Cope MB, Allison DB. Critical review of the World Health Organization's (WHO) 2007 report on evidence of the long-term effects of breast feeding: Systematic reviews and meta-analysis' with respect to obesity. *Obesity Reviews*. 2008;9(6):594-605.

109. Baird J, Poole J, Robinson S, et al. Milk feeding and dietary patterns predict weight and fat gains in infancy. *Paediatr Perinat Epidemiol*. 2008;22(6):575-586.

110. Baker JL, Michaelsen KF, Rasmussen KM, Sorensen TIA. Maternal prepregnant body mass index, duration of breast feeding, and timing of complementary food introduction are associated with infant weight gain. *Am J Clin Nutr*. 2004;80(6):1579-1588.

111. Ong KK, Emmett PM, Noble S, Ness A, Dunger DB. Dietary energy intake at the age of 4 months predicts postnatal weight gain and childhood body mass index. *Pediatrics*. 2006;117(3):e503-e508.

112. Heinig M, Nommsen L, Peerson J, Lonnerdal B, Dewey K. Energy and protein intakes of breast-fed and formula-fed infants during the first year of life and their association with growth velocity: The DARLING study. *Am J Clin Nutr*. 1993;58(2):152-161.

113. Horta BL, Bahl R, Martines JC, Victora CG. Evidence on the long-term effects of breast feeding: Systematic reviews and meta-analysis. *Systematic Reviews and Meta-analyses. Geneva: World Health Organisation*. 2007.

114. Wright CM, Parkinson KN, Drewett RF. Why are babies weaned early? Data from a prospective population based cohort study. *Arch Dis Child*. 2004;89(9):813-816.

115. Forsyth JS, Ogston SA, Clark A, Florey CD, Howie PW. Relation between early introduction of solid food to infants and their weight and illnesses during the first two years of life. *BMJ*. 1993;306(6892):1572-1576.

116. Dennison BA, Edmunds LS, Stratton HH, Pruzek RM. Rapid infant weight gain predicts childhood overweight. *Obesity*. 2006;14(3):491-499.

117. Chomtho S, Wells JCK, Williams JE, Davies PSW, Lucas A, Fewtrell MS. Infant growth and later body composition: Evidence from the 4-component model. *Am J Clin Nutr*. 2008;87(6):1776-1784.

118. Botton J, Heude B, Maccario J, Ducimetiere P, Charles MA. Postnatal weight and height growth velocities at different ages between birth and 5 y and body composition in adolescent boys and girls. *Am J Clin Nutr*. 2008;87(6):1760-1768.

119. Krebs NF, Jacobson MS, American Academy of Pediatrics Committee on Nutrition. Prevention of pediatric overweight and obesity. *Pediatrics*. 2003;112(2):424-430.

120. Nader PR, O'Brien M, Houts R, et al. National Institute of Child Health and Human Development Early Child Care Research Network. Identifying risk for obesity in early childhood. *Pediatrics*. 2006;118(3):e594-e601.

CHAPTER III

METHODS

The purpose of this research was to determine how maternal prepregnancy BMI and gestational weight gain, according to the 2009 IOM recommendations, relate to offspring anthropometric outcomes within the first 3 years of life. Mother-infant pairs were recruited from the Pregnancy, Infection and Nutrition Study. Multivariable linear regression, modified Poisson regression, and linear mixed-effects regression were used to examine the specific research aims. Details about the study design and analysis are described in the following sections.

Study Design and Population

The Pregnancy, Infection, and Nutrition (PIN) study is a longitudinal, prospective cohort study of risk factors for preterm birth. The current research is a secondary data analysis using data collected from women recruited into the third cohort of the PIN study (PIN 3) who were followed-up at 3 and 12 months (PIN Postpartum) and 3 years (PIN Pediatric) postpartum. Figure 2 displays participant retention between the prenatal, postpartum, and pediatric studies. The PIN study protocols were reviewed and approved by the Institutional Review Boards of the School of Medicine at the University of North Carolina at Chapel Hill and Wake Medical Center.

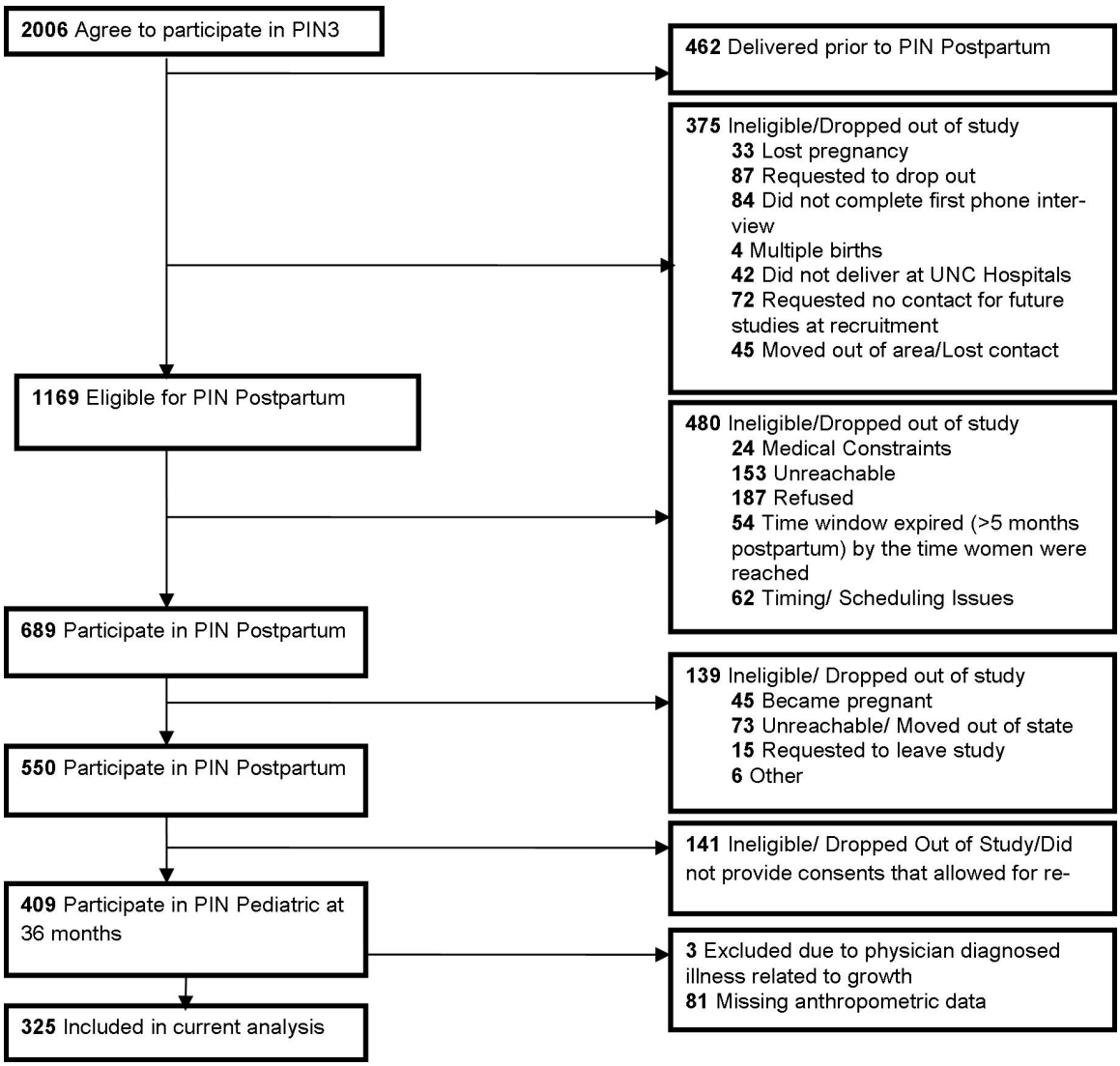
PIN 3. PIN 3 recruited women from public and private prenatal care clinics at the University of North Carolina (UNC) Hospitals beginning January 1, 2001- June 30, 2005. Women who were eligible for the study included those who were less than 20 weeks' gestation, 16 years of age at conception and older, English-speaking, carrying a singleton fetus, planning to continue prenatal care and deliver at the study site, and had access to a telephone for study interviews. Interviews of women were conducted at 15-20 weeks' (first clinic visit), 17-22 weeks' (first telephone interview), 24-29 weeks' (second clinic visit), 27-30 weeks' (second telephone interview) gestation, and post-delivery in the hospital. Data collection included biological specimens and information on socio-demographic characteristics, psychosocial indicators, health habits, physical activity (leisure and work related), dietary intakes, previous as well as current medical history, and birth outcome. Medical charts were abstracted for all women to collect information on reproductive history, weight gain, pregnancy complications, and labor and delivery events. A total of 2,006 pregnant women were recruited for PIN 3. Details on the PIN study can be found at http://www.cpc.unc.edu/projects/pin.

PIN Postpartum. Women who were enrolled in PIN3 and gave birth to a live infant between October 2002 and December 2005 were invited to participate in the PIN Postpartum study. PIN Postpartum was a longitudinal study aimed to investigate factors related to postpartum weight loss, and included home visits at 3 and 12 months postpartum. Data collection included maternal height, weight, and percent body fat, information on breast feeding status, dietary intake and physical activity behaviors, measurement of psychosocial status, body image, restrained eating, and updated socio-

demographic information. Additionally, information on infant weight and length measurements was collected from study provided doctor's cards (described in the following section). Only those women who gave birth after the postpartum study recruitment began and who lived within the study's catchment area (required to conduct in-home visits) were eligible for the study; women who had a pregnancy loss, did not complete the first telephone interview, or delivered at a hospital other than UNC were excluded. Of the 2,006 women recruited for PIN3, there were 1,169 women available for recruitment for the PIN Postpartum Study. One hundred and eighty-seven women refused to participate and 293 women were excluded from the study for the following reasons: 24 had medical constraints, 153 were unreachable, 62 had timing conflicts, and 54 were greater than 5 months postpartum by the time they were located. The remaining 689 women agreed to participate and completed an in-home interview at 3 months. One hundred and thirty-eight of these women were ineligible or dropped out of the study after the 3 month interview; 550 women completed an in-home interview at 12 months postpartum.

PIN Pediatric. The PIN Pediatric study (beginning 2004) followed-up the index infant at 3 years. Children with no major birth defects whose mothers participated in the PIN 3 and PIN Postpartum studies were eligible. Data collection included children's heights, weights, health status, diet and physical activity behaviors, as well as maternal and sociodemographic information. Four hundred and nine mother-child pairs completed the 36 month visit.

Figure 2. Participant retention across the PIN studies.



The distributions of selected baseline characteristics between the eligible mother-child pairs who participated in PIN Pediatric (n=409), the PIN Postpartum pairs who were excluded or did not participate in PIN Pediatric (n=280), and the eligible PIN3 pairs who were excluded from or did not participate in PIN Postpartum study (n=480) were examined (Appendix – Tables 1 and 2). In comparison to mothers who participated in PIN Postpartum (n=689), eligible mothers who were excluded or refused to participate in

PIN Postpartum (n=480) were younger, more likely to be overweight/obese, black, unmarried, less educated (≤grade 12), from low income households (≤185% of the 2001 Federal Poverty Guidelines), smokers, and have infants at earlier gestational ages (Appendix- Table 1). Similar differences in the distributions of baseline characteristics were seen between mothers who participated in PIN Pediatric (n=409) and mothers participated in PIN Postpartum but were excluded or refused to participate in PIN Pediatric (n=280). The exception being that there was no difference in mean infant gestational age but a significant difference across categories of infant birthweight (Appendix –Table 2). All other comparisons of measured characteristics were not significant.

Anthropometric Outcomes

The offspring anthropometric outcomes considered for this research were: WAZ, LAZ, and WLZ, and BMI z-scores as well as rapid infant weight gain. Infant birthweight and sex were abstracted from delivery logs. Gestational age at birth was calculated from ultrasound measurements conducted prior to 22 weeks' gestation (up to 21 weeks, 6 days). If no ultrasound was performed or if it was not performed prior to the start of the 22nd week then the date of the last menstrual period was used. Infant weights and lengths (between birth and approximately 12 months) were measured and recorded on doctor's cards during well-baby visits. Doctor's cards were provided to mothers by the PIN study staff. Mothers brought these cards to each pediatrician visit and the date of the visit and weight and length of the infant were recorded by medical staff. These cards were collected by the PIN staff at the 12 month home visit. The exact age of the infant at the

time of each measurement was calculated by subtracting the infant's birth date from the date of the visit. We used the 15th of the month for infants missing the day of the visit and the pediatrician's recorded age of the infant when both the month and day of the visit were missing. At 3 years, children's heights and weights were measured by PIN study staff using a stadiometer and scale, respectively, according to National Health and Nutrition Examination Surveys (NHANES) protocols.[1]

Weight-for-age, Length-for-age, and Weight-for-Length z-scores. Offspring weights and lengths were converted to sex-specific WAZ, LAZ (height-for-age was calculated when child age was greater than 2 years), and WLZ (weight-for-height was calculated when child age was greater than 2 years) using the 2000 Centers for Disease Control (CDC)/National Center for Health Statistics (NCHS) growth charts.[2] These charts are often used in the United States to screen for overweight/obesity (in the clinic and research settings) and were constructed from samples of US children during the 1960s, 1970s, 1980s, and 1990s (for children less than age 6).

Rapid infant weight gain between birth and 6 months. Rapid infant weight gain was defined as a change in WAZ greater than +0.67 between birth and 6 months, which is clinically interpretable as the upward crossing of a centile line on an infant growth chart.[3]

Child BMI at 3 years. Child BMI at 3 years was calculated using the following formula: BMI = weight (kg)/ height $(m)^2$ and converted to age- and sex-specific BMI z-scores (continuous) and percentiles (categories) using the 2000 CDC/NCHS growth charts. Risk

of overweight/obesity was defined as BMI≥85th percentile (reference, <85th percentile) and risk of obesity was defined as BMI≥95th percentile (reference, <95th percentile).

Maternal Exposures

Maternal Prepregnancy BMI. Maternal prepregnancy BMI (kg/m^2) was calculated using self-reported prepregnancy weight and measured height. Self-reported prepregnancy weight was obtained from the medical record or a prenatal research screening questionnaire. The validity of self-reported weight by pregnant women was examined previously and shown to be good if collected early in pregnancy. For quality assurance, weight measurements taken at the first prenatal clinic visit (within 15 weeks' gestation) were compared to the self-reported prepregnancy weights to identify biologically implausible weight gains. Women with implausible values had their prepregnancy weights imputed following previously published methods.[4,5] BMI was classified following guidelines established by the 2009 IOM recommendations: underweight <18.5 kg/m^2; normal weight 18.5 to 24.9 kg/m^2; overweight 25.0 to 29.9 kg/m^2; and obese ≥30.0 kg/m^2.[6]

Adequacy of Gestational Weight Gain. Gestational weight gain was measured at each prenatal clinic visit and documented in the prenatal record. Total gestational weight gain was defined as the difference between each woman's self-reported prepregnancy weight and her last weight measurement taken prior to delivery. The 2009 IOM gestational weight gain recommendations for total weight gain are: 12.5-18.0 kg for underweight women; 11.5-16.0 kg for normal weight women; 7.0-11.5 kg for overweight women; and

5.0-9.0 kg for obese women. An adequacy of gestational weight gain ratio was calculated by dividing the observed total gestational weight gain by the expected weight gain, based on the 2009 IOM weight gain recommendations specific for a given prepregnancy BMI category and the trimester of gestation. To calculate expected weight gain, the following formula was used:

Expected First Trimester Total Weight Gain + [(Gestational Age at Time of Last Weight Measurement – 13 weeks) x Rate of Weight Gain Expected for the Second and Third Trimesters]

Based on the 2009 IOM report we interpreted expected total first trimester weight gains as 2.0, 1.5, 1.0, and 0.5 kg for underweight, normal weight, overweight, and obese women, respectively. Mean expected rates of weight gain for the second and third trimesters are 0.49, 0.45, 0.30, and 0.24 kg/week for underweight, normal weight, overweight, and obese women, respectively. These rates were calculated as the difference between the prepregnancy BMI-specific expected first trimester weight gain and the midpoint of each total weight gain range, divided by 27 weeks (the length of the 2nd and 3rd trimesters for a 40 week gestation). For example, for underweight women the recommended total weight gain range is 12.5-18.0 kg and the midpoint of this range is 15.25kg. The expected rate of weight gain during the 2nd and 3rd trimesters is calculated as follows: (15.25-2.0)/27 weeks = 0.49 kg/week. The use of rates of weight gain adjusts for the fact that not all women have a weight measurement at the time of delivery.

Cutoffs to determine inadequate, adequate, and excessive weight gains were based on ranges of adequacy ratios using the 2009 IOM weight gain recommendations. Ranges of adequacy ratios were calculated by dividing the lower and upper recommended total weight gain values by the midpoint of the range. Using the calculations for underweight women as the example, the lower, midpoint, and upper recommended total weight gain values are 12.5, 15.25, and 18.0 kg, respectively. This corresponds to an adequacy ratio range (%) of 0.82 (82%) to 1.18 (118%). Underweight women with adequacy ratios within this range would be defined as having adequate gestational weight gain. Underweight women who have an adequacy ratio <0.82 would be defined as having inadequate weight gain (below the 2009 IOM recommendation) and those who have an adequacy ratio >1.18 would be defined as having excessive weight gain (above the 2009 IOM recommendation). Using this convention, the range of adequacy ratios defined as adequate weight gain among normal weight, overweight, and obese women are 0.84 to 1.16, 0.76 to 1.24, and 0.71 to 1.29, respectively. Women who have an adequacy ratio less than the lower value of the range were defined as having inadequate weight gain and those with a ratio greater than the upper value of the range were defined as having excessive weight gain. Due to the large distribution of adequacy ratios within the excessive weight gain category, excessive weight gain was dichotomized at an adequacy ratio of 2.00, or 200%, to examine the effects of excessive weight gain within the upper adequacy ratios. These variables are designated excessive I and excessive II weight gain (≥200% IOM recommendations). Table 1 displays the ranges of adequacy ratios for inadequate, adequate, excessive I, and excessive II gestational weight gain specific to

prepregnancy BMI status. In all gestational weight gain analyses, adequate weight gain was used as the reference category.

Table 1. Gestational weight gain categories specific to prepregnancy BMI based on the 2009 IOM recommendations

Prepregnancy BMI	Inadequate	Adequate	Excessive I	Excessive II
Underweight	<82%	82-118%	>118-199%	≥200%
Normal weight	<84%	84-116%	>116-199%	≥200%
Overweight	<76%	76-124%	>124-199%	≥200%
Obese	<71%	71-129%	>129-199%	≥200%

Other Variables

The following section describes the data collection methods and variable construction of the covariates of interest, several of which were discussed previously in the *Background and Significance* section. They are organized as maternal, offspring, and demographic factors.

Maternal Variables

Maternal Glucose Tolerance Status. Maternal glucose tolerance was derived from universal screens that were conducted during the second trimester (mean gestational age ~27 weeks) on all women without pre-existing diabetes mellitus. The universal screen involved administration of a random one hour 50-g glucose challenge test to the women. Women with abnormal values on the random screen were administered a three-hour oral glucose tolerance test (OGTT) to confirm gestational diabetes (GDM). The OGTT was administered on serum samples using a glucose oxidase method with glucose tolerance analysis at fasting, and at 1, 2, and 3 hours after the oral glucose load. Cut points

established by Carpenter & Coustan[7] were used to define abnormal values: 95 mg/dl for fasting, 180 mg/dl for 1-hour, 155 mg/dl for 2-hour, and 135 mg/dl for 3-hour. Normal and impaired glucose tolerance (IGT) were defined as blood glucose <140 mg/dl and ≥140 on the universal screen, respectively. GDM was defined as having two abnormal values on the OGTT or a GDM diagnosis by a physician listed on the medical record.

Prenatal smoking. Women reported whether or not they smoked during pregnancy (months 1-6) at the first and second telephone interviews of PIN3. This variable was dichotomized as non-smoker and smoker.

Birth Order (or Parity). Women reported the number of previous births that occurred prior to the index pregnancy at entry into the PIN3 study. This variable was dichotomized as nulliparous and parous.

Offspring Variables

Birthweight. Birthweights were converted to birthweight-for-gestational age and sex z-scores (birthweight z-scores) using US reference data.[8] This variable was used in the statistical analyses for Aims 1 and 2.

Infant Diet. At the 3 and 12 month PIN Postpartum home visits, data was collected about infant feeding behaviors including breast feeding, formula feeding, and complementary food intakes. Duration of exclusive breast feeding (months) and age (months) at

introduction of solid foods (any food/beverage not including breast milk, formula, or water) were considered.

Infant/Child Health Status. Information on infant and child health status was collected at the 3 and 12 month and 3 year home visits. Children with physician-diagnosed illness related to growth were identified and excluded.

Socio-demographic Variables

Data on socio-demographic variables were collected in the PIN3 study during the 2nd trimester interviews.

Maternal Race. Maternal and infant race/ethnicity were based on maternal self-identified race/ethnicity collected during pregnancy. Given the small number of women reporting a race/ethnicity other than "white" or "black", race was dichotomized for these analyses as non-black and black.

Maternal Age. Women reported their age (years) at the time of conception. Categories of age were: 16-24, 25-29, 30-34, and ≥35 years.

Education. Women reported the number of years (grades) of education completed. Categories of education were: ≤Grade 12 (completion of high school or less), Grades 13-16 (high school graduate with some college or completion of college), and ≥Grade 17 (reference, at least some post-college education).

Household Income. Household income was based on percent of the poverty line using the 2001 U.S. Department of Health and Human Services Federal Poverty Guidelines.[9] A percentage ≤185% is the household income cut-off for the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). Categories were based on WIC eligibility guidelines: <185%, 185-<350%, and ≥350%.

Marital status. Women reported their cohabitation status as married, single, separated, divorced, widowed, or living with a partner. This variable was dichotomized: married and not married.

Statistical Analysis

All statistical analyses were performed using Stata 11 (College Station, TX). Descriptive statistics (means, standard deviations, frequencies, proportions, and graphical displays, including plots of growth measures over time) were computed for all study variables of interest. Potential effect measure modifiers and confounders were identified a priori from a review of previous literature and causal diagrams.[10,11] The interaction of continuous maternal prepregnancy BMI with adequacy of gestational weight gain was tested in a crude model using interaction terms and Wald tests with an a priori significance p-value of <0.15. All regression analyses were adjusted for clustering at the individual level[12-15] since there were some women with more than one child included in study.

The statistical analyses used for each aim of this dissertation are briefly described below and detailed in their respective chapters:

Aim 1. Determine the association between modifiable prenatal maternal factors and early infant anthropometric outcomes, WAZ, LAZ, and WLZ, and rapid weight gain in the first 6 months of life.

Multivariable linear regression models were used to examine associations of continuous infant outcomes (WAZ, LAZ, and WLZ at 6 months) with categorical maternal exposures, prepregnancy BMI and adequacy of gestational weight gain. Multivariable modified Poisson regression (Poisson regression with a robust error variance) estimated incidence risk ratios of rapid infant weight gain between birth and 6 months. The use of this method with prospective cohort data has been validated.[16,17] Full models were separately adjusted for birthweight z-score, duration of exclusive breast feeding, and age at introduction of solids. These additional analyses were used to determine whether the observed associations persisted after controlling for postnatal factors that are associated with the selected maternal exposures and predictive of infant growth.

Aim 2. Determine the association between modifiable prenatal maternal factors and childhood BMI at 3 years of age (defined as BMI z-scores and BMI percentile cut-points of ≥85th and ≥95th).

The analysis for Aim 2 is similar to that of Aim 1. Multivariable linear regression was used to examine the association between continuous child BMI z-scores at age 3 years and each maternal exposure, prepregnancy BMI (continuous, kg/m^2 and categories) and adequacy of gestational weight gain (continuous, per 0.10 and categories).

Multivariable modified Poisson regression was used to estimate incidence risk ratios for overweight/obese status (BMI≥85th percentile) compared to not overweight status (BMI<85th percentile) and obese status (BMI≥95th percentile) compared to not overweight status (BMI<95th percentile) at 3 years by maternal exposure, prepregnancy BMI (continuous, kg/m^2 and categories) and adequacy of gestational weight gain (continuous, per 0.10 and categories). Full models were separately adjusted for birthweight z-score, duration of exclusive breast feeding, and age at introduction of solids.

Aim 3. Determine the association between modifiable prenatal maternal factors and WAZ, LAZ, and WLZ from birth to3 years using longitudinal models.

This aim was designed to take advantage of the longitudinal weight and length measurements of the children provided by the doctor's cards and the PIN study staff at 3 years. Linear mixed effects regression models[18-20] were used to examine whether the effects of the selected maternal exposures, prepregnancy BMI and adequacy of gestational weight gain, on offspring anthropometric outcomes (WAZ, LAZ, and WLZ) varied over between birth and 3 years. These models are more powerful than the simple logistic models for investigating these research questions because they allow for the use of multiple measurements of the children between birth and 3 years. They also account for the irregular measurement times across subjects, unequal numbers of measurements within subjects, and correlation of measurements within subjects. Models were fit using maximum restricted likelihood specified by the *xtmixed* function in Stata 11 (College Station, TX). We indicated an unstructured covariance structure for the repeated

dependent measures, which allowed for all variances and covariances to be distinctly estimated.

The following initial model with a random intercept and random slope was considered for categories of prepregnancy BMI exposure (included as dummy variables):

$$y_{ij} = \beta_1 + \beta_2(underweight)_{ij} + \beta_3(overweight)_{ij} + \beta_4(obese)_{ij} + \beta_5 x_{ij} + \zeta_{1j} + \zeta_{2j} x_{ij} + \epsilon_{ij}$$

where y_{ij} is the anthropometric outcome (i.e. WAZ) for child j at age i, x_{ij} is the corresponding age, ζ_{1j} is the random intercept, ζ_{2j} is the random slope of age, and ϵ_{ij} is the child and age-specific error term. The dummy variables for prepregnancy BMI status are represented by x_2 (underweight), x_3 (overweight), and x_4 (obese), with normal prepregnancy BMI as the reference. The inclusion of a random slope allows for a different rate of growth between children and was tested using a likelihood ratio test with 50:50 mixture χ^2 distribution.[21]

A similar model with a random intercept and random slope was considered for categories of adequacy of gestational weight gain exposure (included as dummy variables):

$$y_{ij} = \beta_1 + \beta_2(inadequate)_{ij} + \beta_3(excessive\ I)_{ij} + \beta_4(excessive\ II)_{ij} + \beta_5 x_{ij} + \zeta_{1j} + \zeta_{2j} x_{ij} + \epsilon_{ij}$$

The dummy variables for adequacy of gestational weight gain are represented by x_2 (inadequate), x_3 (excessive I), and x_4 (excessive II), with adequate weight gain as the reference.

Child WAZ, LAZ, and WLZ were individually plotted over time between birth and 3 years to visually inspect the longitudinal pattern. The resulting graphs suggested a non-linear relation for WAZ but linear relations for LAZ and WLZ. Therefore, a quadratic term for child's age (child's age^2) was included in the WAZ models.

Interactions between the maternal exposures with child's age (prepregnancy BMI/ adequacy of gestational weight gain × child's age) were examined to determine whether associations between offspring anthropometric measurements and categories of maternal exposures varied over time. Due to potential differences in weight and length development by gestational age, we tested for an interaction between gestational age and child's age (gestational age × child's age). We also tested for an interaction between prepregnancy BMI and weight gain adequacy. All fixed effects interaction terms were tested using Wald tests with an a priori significance p-value of <0.15. Prenatal variables identified as confounders were included as fixed effects in the full models.

References

1. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Protocol 1999-2000. http://www.cdc.gov.libproxy.lib.unc.edu/nchs/data/nhanes/meccomp.pdf.

2. Vidmar S, Carlin J, Hesketh K, Cole T. Standardizing anthropometric measures in children and adolescents with new functions for egen. *Stata J*. 2004;4(1):50-55.

3. Ong KK, Loos RJF. Rapid infancy weight gain and subsequent obesity: Systematic reviews and hopeful suggestions. *Acta Paediatrica*. 2006;95(8):904-908.

4. Siega-Riz AM, Adair LS, Hobel CJ. Institute of Medicine maternal weight gain recommendations and pregnancy outcome in a predominantly Hispanic population. *Obstet Gynecol*. 1994;84(4, Part 1):565-573.

5. Vahratian A, Zhang J, Troendle JF, Savitz DA, Siega-Riz AM. Maternal prepregnancy overweight and obesity and the pattern of labor progression in term nulliparous women. *Obstet Gynecol*. 2004;104(5, Part 1):943-951.

6. IOM (Institute of Medicine), NRC (National Research Council). *Weight Gain during Pregnancy: Reexamining the Guidelines.* Washington, DC: The National Academies Press; 2009.

7. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol*. 1982;144(7):768-773.

8. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr*. 2003;3:6.

9. Proctor BD, Dalaker J, US Census Bureau, Current Population Reports, P60-219. Poverty in the United States: 2001, U.S. Government Printing Office, Washington, DC. 2002.

10. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48.

11. Pearl J. Causal diagrams for empirical research. *Biometrika*. 1995;82(4):669-688.

12. Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics*. 2000;56(2):645-646.

13. Wooldridge JM. *Econometric Analysis of Cross Section and Panel Data.* The MIT press; 2002.

14. Rogers W. Regression standard errors in clustered samples. *Stata Technical Bulletin*. 1993;13:19-23.

15. Froot KA. Consistent covariance matrix estimation with cross-sectional dependence and heteroskedasticity in financial data. *Journal of Financial and Quantitative Analysis*. 1989;24(3):333-355.

16. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol*. 2003;157(10):940-943.

17. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706.

18. Harville DA. Maximum likelihood approaches to variance component estimation and to related problems. *Journal of the American Statistical Association*. 1977;72(358):320-338.

19. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38(4):963-974.

20. Ware JH. Linear models for the analysis of longitudinal studies. *American Statistician*. 1985:95-101.

21. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis.* John Wiley & Sons, Inc.; 2004.

CHAPTER IV

MATERNAL PREPREGNANCY BODY MASS INDEX AND GESTATIONAL WEIGHT GAIN DIFFERENTIALLY INFLUENCE INFANT POSTNATAL GROWTH

Abstract

Background: It is not clear whether maternal prepregnancy body mass index (BMI) and gestational weight gain influence infant postnatal growth.

Objective: To determine how prepregnancy BMI and gestational weight gain relate to infant weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length z-scores (WLZ) at 6 months as well as rapid weight gain between birth and 6 months.

Design: Mother-infant pairs were recruited from the Pregnancy, Infection, and Nutrition Study, a recent prospective pregnancy cohort. Term infants with a weight or length measurement at approximately 6 months were included (n=363). Linear regression estimated associations for continuous WAZ, LAZ, and WLZ with categorical maternal exposures defined by the 2009 Institute of Medicine recommendations. Modified Poisson regression estimated incidence risk ratios of rapid weight gain.

Results: Prepregnancy overweight and obesity were associated with higher WAZ (multivariable linear regression coefficient (β), 0.32; 95% confidence interval [CI], 0.04-

0.61) and WLZ (β, 0.39; 95% CI, 0.02-0.76), respectively. Prepregnancy BMI was not associated with LAZ. Excessive gestational weight gain was associated with higher WAZ (β, 0.39; 95% CI, 0.15-0.62) and LAZ (β, 0.34; 95% CI, 0.12-0.56) compared to adequate weight gain. Excessive weight gain ≥200% of recommended amount was associated with higher WAZ (β, 0.68; 95% CI, 0.28-1.07), LAZ (β, 0.45; 95% CI, 0.06-0.83), and WLZ (β, 0.43; 95% CI, 0.04-0.82). Risk of rapid infant weight gain increased across maternal exposure categories; however, none of the estimates were significant.

Conclusions: Prepregnancy BMI and gestational weight gain are modifiable intrauterine exposures that differentially influence postnatal infant anthropometric outcomes. Further investigation with measurements of infant body composition is warranted.

Introduction

In the United States, more than half of women of reproductive ages are overweight or obese[1] and the majority of women gain excessive amounts of weight during pregnancy.[2-5] These trends have motivated research on the impact of fetal exposure to increased concentrations of nutrients and metabolic hormones on later health outcomes, including the development of obesity.[4] Results from animal and human studies suggest that increased maternal nutrition via prepregnancy obesity and/or excess nutrient intakes during gestation leads to adiposity, insulin resistance, hyperphagia, hyperleptinemia, and hypertension in the offspring[6-13], however the evidence is not conclusive.

Observational studies of the effects of maternal prepregnancy body mass index (BMI) and gestational weight gain on offspring anthropometric outcomes are somewhat limited. Much of the existing literature has focused on offspring birthweight or BMI as the main outcome of interest. Birthweight[14-16], rapid rates of weight gain during infancy and childhood[17,18], and early childhood BMI status[19-21] are all predictors of overweight and obesity later in life. Maternal prepregnancy BMI and gestational weight gain are positively associated with birthweight[22-25] and offspring BMI[26-29]; however, there is little information about how these maternal factors influence early infant anthropometric outcomes, especially length.

In the present study, we utilize data from a recent prospective, longitudinal pregnancy cohort study to investigate the effects of maternal prepregnancy BMI and gestational weight gain on infant weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length z-scores (WLZ) at 6 months as well as rapid infant weight gain between birth and 6 months. This research is necessary to fill gaps in the current literature regarding the influence of modifiable maternal behavioral factors on infant growth and the development of pediatric obesity.

Methods

Participants

Women were recruited from the third cohort of the Pregnancy Infection and Nutrition study (PIN3), January 1, 2001- June 30, 2005, and were followed through 12 months postpartum. The recruitment protocols for the study have been documented previously.[30] Briefly, pregnant women who were at least 16 years of age at conception,

English-speaking, prior to 20 weeks' gestation at recruitment, and receiving prenatal care from public and private clinics at the University of North Carolina (UNC) Hospitals were eligible for participation. Data collection throughout the prenatal period included socio-demographic characteristics, health behaviors, biological specimens, and medical chart abstraction for pre-existing and pregnancy complications as well as other outcomes.

Beginning in 2003, the PIN Postpartum study recruited women from PIN3 and followed-up the index infant at 3 and 12 months postpartum.[30] Women who had a pregnancy loss or multiple births, did not complete the first PIN3 telephone interview, delivered at a hospital other than UNC, or delivered prior to PIN Postpartum recruitment were not eligible for the study. Data collected during the 3 and 12 month home visits was similar to that collected during the prenatal period and included information on infant health status and feeding behaviors. Infant weights and lengths were measured by medical care providers during well-baby visits and recorded on study provided doctor's cards (described below). The PIN study protocols were reviewed and approved by the Institutional Review Boards of the School of Medicine at UNC at Chapel Hill and Wake Medical Center.

Of the 550 mother-infant pairs participating at 12 months postpartum, 3 were excluded due to physician diagnosed illnesses related to infant growth, 112 were missing anthropometric measurements because they did not return the doctor's cards, and 27 did not have anthropometric measurements at ~6 months. Due to potential confounding by differences in gestational weight gain and early growth patterns between preterm (gestational age <37 weeks) and term infants (gestational age ≥37 weeks), preterm infants were also excluded (n=45). The remaining 363 mother-infant pairs were included in the

current study. Compared to the included mothers, excluded mothers were younger, less educated, lower income, more likely to be black, not married, obese, and had higher glucose tolerance values. Excluded infants had younger gestational ages, lower birthweights, and were exclusively breastfed for shorter durations compared to included infants. All other comparisons between the included and excluded samples were not significant.

Outcome Measurements

Infant anthropometric outcomes were WAZ, LAZ, and WLZ at 6 months and rapid infant weight gain between birth and 6 months. Infant birthweights (n=362) and sex (n=363) were abstracted from delivery logs. All other weights and lengths were measured and recorded on doctor's cards during well-baby visits. Doctor's cards were provided to mothers by the PIN study staff. Mothers brought these cards to each pediatrician visit and the date of the visit and weight and length of the infant were recorded by medical staff. These cards were collected by the PIN staff at the 12 month home visit. In order to take advantage of the largest possible sample size, infant measurements from well-baby visits between approximately 5 and 7 months (median: 6.2; range: 4.8-7.4) were included in analyses. Of the 363 infants with a weight or length measurement at approximately 6 months, there were 354 infants with weight measurements, 355 infants with length measurements, and 346 infants with both weight and length measurements. The exact age of the infant at the time of each measurement was calculated by subtracting the infant's birth date from the date of the visit. We used the 15th of the month for infants missing the

day of the visit (n=5). We used the pediatrician's recorded age of the infant when both the month and day of the visit were missing (n=9).

Gestational age at birth was calculated from ultrasound measurements conducted prior to 22 weeks' gestation (up to 21 weeks, 6 days). If no ultrasound was performed or if it was not performed prior to the start of the 22nd week then the date of the last menstrual period was used. Infant birthweights were converted to birthweight-for-gestational age and sex z-scores (birthweight z-scores) using US reference data.[31] Infant weights, lengths, and weight-for-lengths at 6 months were converted to sex-and age-specific z-scores using the 2000 CDC/NCHS growth charts.[32] Rapid infant weight gain was defined as a change in z-scores greater than +0.67 between birth and 6 months, which is clinically interpretable as the upward crossing of a centile line on an infant growth chart.[33]

Maternal Exposures

Maternal prepregnancy BMI (kg/m^2) was calculated using self-reported prepregnancy weight and measured height. For quality assurance, weight measurements at the first prenatal clinic visit (within 15 weeks' gestation) were compared to the self-reported prepregnancy weights to identify biologically implausible weight gains. Women with implausible values (n=6) had their prepregnancy weights imputed following previously published methods.[34,35] BMI was classified following guidelines established by the 2009 IOM recommendations: underweight <18.5 kg/m^2; normal weight 18.5 to 24.9 kg/m^2; overweight 25.0 to 29.9 kg/m^2; and obese ≥30.0 kg/m^2.[36]

Total gestational weight gain was defined as the difference between self-reported prepregnancy weight and the last weight measurement taken prior to delivery. The 2009 IOM gestational weight gain recommendations for total weight gain are: 12.5-18.0 kg for underweight women; 11.5-16.0 kg for normal weight women; 7.0-11.5 kg for overweight women; and 5.0-9.0 kg for obese women.[36] An adequacy of gestational weight gain ratio was calculated by dividing the observed total gestational weight gain by the expected weight gain, based on the IOM recommendations specific for a given prepregnancy BMI category and the trimester of gestation, as described previously.[3,34,35,37]

Based on the 2009 IOM report we interpreted expected total first trimester weight gains as 2.0, 1.5, 1.0, and 0.5 kg for underweight, normal weight, overweight, and obese women, respectively. Mean expected rates of weight gain for the second and third trimesters were 0.49, 0.45, 0.30, and 0.24 kg/week for underweight, normal weight, overweight, and obese women, respectively. These rates were calculated as the difference between the prepregnancy BMI-specific expected total first trimester weight gain and the midpoint of each weight gain range, divided by 27 weeks. For example, for underweight women the recommended total weight gain range is 12.5-18.0 kg and the midpoint of this range is 15.25kg. The expected rate of weight gain during the 2nd and 3rd trimesters is calculated as follows: (15.25-2.0)/27 weeks = 0.49 kg/week. The use of rates of weight gain adjusts for the fact that not all women have a weight measurement at the time of delivery.

Cutoffs to determine inadequate, adequate, and excessive weight gains were based on ranges of adequacy ratios using the 2009 IOM total weight gain recommendations, as described previously.[3,35,37] Ranges of adequacy ratios were calculated by dividing the

lower and upper recommended total weight gain values by the midpoint of the range. Using the calculations for underweight women as the example, the lower, midpoint, and upper recommended total weight gain values are 12.5, 15.25, and 18.0 kg, respectively. This corresponds to an adequacy ratio (%) range of 0.82 (82%) to 1.18 (118%). Underweight women with adequacy ratios within this range were defined as having adequate gestational weight gain. Underweight women who have an adequacy ratio <0.82 were defined as having inadequate weight gain (below the IOM recommendation) and those who have an adequacy ratio >1.18 were defined as having excessive weight gain (above the IOM recommendation). Using this convention, the range of adequacy ratios defined as adequate weight gain among normal weight, overweight, and obese women were 0.84 to 1.16, 0.76 to 1.24, and 0.71 to 1.29, respectively. Due to the large distribution of adequacy ratios within the excessive weight gain category, excessive weight gain was dichotomized at an adequacy ratio of 2.00, or 200%, to examine the effects of excessive weight gain within the upper adequacy ratios. Excessive I weight gain (n=154) was defined as an adequacy ratio greater than the upper value of the BMI-specific adequate range to 1.99. Excessive II gestational weight gain (n=55) was defined as an adequacy ratio ≥2.00 (or ≥200% of the recommended amount).

Other Variables

Data concerning maternal prenatal smoking, household income, education, marital status, age at conception, race/ethnicity, pre-existing diabetes, and parity (the number of viable previous pregnancies) were collected from interviews during the prenatal period and categorized as shown in Table 2. Household income was expressed as

percent of the poverty line and calculated using the 2001 U.S. Department of Health and Human Services Federal Poverty Guidelines[38]; a percentage ≤185% is the household income cut-off for the Special Supplemental Nutrition Program for Women, Infants, and Children. Household income at the 3 month interview was used for women who were missing this information from the prenatal period (n=7).

Maternal glucose tolerance status was derived from universal screens and oral glucose tolerance tests (OGTT) that were conducted during the second trimester (mean gestational age ~27 weeks) on all women without pre-existing diabetes mellitus. Normal and impaired glucose tolerance (IGT) were defined as blood glucose <140 mg/dl and ≥140 on the universal screen, respectively. Gestational diabetes mellitus (GDM) was defined as having two abnormal values on the OGTT or a physician diagnosis of GDM listed on the medical record.

Infant feeding information was collected at the 3 and 12 month postpartum interviews. Duration of exclusive breast feeding (feeding only breast milk or water) and the age at introduction of solids and liquids (any food/beverage other than breast milk, formula, or water), was collected at 3 and 12 month interviews. These variables were dichotomized at 4 months (<4 months and ≥4 months) for inclusion in analyses.

Statistical Analysis

To take advantage of our entire sample of infants with anthropometric measurements at ~6 months (n=363), we used multiple imputation techniques using SAS 9.2 (SAS Institute, Cary, NC) and PROC MI to estimate values of the missing covariate data for the sample: gestational weight gain (n=2), glucose tolerance (n=4), maternal

prenatal smoking (n=9), household income (n=1), duration of exclusive breast feeding (n=17), and birthweight (n=1). All of the pre- and postnatal variables discussed in the previous section were included in the multiple imputation models. We generated ten imputed data sets that were combined into a single set of parameter estimates for the final regression models.[39,40] All analyses were completed using the imputed data set and the results were compared to those from the complete case analyses.

Other statistical analyses were performed using STATA 11 (College Station, TX). Potential effect measure modifiers and confounders were identified a priori from a review of previous literature and causal diagrams.[41,42] The interaction of continuous maternal prepregnancy BMI with adequacy of gestational weight gain ratios was tested in a crude model using interaction terms and Wald tests with an a priori significance p-value of <0.15. Full models were separately adjusted for birthweight z-scores, duration of exclusive breast feeding, and age at introduction of solids. These additional analyses were performed to determine whether the observed associations persisted after controlling for postnatal factors that are associated with the selected maternal exposures and predictive of infant growth.

T-tests of means and analyses of variance were used to analyze distributions of baseline characteristics. Multivariable linear regression models were used to examine associations of continuous infant outcome variables with categorical maternal exposures. Multivariable modified Poisson regression (Poisson regression with a robust error variance) estimated incidence risk ratios of rapid infant weight gain between birth and 6 months. The use of this method to estimate risk with prospective cohort data has been validated.[43,44] All regression analyses were adjusted for clustering at the individual

level[45-48] since there were 13 women with more than one child included in the analyses. Adequate weight gain and normal prepregnancy BMI were used as the reference categories.

Results

The mean (standard deviation [SD]) prepregnancy BMI was 24.2 (5.6) kg/m^2; approximately 29.2% of the women were overweight or obese. The mean (SD) gestational weight gain for the sample was 16.0 (5.4) kg with 57.9% of the women gaining in excess of the 2009 IOM recommendations. The distribution (n) of inadequate, adequate, excessive I, and excessive II weight gains across prepregnancy BMI categories were: 4, 7, 9, and 0 among underweight women; 35, 86, 107, and 8 among normal weight women; 2, 6, 29, and 23 among overweight women; and 5, 7, 9, and 24 among obese women. The mean (SD) weight and gestational age of the infants at birth were 3433.8 (425.6) g and 39.2 (1.1) weeks, respectively.

Maternal characteristics of prepregnancy BMI, gestational weight gain, race, prepregnancy diabetes mellitus, and prenatal smoking were associated with a significant difference in the means of at least one infant anthropometric outcome (Table 2). Mean WLZ and WAZ increased across categories of prepregnancy BMI and gestational weight gain, respectively. Women with prepregnancy diabetes mellitus had infants with lower mean WAZ and LAZ, while smokers had infants with lower LAZ and black women had infants with greater WLZ. Lower mean WAZ and WLZ were also observed among infants who were exclusively breastfed or introduced to solid foods at 4 months of age or

older. Mean z-scores for all three infant anthropometric outcomes increased across categories of birthweight.

In full models (Tables 3-6, Model 1), WAZ (Table 3) and WLZ (Table 5) at 6 months increased across categories of maternal prepregnancy BMI. Prepregnancy overweight was associated with higher WAZ (β, 0.32; 95% confidence interval [CI], 0.04-0.61) and prepregnancy obesity was associated with higher WLZ (β, 0.39; 95% CI, 0.02-0.76). Risks of rapid infant weight gain between birth and 6 months also increased across maternal prepregnancy BMI categories, with an approximate 50% (Incidence risk ratio[IRR],1.52; 95% CI, 1.03-2.23) increased risk among infants of obese mothers; however, this association was not statistically significant in the full model (Table 6). Maternal prepregnancy BMI was not associated with LAZ at 6 months (Table 4).

Adjustment of full models for birthweight z-score (Tables 3-6, Model 2) attenuated the observed associations among overweight and obese women. Adjustment for infant feeding similarly attenuated associations; age at introduction of solids had slightly stronger attenuating effects compared to duration of exclusive breast feeding (data not shown).

Inadequate weight gain was not associated with any of the infant anthropometric outcomes in the full models (Tables 3-6, Model 1). Total excessive gestational weight gain (excessive I and excessive II combined, data not shown in tables) was associated with higher WAZ (β, 0.39; 95% CI, 0.15-0.62) and LAZ (β, 0.34; 95% CI, 0.12-0.56) at 6 months but not WLZ, compared to adequate gestational weight gain. Excessive II weight gain was associated with higher WAZ (Table 3; β, 0.68; 95% CI, 0.28-1.07), LAZ (Table 4; β, 0.45; 95% CI, 0.06-0.83), and WLZ (Table 5; β, 0.43; 95% CI, 0.04-0.82). Risks of

rapid infant weight gain increased across gestational weight gain categories; however, none of the associations were significant (Table 6).

Adjustment of full models for birthweight z-score (Tables 3-6, Model 2) attenuated the observed associations for gestational weight gain and infant size outcomes but significant associations remained for WAZ with excessive II weight gain (Table 3) and LAZ with total excessive weight gain (data not shown in tables; β, 0.22; 95% CI, 0.004-0.43]. In contrast, risks of rapid weight gain were strengthened after adjustment for birthweight z-score (Table 6); excessive II weight gain was associated with a 1.61 (95% CI, 1.00-2.60) times increased risk of rapid weight gain. The addition of duration of exclusive breast feeding and age at introduction of solid foods to the models did not alter the observed associations (data not shown). There was no evidence for an interaction between gestational weight gain and prepregnancy BMI for any of the infant anthropometric outcomes.

Discussion

Previous systematic reviews identified infant size and growth rate as early predictors of later life obesity.[49,50] Our results suggest that prepregnancy BMI and gestational weight gain are modifiable intrauterine exposures that differentially influence infant size and rapid infant weight gain, a measure of infant growth rate, within the first 6 months of life.

We found that while both prepregnancy BMI and gestational weight gain were positively associated with WAZ, only gestational weight gain was associated with LAZ at 6 months. Prepregnancy overweight and obesity and excessive weight gain ≥200% of

the IOM recommended amount were associated with higher WLZ. These relationships represent the total effects of prepregnancy BMI and gestational weight gain on infant size outcomes (i.e. including their effects on birthweight) and suggest that the relative body size of infants differs by maternal exposure. Compared to infants of normal weight mothers, those of overweight/obese mothers have greater weights relative to their lengths (i.e. they appear heavy relative to their length). Compared to infants of mothers with adequate gestational weight gain, those of mothers with excessive gestational weight gain have greater weights but they have proportionally greater lengths; the exception being that those of mothers with excessive weight gain ≥200% of the IOM recommendations have increases in weight that exceed those in length (i.e. they appear long and heavy).

Although risk estimates increased across maternal exposure categories, neither prepregnancy BMI nor gestational weight gain was associated with rapid infant weight gain in the full models, which is consistent with previous studies.[51,52] Rapid infant weight gain represents the crossing of a growth chart centile line but it does not account for differences in initial or concomitant linear growth. Despite these limitations, it is associated with the development of obesity later in life.[50,53] The lack of an association of prepregnancy BMI and gestational weight gain with rapid infant weight gain suggests that the main effect of these maternal exposures relates to changes in infant size while other previously identified factors, such as early weaning[54], may have greater influence on rate of weight gain.

Birthweight and infant feeding are associated with prepregnancy BMI and predictive of infant adiposity. The addition of these variables to the full models attenuated the associations for prepregnancy BMI with infant WAZ and WLZ.

Birthweight has been shown in another study to explain approximately 34% and 17% of the effect of prepregnancy BMI on infant weight (g) and BMI (kg/m^2) at 14 months.[55] Overweight and obese mothers are more likely to have shorter durations of exclusive breast feeding and introduce their infants to solid foods at earlier ages compared to normal weight mothers.[56-58] Early introduction to solid foods during infancy (between 1 and 4 months) is associated with greater energy intakes at 4 months[59] and infants weaned prior to 4 months have significantly higher WAZ at 7 months and 14 months compared to infants breastfed for more than 4 months.[54] Our results suggest that the effects of prepregnancy overweight/obesity on infant size are not only expressed through fetal growth and the birthweight of the infant but also carry over into the postnatal environment.

The associations between gestational weight gain and infant size outcomes were also attenuated by birthweight; however, significant differences in infant WAZ among women with excessive weight gain ≥200% of the IOM recommendations and LAZ among women with excessive gains (excessive I and excessive II combined) persisted. Infant feeding did not attenuate any of the observed associations. These results indicate that, in contrast to prepregnancy BMI, gestational weight gain has an effect on infant size that is not explained by its influence on fetal growth and birthweight and is unrelated to postnatal feeding practices. After adjustment for birthweight, there was also a significant 60% increased risk of rapid infant weight gain among women with excessive weight gain ≥200% of the IOM recommendations. Although this is consistent with our finding of higher infant WAZ among this subgroup, the observed strengthening of risk estimates after adjustment for birthweight may be a statistical artifact: Gestational weight gain is

positively associated with birthweight z-score and birthweight z-score is inversely associated with rapid weight gain (infants with low birthweights are more likely to have rapid weight gain compared to infants with high birthweights), which in turn strengthens the association between gestational weight gain and rapid weight gain when it is added to the model.

It is not clear why prepregnancy BMI and gestational weight gain relate differently to the selected infant outcomes. A plausible hypothesis is that variations in infant size reflect differences in the fetal exposures associated with these maternal factors: Prepregnancy BMI represents maternal nutritional stores and metabolic/hormonal status while gestational weight gain is more reflective of nutrient intakes and energy expenditure (as well as maternal tissue and fluid expansion and fetal weight) during pregnancy. The intrauterine environment and metabolic changes associated with maternal obesity are detailed in a review by King[60]. Fetuses of obese women have increased levels of proinflammatory markers[61,62], cord blood leptin, and insulin resistance[9], as well as greater neonatal adiposity[9,63-65], independent of birthweight and glucose tolerance status[65], compared to those of lean women. Sewell et.al.[64] found significant increases in percent body fat and fat mass but not lean body mass in neonates of overweight/obese compared to lean/average women; observed increases in infant birthweights of overweight/obese women were due to increases in fat mass but not lean body mass. Neonatal adiposity is correlated with percent body fat in childhood.[66] In a study of obesity transmission, among obese women who underwent weight loss surgery, offspring born after surgery had lower birthweights and lower BMI percentile and prevalence of severe obesity compared to siblings born prior to the surgery.[67] Results from these highlighted studies suggest that

prepregnancy BMI is an important determinant of weight and adiposity outcomes in early infancy that persist into later life.

Gestational weight gain is positively associated with total calories[68], protein, and animal fat intakes[69] and there is substantial evidence linking gestational weight gain and birthweight.[22] However, there is little information about an association for either maternal diet and/or gestational weight gain with infant body composition. Though results are inconsistent, fetal growth may differ by maternal dietary macronutrient composition [70-73] and glycemic index.[74] Ay et.al.[25], found no association of gestational weight gain during the first 30 weeks of pregnancy with infant percent fat mass (truncal, peripheral, or total fat mass) at 6 months, while prepregnancy BMI was associated with increased peripheral fat mass in these infants. Analyses of the PIN cohort at 3 years (Chapter V of this dissertation), found higher BMI z-scores associated with excessive weight gain but an increased risk of child obesity ($\geq 95^{th}$ percentile) was only associated with excessive weight gain ≥200% of the IOM recommendations. The effects of gestational weight gain on infant body composition may also differ by prepregnancy BMI status. In the study by Sewell et.al. [64], neonatal lean body mass but not percent body fat was correlated with gestational weight gain among lean/average women (BMI<25 kg/m^2), while only percent body fat was correlated with gestational weight gain among overweight/obese women (BMI≥25 kg/m^2). Though we did not find an interaction for the selected infant outcomes, it is possible that more detailed infant body composition measurements would reveal similar effects. Considering that both child height[75] and BMI[19,21] are predictors for later life obesity, more research is needed to examine the effects of maternal diet and

gestational weight gain in relation to prepregnancy BMI status to determine how they contribute to body composition at birth and throughout childhood.

Our results should be interpreted within the context of several limitations of the study. With the exception of birthweight, infant anthropometrics came from well-baby visits recorded on doctor's cards. These measurements are subject to the inherent errors of clinical data because they were collected at multiple clinic sites by medical staff who were not trained using a standardized method. Infant weight and length are not measurements of infant adiposity so we cannot state whether the observed changes in infant size are due to fat or fat free mass. Attrition between PIN3 and the PIN Postpartum studies resulted in a disproportionate loss of women among high risk groups. Although the exposure-disease relationship is not expected to differ across many of these factors, losses from high risk groups, such as obese women, may have weakened the observed associations reported here. Lastly, although women were enrolled into PIN 3 during early pregnancy, enrollment within the first month of pregnancy is rare and therefore a self-reported measure of prepregnancy weight was used in the analyses. Since prepregnancy weight is used in the calculation of prepregnancy BMI (height was measured) and gestational weight gain, misclassification of women with regards to the outcomes of interest may occur.[76] This type of error may result in an underestimation of prepregnancy BMI and an overestimation of total gestational weight gain, possibly weakening the observed associations.

Despite these limitations, using data from a prospective, longitudinal cohort study, we found that the relative body size of infants at 6 months differs by in utero exposure to prepregnancy BMI and gestational weight gain based on the current 2009

IOM guidelines. Both prepregnancy BMI and gestational weight gain were positively associated with WAZ but only gestational weight gain was associated with LAZ at 6 months. Prepregnancy overweight and obesity and gestational weight gain ≥200% of the IOM recommendations were associated with higher WLZ. These findings provide evidence for an influence of maternal nutrition-related factors on offspring anthropometric outcomes in early infancy. Further research with precise measurements of infant body composition is warranted to confirm our results.

Table 2. Distribution of selected baseline characteristics by mean infant weight-for-age (n=354), length-for-age (n=355), and weight-for-length (n=346) z-scores at 6 months in the Pregnancy Infection and Nutrition Study.

Variable	N	Mean WAZ at 6 months (SD)	*P* value	N	Mean LAZ at 6 months (SD)	*P* value	N	Mean WLZ at 6 months (SD)	*P* value
Age (years)									
16-24	44	0.14 (0.84)		45	0.28 (0.74)		42	0.07 (1.14)	
25-29	98	0.19 (1.07)	0.67	101	0.44 (0.98)	0.58	97	0.02 (1.08)	0.49
30-34	145	0.10 (0.98)		143	0.49 (0.96)		142	-0.15 (1.10)	
35-47	67	0.28 (0.96)		66	0.50 (0.77)		65	0.04 (1.14)	
Prepregnancy BMI Category (kg/m^2)									
Underweight	21	-0.12 (0.76)		20	0.13 (0.84)		20	-0.11 (0.94)	
Normal Weight	231	0.11 (0.98)	0.10	229	0.48 (0.87)	0.31	224	-0.16 (1.13)	0.02
Overweight	58	0.36 (0.89)		61	0.51 (0.90)		58	0.18 (1.10)	
Obese	44	0.35 (1.17)		45	0.35 (1.08)		44	0.32 (0.99)	
Gestational Weight Gain (2009 IOM Category)									
Inadequate	46	0.002 (0.95)		46	0.39 (0.82)		46	-0.24 (1.17)	
Adequate	106	-0.04 (0.92)	0.003	104	0.31 (0.84)	0.18	104	-0.17 (1.07)	0.01
Excessive I	148	0.24 (1.03)		149	0.55 (1.00)		143	-0.05 (1.15)	
Excessive II	52	0.52 (0.91)		54	0.50 (0.81)		51	0.41 (0.89)	
Race									
Non-Black	321	0.16 (0.98)	0.67	322	0.48 (0.91)	0.06	313	-0.08 (1.12)	0.03
Black	33	0.23 (0.99)		33	0.17 (0.17)		33	0.35 (0.92)	
Marital Status									
Married	309	0.18 (0.98)	0.43	310	0.49 (0.87)	0.06	304	-0.05 (1.12)	0.54
Other	45	0.06 (1.01)		45	0.21 (1.11)		42	0.06 (1.04)	
Education									
≤ Grade 12	31	0.22 (1.01)		33	0.36 (1.15)		29	0.18 (0.99)	
Grades 13 -16	172	0.20 (1.02)	0.73	171	0.45 (0.90)	0.83	168	0.01 (1.15)	0.27
≥Grade 17	151	0.12 (0.94)		151	0.47 (0.86)		149	-0.14 (1.08)	
Family Income (% Poverty)									
<185%	40	0.17 (1.00)		41	0.35 (0.86)		38	0.03 (1.28)	
185-350%	70	0.19 (0.99)	0.96	69	0.39 (1.04)	0.55	68	0.09 (0.97)	0.49
>350%	242	0.16 (0.98)		243	0.48 (0.88)		238	-0.08 (1.12)	
Prepregnancy Diabetes Mellitus									
No	339	0.18 (0.96)	0.05	341	0.48 (0.87)	0.003	332	-0.04 (1.11)	0.94

Yes	14	-0.34 (1.43)		13	-0.28 (1.51)		13	-0.02 (1.05)	
Glucose Tolerance									
Normal	300	0.17 (0.95)		304	0.49 (0.85)		296	-0.06 (1.12)	
Impaired Glucose Tolerance	29	0.32 (1.05)	0.64	28	0.51 (1.03)	0.51	27	0.12 (1.17)	0.71
Gestational Diabetes	9	0.02 (1.08)		8	0.13 (0.75)		8	-0.15 (1.01)	
Parity									
Nulliparous	176	0.15 (0.96)	0.80	179	0.48 (0.86)	0.52	173	-0.09 (1.12)	0.43
1 or More Births	178	0.18 (1.01)		176	0.42 (0.95)		173	0.007 (1.10)	
Smoking in Months 1-6 of Pregnancy									
No	322	0.18 (0.98)	0.58	322	0.47 (0.86)	0.05	315	-0.04 (1.12)	0.20
Yes	24	0.07 (1.04)		24	0.10 (1.36)		23	0.26 (0.73)	
Infant Sex									
Male	183	0.13 (1.00)	0.51	185	0.42 (0.85)	0.56	177	0.03 (1.12)	0.23
Female	171	0.20 (0.96)		170	0.48 (0.97)		169	-0.11 (1.09)	
Exclusive Breast feeding									
<4 months	142	0.30 (0.99)	0.02	143	0.46 (0.92)	0.90	139	0.14 (1.05)	0.009
≥4 months	195	0.05 (0.96)		196	0.45 (0.88)		191	-0.19 (1.14)	
Introduction to Solid Foods									
0-4 months	57	0.49 (0.98)	0.01	54	0.50 (0.89)	0.68	53	0.34 (1.06)	0.006
≥4 months	297	0.10 (0.97)		301	0.44 (0.91)		293	-0.11 (1.10)	
Birthweight Category (g)									
<3000	44	-0.59 (0.90)		44	-0.08 (1.11)		44	-0.53 (1.10)	
3000-<3500	172	0.04 (0.90)	<0.001	174	0.33 (0.79)	<0.001	168	-0.09 (1.11)	0.0001
3500-<4000	102	0.37 (0.90)		101	0.66 (0.86)		100	0.05 (1.05)	
≥4000	35	1.09 (0.83)		35	1.12 (0.75)		33	0.58 (1.02)	

Table 3. Difference in weight-for-age z-scores at 6 months associated with categories of maternal prepregnancy BMI status and gestational weight gain according to the 2009 IOM Guidelines (n=354)

	Model 1[a]		Model 2[b]	
	β (95%CI)[c]	*P* value	β (95%CI) [c]	*P* value
Prepregnancy BMI				
Underweight	-0.21 (-0.57, 0.15)	0.26	-0.17 (-0.51, 0.16)	0.31
Normal Weight	Reference		Reference	
Overweight	0.32 (0.04, 0.61)	0.03	0.20 (-0.06, 0.45)	0.13
Obese	0.30 (-0.07, 0.67)	0.11	0.24 (-0.14, 0.62)	0.24
Gestational Weight Gain				
Inadequate	0.08 (-0.24,0.40)	0.61	0.08 (-0.22, 0.38)	0.59
Adequate	Reference		Reference	
Excessive I	0.32 (0.07, 0.56)	0.01	0.18 (-0.05, 0.40)	0.12
Excessive II	0.68 (0.28, 1.07)	0.001	0.46 (0.10, 0.83)	0.01

[a]Model 1 adjusted for gestational age, maternal height, maternal race/ethnicity, marital status, prenatal smoking, household income, and education. For gestational weight gain models, additional adjustments were made for prepregnancy BMI and prepregnancy diabetes mellitus.

[b]Model 2 adjusted for Model 1 and birthweight z-score.

[c]β, coefficient from linear regression; 95% CI, 95% Confidence Interval

Table 4. Difference in length-for-age z-scores at 6 months associated with categories of maternal prepregnancy BMI status and gestational weight gain according to the 2009 IOM Guidelines (n=355)

	Model 1[a]		Model 2[b]	
	β (95%CI)[c]	*P* value	β (95%CI)[c]	*P* value
Prepregnancy BMI				
Underweight	-0.35 (-0.75, 0.05)	0.09	-0.34 (-0.71, 0.03)	0.07
Normal Weight	Reference		Reference	
Overweight	0.14 (-0.14, 0.41)	0.33	0.05 (-0.22, 0.32)	0.71
Obese	0.02 (-0.29, 0.32)	0.92	-0.02 (-0.34, 0.29)	0.89
Gestational Weight Gain				
Inadequate	0.19 (-0.08, 0.47)	0.16	0.18 (-0.09, 0.45)	0.19
Adequate	Reference		Reference	
Excessive I	0.30 (0.07, 0.52)	0.01	0.20 (-0.03, 0.42)	0.08
Excessive II	0.45 (0.06, 0.83)	0.02	0.31 (-0.05, 0.68)	0.09

[a]Model 1 adjusted for gestational age, maternal height, maternal race/ethnicity, marital status, prenatal smoking, household income, and education. For gestational weight gain models, additional adjustments were made for prepregnancy BMI and prepregnancy diabetes mellitus.

[b]Model 2 adjusted for Model 1 and birthweight z-score.

[c]β, coefficient from linear regression; 95% CI, 95% Confidence Interval

Table 5. Difference in weight-for-length z-scores at 6 months associated with categories of maternal prepregnancy BMI status and gestational weight gain according to the 2009 IOM Guidelines (n=346)

	Model 1[a]		Model 2[b]	
	β (95%CI)[c]	*P* value	β (95%CI)[c]	*P* value
Prepregnancy BMI				
Underweight	0.07 (-0.36, 0.50)	0.76	0.09 (-0.35, 0.53)	0.67
Normal Weight	Reference		Reference	
Overweight	0.34 (-0.01, 0.69)	0.05	0.24 (-0.08, 0.56)	0.15
Obese	0.39 (0.02, 0.76)	0.04	0.34 (-0.04, 0.71)	0.08
Gestational Weight Gain				
Inadequate	-0.14 (-0.55, 0.26)	0.49	-0.13 (-0.52, 0.27)	0.53
Adequate	Reference		Reference	
Excessive I	0.10 (-0.20, 0.40)	0.51	0.03 (-0.24-0.30)	0.83
Excessive II	0.43 (0.04, 0.82)	0.03	0.30 (-0.08, 0.67)	0.13

[a]Model 1 adjusted for gestational age, maternal height, maternal race/ethnicity, marital status, prenatal smoking, household income, and education. For gestational weight gain models, additional adjustments were made for prepregnancy BMI and prepregnancy diabetes mellitus.

[b]Model 2 adjusted for Model 1 and birthweight z-score.

[c]β, coefficient from linear regression; 95% CI, 95% Confidence Interval

Table 6. Risk of rapid infant weight gain between birth and 6 months associated with categories of maternal prepregnancy BMI status and gestational weight gain according to the 2009 IOM Guidelines (n=354)

	Model 1[a]		Model 2[b]	
	IRR (95%CI)[c]	***P* value**	**IRR (95%CI)[c]**	***P* value**
Prepregnancy BMI				
Underweight	0.47 (0.16, 1.41)	0.18	0.47 (0.16, 1.36)	0.16
Normal Weight	1.00 (Reference)		1.00 (Reference)	
Overweight	1.18 (0.74, 1.68)	0.59	1.23 (0.84, 1.80)	0.30
Obese	1.41 (0.90, 2.20)	0.14	1.40 (0.95, 2.07)	0.09
Gestational Weight Gain				
Inadequate	0.94 (0.53, 1.67)	0.82	0.97 (0.56, 1.68)	0.92
Adequate	1.00 (Reference)		1.00 (Reference)	
Excessive I	1.11 (0.74, 1.65)	0.61	1.28 (0.89, 1.84)	0.19
Excessive II	1.29 (0.76, 2.18)	0.34	1.61 (1.00, 2.60)	0.05

[a]Model 1 adjusted for gestational age, maternal height, maternal race/ethnicity, marital status, prenatal smoking, household income, and education. For gestational weight gain models, additional adjustments were made for prepregnancy BMI and prepregnancy diabetes mellitus.

[b]Model 2 adjusted for Model 1 and birthweight z-score.

[c]IRR, Incidence Risk Ratio from modified Poisson regression; 95% CI, 95% Confidence Interval

References

1. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA*. 2006;295(13):1549-1555.

2. Cogswell ME, Scanlon KS, Fein SB, Schieve LA. Medically advised, mother's personal target, and actual weight gain during pregnancy. *Obstet Gynecol*. 1999; 94(4):616-622.

3. Deierlein AL, Siega-Riz AM, Herring A. Dietary energy density but not glycemic load is associated with gestational weight gain. *Am J Clin Nutr*. 2008;88(3):693-699.

4. Dietz WH. Periods of risk in childhood for the development of adult obesity—what do we need to learn? *J Nutr*. 1997;127(9):1884S-1886S.

5. Dietz PM, Callaghan WM, Cogswell ME, Morrow B, Ferre C, Schieve LA. Combined effects of prepregnancy body mass index and weight gain during pregnancy on the risk of preterm delivery. *Epidemiology*. 2006;17(2):170-177.

6. Bayol SA, Farrington SJ, Stickland NC. A maternal 'junk food' diet in pregnancy and lactation promotes an exacerbated taste for 'junk food' and a greater propensity for obesity in rat offspring. *Br J Nutr*. 2007;98(4):843-851.

7. Smith NA, McAuliffe FM, Quinn K, Lonergan P, Evans ACO. Transient high glycaemic intake in the last trimester of pregnancy increases offspring birthweight and postnatal growth rate in sheep: A randomised control trial. *BJOG*. 2009;116(7):975-983.

8. Clapp JF. Maternal carbohydrate intake and pregnancy outcome. *Proc Nutr Soc*. 2007;61(01):45-50.

9. Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S. Fetuses of obese mothers develop insulin resistance in utero. *Diabetes Care*. 2009;32(6):1076-1080.

10. Nivoit P, Morens C, Van Assche FA, et al. Established diet-induced obesity in female rats leads to offspring hyperphagia, adiposity and insulin resistance. *Diabetologia*. 2009;52(6):1133-1142.

11. Muhlhausler BS, Adam CL, Findlay PA, Duffield JA, McMillen IC. Increased maternal nutrition alters development of the appetite-regulating network in the brain. *FASEB J*. 2006;20(8):1257-1259.

12. Samuelsson AM, Matthews PA, Argenton M, et al. Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance: A novel murine model of developmental programming. *Hypertension*. 2008;51(2):383-392.

13. Howie GJ, Sloboda DM, Kamal T, Vickers MH. Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet. *Exp Physiol*. 2009;587(4):905-915.

14. Curhan GC, Chertow GM, Willett WC, et al. Birth weight and adult hypertension and obesity in women. *Circulation*. 1996;94(6):1310-1315.

15. Rasmussen F, Johansson M. The relation of weight, length and ponderal index at birth to body mass index and overweight among 18-year-old males in Sweden. *Eur J Epidemiol*. 1998;14(4):373-380.

16. Sorensen HT, Sabroe S, Rothman KJ, Gillman M, Fischer P, Sorensen TIA. Relation between weight and length at birth and body mass index in young adulthood: Cohort study. *Br Med J*. 1997;315(7116):1137.

17. Stettler N, Zemel BS, Kumanyika S, Stallings VA. Infant weight gain and childhood overweight status in a multicenter cohort study. *Pediatrics*. 2002;109(2):194-199.

18. Ekelund U, Ong KK, Linne Y, et al. Association of weight gain in infancy and early childhood with metabolic risk in young adults. *Journal of Clinical Endocrinology & Metabolism*. 2007;92(1):98-103.

19. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of childhood BMI to adult adiposity: The Bogalusa Heart Study. *Pediatrics*. 2005;115(1):22-27.

20. Guo SS, Wu W, Chumlea WC, Roche AF. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. *Am J Clin Nutr*. 2002;76(3):653-658.

21. Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, Byers T. Do obese children become obese adults? A review of the literature. *Prev Med*. 1993;22(2):167-177.

22. Viswanathan M, Siega-Riz AM, Moos MK, et al. Outcomes of maternal weight gain. *Evidence report/technology assessment*. 2008;168:1-223.

23. Rode L, Hegaard HK, Kjaergaard H, Møller LF, Tabor A, Ottesen B. Association between maternal weight gain and birth weight. *Obstet Gynecol*. 2007;109(6):1309-1315.

24. Dietz PM, Callaghan WM, Sharma AJ. High pregnancy weight gain and risk of excessive fetal growth. *Am J Obstet Gynecol*. 2009;201(1):51.e1-6.

25. Ay L, Van Houten VAA, Steegers EAP, et al. Fetal and postnatal growth and body composition at 6 months of age. *J Clin Endocrinol Metab*. 2009;94(6):2023-2030.

26. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. *Obstet Gynecol*. 2007;196(4):322.e1-322.e8.

27. Olson CM, Strawderman MS, Dennison BA. Maternal weight gain during pregnancy and child weight at age 3 years. *Matern Child Health J*. 2009;13(6):839-846.

28. Whitaker RC. Predicting preschooler obesity at birth: The role of maternal obesity in early pregnancy. *Pediatrics*. 2004;114(1):e29-e36.

29. Li C, Goran MI, Kaur H, Nollen N, Ahluwalia JS. Developmental trajectories of overweight during childhood: Role of early life factors. *Obesity*. 2007;15(3):760-771.

30. Siega-Riz AM, Herring AH, Carrier K, Evenson KR, Dole N, Deierlein A. Sociodemographic, perinatal, behavioral, and psychosocial predictors of weight retention at 3 and 12 months postpartum. *Obesity (Silver Spring)*. 2009;Dec(24):[Epub ahead of print].

31. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr*. 2003;3:6.

32. Vidmar S, Carlin J, Hesketh K, Cole T. Standardizing anthropometric measures in children and adolescents with new functions for egen. *Stata J*. 2004;4(1):50-55.

33. Ong KK, Loos RJF. Rapid infancy weight gain and subsequent obesity: Systematic reviews and hopeful suggestions. *Acta Paediatrica*. 2006;95(8):904-908.

34. Vahratian A, Zhang J, Troendle JF, Savitz DA, Siega-Riz AM. Maternal prepregnancy overweight and obesity and the pattern of labor progression in term nulliparous women. *Obstet Gynecol*. 2004;104(5, Part 1):943-951.

35. Siega-Riz AM, Adair LS, Hobel CJ. Institute of Medicine maternal weight gain recommendations and pregnancy outcome in a predominantly Hispanic population. *Obstet Gynecol*. 1994;84(4, Part 1):565-573.

36. IOM (Institute of Medicine), NRC (National Research Council). *Weight Gain during Pregnancy: Reexamining the Guidelines.* Washington, DC: The National Academies Press; 2009.

37. Bodnar LM, Siega-Riz AM, Arab L, Chantala K, McDonald T. Predictors of pregnancy and postpartum haemoglobin concentrations in low-income women. *Public Health Nutr*. 2007;7(6):701-711.

38. Proctor BD, Dalaker J, US Census Bureau, Current Population Reports, P60-219. Poverty in the United States: 2001, U.S. Government Printing Office, Washington, DC. 2002.

39. Rubin DB. Multiple imputation after 18 years. *Journal of the American Statistical Association*. 1996;91(434):473-489.

40. Rubin DB. *Multiple Imputation for Nonresponse in Sample Surveys.* New York: John Wiley & Sons, Inc.; 1987.

41. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48.

42. Pearl J. Causal diagrams for empirical research. *Biometrika*. 1995;82(4):669-688.

43. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol*. 2003;157(10):940-943.

44. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706.

45. Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics*. 2000;56(2):645-646.

46. Wooldridge JM. *Econometric Analysis of Cross Section and Panel Data.* The MIT press; 2002.

47. Rogers W. Regression standard errors in clustered samples. *Stata Technical Bulletin*. 1993;13:19-23.

48. Froot KA. Consistent covariance matrix estimation with cross-sectional dependence and heteroskedasticity in financial data. *Journal of Financial and Quantitative Analysis*. 1989;24(3):333-355.

49. Druet C, Ong KK. Early childhood predictors of adult body composition. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2008;22(3):489-502.

50. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: Systematic review of size and growth in infancy and later obesity. *Br Med J*. 2005; 331(7522):929.

51. Ekelund U, Ong K, Linne Y, et al. Upward weight percentile crossing in infancy and early childhood independently predicts fat mass in young adults: The Stockholm Weight Development Study (SWEDES). *Am J Clin Nutr*. 2006;83(2):324-330.

52. Karaolis-Danckert N, Buyken AE, Kulig M, et al. How pre-and postnatal risk factors modify the effect of rapid weight gain in infancy and early childhood on subsequent fat mass development: Results from the multicenter allergy study 90. *Am J Clin Nutr*. 2008;87(5):1356-1364.

53. Monteiro POA, Victora CG. Rapid growth in infancy and childhood and obesity in later life-a systematic review. *Obes Rev*. 2005;6(2):143-154.

54. Sloan S, Gildea A, Stewart M, Sneddon H, Iwaniec D. Early weaning is related to weight and rate of weight gain in infancy. *Child Care Health Dev*. 2008;34(1):59-64.

55. Mesman I, Roseboom TJ, Bonsel GJ, Gemke RJ, van der Wal MF, Vrijkotte TGM. Maternal pre-pregnancy body mass index explains infant's weight and BMI at 14 months: Results from a multi-ethnic birth cohort study. *Br Med J*. 2009;94(8):587-595.

56. Baker JL, Michaelsen KF, Rasmussen KM, Sorensen TIA. Maternal prepregnant body mass index, duration of breast feeding, and timing of complementary food introduction are associated with infant weight gain. *Am J Clin Nutr*. 2004;80(6):1579-1588.

57. Rising R, Lifshitz F. Relationship between maternal obesity and infant feeding-interactions. *Nutr J*. 2005;4:17.

58. Li R, Jewell S, Grummer-Strawn L. Maternal obesity and breast-feeding practices. *Am J Clin Nutr*. 2003;77(4):931-936.

59. Ong KK, Emmett PM, Noble S, Ness A, Dunger DB. Dietary energy intake at the age of 4 months predicts postnatal weight gain and childhood body mass index. *Pediatrics*. 2006;117(3):e503-e508.

60. King JC. Maternal obesity, metabolism, and pregnancy outcomes. *Annu Rev Nutr*. 2006;26:271-291.

61. Bugatto F, Fernández-Deudero Á, Bailén Á, Fernández-Macías R, Hervías-Vivancos B, Bartha JL. Second-trimester amniotic fluid proinflammatory cytokine levels in normal and overweight women. *Obstet Gynecol*. 2010;115(1):127-133.

62. Challier JC, Basu S, Bintein T, et al. Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. *Placenta*. 2008;29(3):274-281.

63. Silliman K, Kretchmer N. Maternal obesity and body composition of the neonate. *Neonatology*. 1995;68(6):384-393.

64. Sewell MF, Huston-Presley L, Super DM, Catalano P. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. *Obstet Gynecol*. 2006;195(4):1100-1103.

65. Hull HR, Dinger MK, Knehans AW, Thompson DM, Fields DA. Impact of maternal body mass index on neonate birthweight and body composition. *Am J Obstet Gynecol*. 2008;198(4):416e1-e6.

66. Catalano PM, Farrell K, Thomas A, et al. Perinatal risk factors for childhood obesity and metabolic dysregulation. *Am J Clin Nutr*. 2009;90(5):1303-1313.

67. Smith J, Cianflone K, Biron S, et al. Effects of bariatric surgical weight loss in mothers on intergenerational transmission of obesity. *Endocrinology*. 2009; 150(10):4816-4823.

68. Stuebe AM, Oken E, Gillman MW. Associations of diet and physical activity during pregnancy with risk for excessive gestational weight gain. *Obstet Gynecol*. 2009; 201:58.e1-58.e8.

69. Lagiou P, Tamimi RM, Mucci LA, Adami HO, Hsieh CC, Trichopoulos D. Diet during pregnancy in relation to maternal weight gain and birth size. *Eur J Clin Nutr*. 2004;58(2):231-237.

70. Andreasyan K, Ponsonby AL, Dwyer T, et al. Higher maternal dietary protein intake in late pregnancy is associated with a lower infant ponderal index at birth. *Eur J Clin Nutr*. 2006;61(4):498-508.

71. Olsen SF, Halldorsson TI, Willett WC, et al. Milk consumption during pregnancy is associated with increased infant size at birth: Prospective cohort study. *Am J Clin Nutr*. 2007;86(4):1104-1110.

72. Godfrey K, Robinson S, Barker DJP, Osmond C, Cox V. Maternal nutrition in early and late pregnancy in relation to placental and fetal growth. *Br Med J*. 1996; 312(7028):410-414.

73. Watson PE, McDonald BW. The association of maternal diet and dietary supplement intake in pregnant New Zealand women with infant birthweight. *Eur J Clin Nutr*. 2009; 64(2):184-193.

74. Scholl TO, Chen X, Khoo CS, Lenders C. The dietary glycemic index during pregnancy: Influence on infant birth weight, fetal growth, and biomarkers of carbohydrate metabolism. *Am J Epidemiol*. 2004;159(5):467-474.

75. Stovitz SD, Hannan PJ, Lytle LA, Demerath EW, Pereira MA, Himes JH. Child height and the risk of young-adult obesity. *Am J Prev Med*. 2010;38(1):74-77.

76. Brunner Huber LR. Validity of self-reported height and weight in women of reproductive age. *Matern Child Health J*. 2007;11(2):137-144.

CHAPTER V

THE EFFECTS OF MATERNAL PREPREGNANCY BODY MASS INDEX AND GESTATIONAL WEIGHT GAIN ON CHILD BODY MASS INDEX AT 3 YEARS

Abstract

Objective: To determine how maternal prepregnancy body mass index (BMI) and gestational weight gain relate to child BMI and risk of overweight/obesity at 3 years.

Subjects and Methods: Subjects were recruited from a recent pregnancy cohort and followed through 36 months postpartum (n=325). Linear regression estimated associations between the maternal exposures and continuous child BMI z-scores. Modified Poisson regression estimated incidence risk ratios of child BMI≥ 85th and ≥95th percentile.

Results: Maternal prepregnancy BMI and gestational weight gain were positively associated with child BMI z-scores and risks overweight/obesity at 36 months. Compared to children of normal weight mothers, children of overweight and obese mothers were 1.72 (95%CI: 1.02-2.91) and 2.21 (95%CI: 1.34-3.64) times more likely to be ≥85th percentile and 3.66 (95%CI: 1.18-11.34) and 8.42 (95%CI: 2.88-24.62) times more likely to be ≥95th percentile, respectively. Each 10.0% increase in adequacy of gestational weight gain was associated with 0.03 (95%CI: 0.01-0.05) unit increase in child BMI z-score. Risks of BMI≥85th percentile increased across categories of gestational weight gain but none were significant.

Risk of BMI≥95th percentile was 2.94 (95%CI: 1.19-7.27) times greater among women with excessive gains ≥200% of the recommendations. Additional adjustment for birthweight and infant feeding behaviors tended to attenuate estimates but did not diminish their significance in most instances.

Conclusions: Maternal prepregnancy BMI and gestational weight gain are positively associated with child BMI z-score and risk of overweight/obesity at 3 years. Prevention efforts to reach women during their reproductive years, prior to becoming pregnant, are necessary to decrease fetal exposure to maternal obesity and excessive gestational weight gains.

Introduction

Recent pediatric obesity prevention efforts have switched their focus from the postnatal to the prenatal period, emphasizing the perceived importance of modifiable prenatal risk factors, such as prepregnancy body mass index (BMI) and gestational weight gain, for weight development in the offspring. Results from animal models suggest that maternal overnutrition, both prior to and during gestation, influences the development of offspring metabolic and appetite regulating systems leading to increased adiposity later in life. Previous studies demonstrate that maternal BMI is positively associated with adiposity in children[1-9] but not all of them evaluated maternal BMI prior to pregnancy.[3,9] There are relatively fewer studies and less consistent evidence to support an association between gestational weight gain and offspring weight status, with studies showing both positive and

no associations for various weight outcomes. It is also not clear whether the effect of gestational weight gain on offspring adiposity varies by prepregnancy BMI status.

In the current study, we utilize data from a recent prospective, longitudinal pregnancy cohort to investigate the independent effects of prepregnancy BMI and gestational weight gain, defined by the 2009 Institute of Medicine recommendations, on offspring BMI at 3 years. The results from this research can be used to inform and guide preconceptional, as well as pediatric obesity, intervention efforts.

Methods

Study Population

Subjects were recruited from the third cohort of the Pregnancy Infection and Nutrition study (PIN3), January 1, 2001- June 30, 2005, and followed through 3 years postpartum by the PIN Postpartum (3 and 12 months postpartum) and PIN Pediatric (3 years postpartum) studies. The recruitment protocols were documented previously.[10,11] The PIN study protocols were approved by the Institutional Review Boards of the School of Medicine at UNC Chapel Hill and Wake Medical Center.

A total of 2,006 pregnant women agreed to participate in PIN3, of which 1,169 were eligible for the PIN Postpartum study; 480 were excluded from (n=293) or refused (n=187) to participate in the study (Figure 2). There were 689 and 550 mother-child pairs who completed the 3 and 12-month postpartum interviews, respectively. Figure 2 displays participant retention and the reasons for exclusions across the three PIN studies. There were 409 children who completed the PIN Pediatric study. Three children were excluded due to a physician diagnosed growth-related illness. Anthropometric measurements were missing for

81 (20.0%) children, mostly because other data was collected by phone interview rather than home visit (n=58) or the child was unavailable, such as napping, during the home interview. The remaining 325 children were included in the current study.

Distributions of selected baseline characteristics between the eligible mother-child pairs who participated in PIN Pediatric (n=406), PIN Postpartum pairs not included in PIN Pediatric (n=283), and eligible PIN3 pairs not included in PIN Postpartum (n=480) were examined. In comparison to mothers in PIN Pediatric, those not included in both PIN3 and PIN Postpartum were significantly younger and had infants with lower mean birthweight and gestational age. They were more likely to be obese, black, unmarried, less educated, and from low income households. Additionally, a higher percentage of PIN Postpartum mothers not included in PIN Pediatric smoked during pregnancy. All other comparisons of characteristics were not significant. There were no significant differences in the baseline characteristics of the PIN Pediatric samples with (n=325) and without (n=81) child anthropometric measurements with the exception that a higher percentage of mothers in the sample missing measurements had gestational diabetes mellitus (GDM) or impaired glucose tolerance (IGT) compared to those with measurements.

Study Variables

At the 3 year home visit, children's heights and weights were measured by trained PIN staff using stadiometers and scales, respectively, according to National Health and Nutrition Examination Surveys (NHANES) protocols.[12] Child BMI (kg/m^2) was converted to age- and sex-specific BMI z-scores (continuous) and percentiles (categories) using the 2000 Centers for Disease Control and Prevention/National Center for Health Statistics growth charts.[13] Risk of overweight/obesity was defined as BMI$\geq 85^{th}$ percentile (reference, $<85^{th}$

percentile) and risk of obesity was defined as BMI≥95th percentile (reference, <95th percentile).

Prepregnancy BMI was calculated using self-reported prepregnancy weight and measured height. Weight measurements at the first prenatal visit (within 15 weeks' gestation) were compared to self-reported prepregnancy weights and biologically implausible values (n=9) were imputed following previously published methods.[14,15] BMI was categorized following the 2009 IOM recommendations[16]: underweight <18.5kg/m^2; normal weight 18.5 to 24.9kg/m^2; overweight 25.0 to 29.9kg/m^2; and obese ≥30.0kg/m^2.

Gestational weight gain was defined as the difference between the self-reported prepregnancy weight and last measured weight prior to delivery. The 2009 IOM recommendations[16] for total gain are: 12.5-18.0kg for underweight women; 11.5-16.0kg for normal weight women; 7.0-11.5kg for overweight women; and 5.0-9.0kg for obese women. An adequacy of gestational weight gain ratio (adequacy ratio) was calculated by dividing the observed weight gain by the expected weight gain based on the IOM recommendations, as described previously.[14,15,17,18] Cutoffs to determine inadequate, adequate, and excessive weight gains were based on ranges of adequacy ratios. Due to the large distribution of adequacy ratios within the excessive weight gain category, excessive weight gain was dichotomized at an adequacy ratio of 2.00, or 200%, to examine the effects of excessive weight gain within the upper adequacy ratios. Excessive I weight gain (n=151) was defined as an adequacy ratio greater than the upper value of the BMI-specific adequate weight gain range to 1.99. Excessive II weight gain (n=53) was defined as an adequacy ratio ≥2.00 (or ≥200% of the recommended amount).

Maternal prenatal smoking (months 1-6 of pregnancy), household income, education, marital status, age at conception, race/ethnicity, pre-existing diabetes, and parity were collected from interviews during the prenatal period and categorized as shown in Table 1. Household income was expressed as percent of the poverty line and calculated using the 2001 U.S. Department of Health and Human Services Federal Poverty Guidelines[19]; a percentage ≤185% is the cut-off for the Special Supplemental Nutrition Program for Women, Infants, and Children. Household income at the 3-month postpartum interview was used for missing information from the prenatal period (n=8).

Infant sex and birthweight were abstracted from medical records. Gestational age was calculated from ultrasound measurements conducted prior to 22 weeks' gestation (up to 21 weeks, 6 days). If no ultrasound was performed or if it was not performed prior to the start of the 22nd week then the date of the last menstrual period was used. Sex- and gestational age adjusted birthweight z-scores were based on US national reference data[20]. Maternal glucose tolerance status was derived from universal screens administered during the second trimester (mean gestational age ~27 weeks) on women without pre-existing diabetes (n=305). Normal and IGT were defined as blood glucose <140 and ≥140mg/dl on the universal screen, respectively. GDM was defined as having two abnormal values on an oral glucose tolerance test or a physician diagnosis. Exclusive breast feeding duration (months) and the age (months) at introduction of solids (any food/beverage other than breast milk, formula, or water) was collected at 3 and 12-months postpartum.

Statistical Analysis

We used multiple imputation techniques using SAS 9.2 (SAS Institute, Cary, NC) and SAS PROC MI to estimate values of the missing covariate data for the sample of children with anthropometric data (n=325): prepregnancy BMI (n=1), gestational weight gain (n=1), glucose tolerance (n=3), prenatal smoking (n=10), and birthweight (n=2). All of the pre- and postnatal variables discussed in the previous section were included in the multiple imputation models. We generated ten imputed data sets that were combined into a single set of parameter estimates for the final regression models.[21,22] Regression analyses using the imputed data were not different from those using the complete case data.

Other statistical analyses were performed using STATA 11 (College Station, TX). Potential effect measure modifiers, confounders, and mediators of interest were identified a priori from a literature review and causal diagrams.[23,24] The interaction of maternal prepregnancy BMI and adequacy ratios was tested in a crude model using interaction terms and Wald tests with an a priori significance p-value of <0.15. Additionally, full models were individually adjusted for maternal glucose status, birthweight z-score, exclusive breast feeding duration, and age at introduction to solids. Although these variables did not satisfy criteria for being confounders, they have been identified as being related to the selected maternal exposures as well as independent predictors of the offspring outcomes.

T-tests of means, Fisher's exact tests, and analyses of variance examined distributions of baseline characteristics. Multivariable linear regression estimated associations between the selected maternal exposures and continuous child BMI z-scores. Multivariable modified Poisson regression (Poisson regression with a robust error variance) estimated incidence risk ratios (IRR) of child overweight/obesity and obesity.[25,26] All regression analyses were

adjusted for clustering at the individual level[27-30] since there were 6 women with more than one child included in the 3 year follow-up.

Results

The mean (SD) prepregnancy BMI was 25.0 (6.7) kg/m^2; approximately 34.0% of the women were overweight or obese. The mean (SD) gestational weight gain was 15.8 (6.2) kg; 63.0% had excessive weight gains. The distribution (n) of inadequate, adequate, excessive I, and excessive II weight gains across prepregnancy BMI categories were: 3, 5, 8, and 0 among underweight women; 26, 56, 106, and 10 among normal weight women; 2, 10, 28, and 21 among overweight women; and 9, 9, 9, and 22 among obese women, respectively. The mean (SD) birthweight and gestational age was 3329.6g (551.1) and 38.7 weeks (2.1), respectively. At 36 months, 71 (21.8%) of the children were overweight/obese and 26 (8.0%) were obese, with a mean (SD) BMI z-score of 0.3 (1.1).

Table 7 shows the distributions of selected characteristics according to mean child BMI z-score and overweight/obesity status. Mean BMI z-scores were highest among mothers who were obese, excessive gainers, black, not married, low education, and smokers, as well as among infants with birthweights ≥4000g and introduced to solids at <4 months. Similar patterns were observed for distributions of overweight/obesity status, with significant differences found across categories of prepregnancy BMI, race/ethnicity, marital status, education, pre-existing diabetes, prenatal smoking, and age at introduction of solids.

Prepregnancy BMI was positively associated with BMI z-scores and risks of overweight/obesity. Each kg/m^2 increase in prepregnancy BMI was associated with a 0.4 unit increase in BMI z-score (Table 8) and a 4.0% and 8.0% increase in risk of ≥85th and ≥95th

percentile, respectively (Table 9). Underweight women had children with significantly lower BMI z-scores while overweight and obese women had children with significantly higher BMI z-scores compared to those of normal weight women.

There were no underweight women with overweight/obese children. Compared to children of normal weight mothers, children of overweight and obese mothers were 1.7 and 2.2 times more likely to be $\geq 85^{th}$ percentile and 3.7 and 8.4 times more likely to be $\geq 95^{th}$ percentile, respectively, compared to children of normal weight mothers (Table 10). Adjustment for maternal glucose status or birthweight z-score did not alter the magnitude or significance of the effect estimates in most instances (data not shown). Adjustment for infant feeding behaviors attenuated effect estimates among overweight and obese women. In general, age at introduction to solids attenuated estimates more than exclusive breast feeding duration (data not shown).

Adequacy ratios were not linearly associated with child BMI z-scores; instead there was a slight U-shaped distribution, which became linear after adjustment for prepregnancy BMI. Each 0.10 (10.0%) increase in adequacy ratio was associated with a 0.03 unit increase in BMI z-score (Table 8). Compared to adequate, excessive I and excessive II weight gains were associated with higher BMI z-scores of 0.4 and 0.5 units, respectively. Risks of overweight/obesity increased across categories of gestational weight gain but none were significant (Table 9). The risk of BMI$\geq 95^{th}$ percentile was nearly three times greater among women with excessive II weight gain compared to women with inadequate and adequate weight gains (Table 10).

Overall, adjustment for birthweight z-score and infant feeding behaviors slightly attenuated effect estimates; however, the significance of the associations was not altered

(data not shown). There was no evidence for an interaction between continuous gestational weight gain adequacy ratios and prepregnancy BMI.

Discussion

Our results suggest that both prepregnancy BMI and adequacy of gestational weight gain are modifiable prenatal risk factors for child BMI at 3 years. Prepregnancy overweight and obesity were associated with increased BMI z-scores and risks of BMI$\geq 85^{th}$ and $\geq 95^{th}$ percentiles. Excessive gestational weight gains were associated with increased BMI z-scores and risk of BMI$\geq 95^{th}$ percentile. Maternal glucose status, birthweight z-score, and infant feeding behaviors did not fully explain the observed associations.

Observational studies demonstrate that prepregnancy BMI is linked to offspring adiposity during infancy[31], childhood[1,5-7,32], adolescence[5,33], and adulthood.[34,35] Studies focusing on early childhood BMI show similar associations to those reported here. Whitaker[1] found significantly higher odds of child obesity at ages 2-4 years, ranging from approximately 1.4-4.3, across maternal BMI (measured during the first trimester) categories of overweight, obesity, and morbid obesity compared to normal weight. Salsberry and Reagan[7] reported that, compared to children of normal weight mothers, those of obese mothers were 1.37 (95%CI: 1.02-1.84) times more likely to be obese at 2-3 years.

Our results suggest that prepregnancy BMI>25kg/m^2 is a prenatal factor that contributes to early childhood overweight/obesity. This association is partly explained by infant feeding behaviors but not maternal glucose status or birthweight z-score. This is in contrast to a previous study[32], which reported that approximately 34% and 17% of the effect of prepregnancy BMI on infant weight and BMI, respectively, at 14 months was explained by

birthweight, sex, and gestational age while adjustment for breast feeding duration did not have an effect. The difference in findings may be attributed to the units of measurement of the offspring outcomes and the ages at which the measurements were attained. Measurements taken at earlier ages may be more influenced by birthweight, while measurements taken at later ages are more influenced by environmental factors, such as feeding. This is supported by our finding that infant feeding behaviors, especially age at introduction to solids, attenuated the observed effect estimates for the associations between prepregnancy BMI and child BMI.

There is less consistent evidence for an association between gestational weight gain and offspring adiposity. Previous studies reveal positive[33,34,36-42] and null[1,6,35,43,44] associations. Two studies examined child BMI at 36 months using recent, prospective pregnancy cohorts. Oken et.al.[36] reported a positive association between gestational weight gain and child BMI z-score, each 5kg of weight gain was associated with an increase in BMI z-score of 0.13 (95%CI:0.08,0.19) units. Using the 1990 IOM recommendations, compared to children of women with inadequate weight gains, children of women with adequate and excessive gains had higher BMI z-scores, 0.47 (95%CI: 0.37,0.57) and 0.52 (95%CI: 0.44,0.61), respectively, and were approximately four times more likely to be $\geq 95^{th}$ percentile (reference, $<50^{th}$ percentile). There was no evidence of an interaction between gestational weight gain and prepregnancy BMI. In contrast, Olson et.al.[6] found no association between net gestational weight gain (total gestational weight gain – birthweight) and odds of child overweight ($>85^{th}$ percentile) but found a significant positive interaction with prepregnancy BMI using an equation developed from a logistic regression model.

Our findings of positive associations between gestational weight gain and child BMI z-scores as well as risk of obesity are consistent with those of Oken et.al.[36]; however, we only found a significant risk of child obesity among women with excessive weight gains ≥200% of the recommended amount compared to women with inadequate/adequate gain. Birthweight z-scores slightly attenuated the observed associations, as shown in previous studies.[36,37,42] Infant feeding behaviors also tended to attenuate effect estimates but did not alter their significance, suggesting that none of these variables fully explains the observed associations between gestational weight gain and child BMI. Though it is difficult to compare our results with those from previous studies due to differences in measurements and statistical methodology; collectively, they suggest an independent effect of gestational weight gain on offspring weight development.

For the present study, we aimed to improve upon shortcomings in the previous literature by using recent data that reflects national trends in excessive weight gain and maternal and pediatric obesity. The adequacy ratio is an optimal measure of gestational weight gain because it accounts for gestational age and allows for an evaluation of the 2009 IOM recommendations. The outcome of child BMI at 3 years is less likely to be influenced by environmental and growth factors (such as the adiposity rebound and puberty) than BMI measured later in childhood and adolescence.[45] Childhood overweight during the preschool years is a predictor of later obesity that may track into adolescence and adulthood.[46] We also included important potential confounding variables identified from the literature.

A main limitation is loss to follow-up between birth and 3 years, which resulted in a disproportionate loss of women from high risk groups and may have weakened the observed associations. Other limitations are due to our measurements of maternal and child

anthropometrics. Women of reproductive ages tend to underestimate their weight[47], which may have underestimated prepregnancy BMI and overestimated gestational weight gain. Child BMI status is not a direct measure of adiposity but it is correlated (r=.75) with percent body fat in children ages 3-8 years.[48] Lastly, it is likely that the observed associations between maternal prenatal factors and child BMI partly reflect the effects of environmental factors (such as child diet and physical activity) related to maternal BMI and health behaviors in the postnatal period, which we were unable to consider in our causal model.

Conclusions

We found that both prepregnancy BMI and gestational weight gain according to the 2009 IOM recommendations are modifiable prenatal exposures that independently influence child BMI status. Prevention efforts to reach women during their reproductive years, prior to pregnancy are necessary to decrease fetal exposure to maternal overweight/obesity and excessive gestational weight gains. Future studies that collect longitudinal data prior to pregnancy through early childhood and include sophisticated measures of child adiposity are needed.

Table 7. Baseline Distributions of Population Characteristics according to child BMI z-score and child overweight/obesity (≥85th percentile) status at 3 years in the Pregnancy, Infection, and Nutrition Study (n=325)

Variable	N	Frequency (%)	Mean child BMI z-score (SD)	p[a]	Child BMI <85th	Child BMI ≥85th	p[b]
Age (years)	325						
16-24	54	16.6	0.39 (0.99)		15.4	21.1	
25-29	93	28.6	0.34 (1.01)	0.91	29.1	26.8	0.39
30-34	117	36.0	0.29 (1.12)		37.8	29.6	
35-47	61	18.8	0.39 (1.09)		17.7	22.5	
Prepregnancy BMI Category (kg/m^2)							
Underweight	16	4.9	-0.25 (0.65)		6.3	0	
Normal Weight	198	61.1	0.15 (0.93)	<0.001	65.6	45.1	<0.001
Overweight	61	18.8	0.61 (1.04)		16.6	26.8	
Obese	49	15.1	0.87 (1.38)		11.5	28.2	
Gestational Weight Gain							
Inadequate	40	12.3	0.08 (0.98)		13.8	7.0	
Adequate	80	24.7	-0.002 (1.06)	<0.001	26.3	19.7	0.02
Excessive I	151	46.6	0.39 (0.93)		46.9	45.1	
Excessive II	53	16.4	0.84 (1.21)		13.1	28.2	
Race/Ethnicity							
Non-Black	289	88.9	0.28 (1.04)	0.01	90.6	83.1	0.09
Black	36	11.1	0.74 (1.16)		9.5	16.9	
Marital Status	325						
Married	278	85.5	0.27 (1.06)	0.004	88.2	76.1	0.01
Other	47	14.5	0.75 (0.97)		11.8	23.9	
Education	325						
≤ Grade 12	42	12.9	0.64 (1.23)		11.0	19.7	
Grades 13 -16	168	51.7	0.40 (1.06)	0.01	50.0	57.8	0.02
≥ Grade 17	115	71.4	0.13 (0.96)		39.0	22.5	
Household Income	324						
<185%	49	15.1	0.61 (1.08)	0.11	12.6	18.3	0.32

185-350%	61	18.8	0.37 (1.21)		19.7	22.5	
>350%	214	66.1	0.27 (1.00)		67.7	59.2	
Glucose Tolerance							
Normal	273	89.5	0.30 (1.01)		90.1	87.3	
Impaired Glucose Tolerance	22	7.2	0.45 (0.92)	0.81	6.2	11.1	0.38
Gestational Diabetes	10	3.3	0.30 (1.10)		3.7	1.6	
Prepregnancy Diabetes							
No	305	93.8	0.31 (1.02)	0.18	95.3	88.7	0.05
Yes	20	6.2	0.64 (1.54)		4.7	11.3	
Parity							
Nulliparous	155	47.7	0.32 (1.02)	0.73	48.0	46.5	0.89
1 or More Births	170	52.3	0.36 (1.10)		52.0	53.5	
Smoking in Months 1-6 of Pregnancy							
Yes	292	92.4	0.29 (1.04)	0.003	5.7	14.3	0.04
No	24	7.6	0.97 (1.11)		94.3	85.7	
Infant Sex							
Male	178	54.8	0.41 (1.05)	0.20	54.7	54.9	1.00
Female	147	45.2	0.26 (1.06)		45.3	45.1	
Birthweight (g)							
<3000	68	21.1	0.19 (1.11)		23.3	12.9	
3000-<3500	146	45.2	0.31 (1.13)	0.004	43.9	50.0	0.06
3500-<4000	79	24.5	0.22 (0.87)		25.3	21.4	
≥4000	30	9.3	0.97 (0.87)		7.5	15.7	
Age (months) at introduction of solids							
<4	64	19.7	1.07 (1.19)		13.8	40.9	
4-5	163	50.2	0.18 (0.94)	<0.001	53.2	39.4	<0.001
≥6	98	30.1	0.10 (0.95)		33.1	19.7	
Exclusive breast feeding duration (months)							
0	68	22.7	0.45 (1.19)		22.0	25.4	

>0 to <4	72	24.0	0.33 (1.16)	0.15	22.0	32.2	0.28
4-<6	98	32.7	0.17 (0.84)		34.4	25.4	
6 or more	62	20.7	0.07 (0.94)		21.6	17.0	

[a]ANOVA, F statistic

[b] Fisher's Exact Test.

Table 8. Difference in child BMI z-score at 3 years associated with maternal prepregnancy BMI and adequacy of gestational weight gain ratio (N=325)

	Model 1[a]			Model 2[b]		
	b	**95% CI**	**p**	**b**	**95% CI**	**p**
Prepregnancy BMI (per kg/m^2)	0.05	(0.03,0.07)	<0.001	0.04	(0.02,0.07)	<0.001
Underweight	-0.41	(-0.74,-0.07)	0.02	-0.43	(-0.78,-0.08)	0.02
Overweight	0.45	(0.16,0.75)	0.003	0.34	(0.03,0.65)	0.03
Obese	0.72	(0.31,1.12)	0.001	0.62	(0.21,1.02)	0.003
Adequacy Ratio (per 0.10)	0.03	(0.01,0.05)	0.001	0.03	(0.01,0.05)	0.002
Inadequate	-0.02	(-0.41,0.37)	0.92	-0.01	(-0.41,0.38)	0.94
Excessive I	0.43	(0.16,0.70)	0.002	0.40	(0.12,0.67)	0.01
Excessive II	0.55	(0.16,0.95)	0.01	0.50	(0.11,0.88)	0.01

[a]Model 1: Prepregnancy BMI models are adjusted for gestational age. Gestational weight gain models adjusted for prepregnancy BMI and gestational age.

[b]Model 2: Prepregnancy BMI models adjusted for Model 1 and maternal race/ethnicity, household income, prenatal smoking, education, marital status. Gestational weight gain models adjusted for Model 1 and maternal race/ethnicity, household income, prenatal smoking, education, marital status, prepregnancy diabetes.

Table 9. Risk of child overweight/obesity (BMI≥85th percentile) at 3 years associated with maternal prepregnancy BMI and adequacy of gestational weight gain ratio (N=325)

	Model 1[a]			Model 2[b]		
	IRR	**95% CI**	**p**	**IRR**	**95% CI**	**p**
Prepregnancy BMI (per kg/m^2)	1.05	(1.03,1.07)	<0.001	1.04	(1.02,1.06)	<0.001
Overweight[c]	1.92	(1.17,3.17)	0.01	1.72	(1.02,2.91)	0.04
Obese[c]	2.53	(1.58,4.05)	<0.001	2.21	(1.34,3.64)	0.002
Adequacy Ratio (per 0.10)	1.02	(1.00,1.04)	0.02	1.02	(1.00,1.04)	0.02
Inadequate	0.62	(0.24,1.70)	0.37	0.64	(0.24,1.74)	0.39
Excessive I	1.33	(0.76,2.30)	0.32	1.27	(0.74,2.21)	0.39
Excessive II	1.65	(0.92,2.94)	0.09	1.54	(0.86,2.74)	0.15

IRR, incidence risk ratio

[a]Model 1: Prepregnancy BMI models are adjusted for gestational age. Gestational weight gain models adjusted for prepregnancy BMI and gestational age.

[b]Model 2: Prepregnancy BMI models adjusted for Model 1 and maternal race/ethnicity, household income, prenatal smoking, education, marital status. Gestational weight gain models adjusted for Model 1 and maternal race/ethnicity, household income, prenatal smoking, education, marital status, prepregnancy diabetes.

[c]Reference is normal weight. There were no underweight women with obese children.

Table 10. Risk of child obesity (BMI≥95th percentile) at 3 years associated with maternal prepregnancy BMI and adequacy of gestational weight gain ratio (N=325)

	Model 1[a]			Model 2[b]		
	IRR	**95% CI**	**p**	**IRR**	**95% CI**	**p**
Prepregnancy BMI (per kg/m^2)	1.10	(1.07,1.12)	<0.001	1.08	(1.04,1.12)	<0.001
Overweight[c]	4.53	(1.49,13.82)	0.01	3.66	(1.18,11.34)	0.03
Obese[c]	11.32	(4.27,29.99)	<0.001	8.42	(2.88,24.62)	<0.001
Adequacy Ratio (per 0.10)	1.04	(1.01,1.07)	0.02	1.04	(1.01,1.07)	0.02
Excessive I[d]	1.63	(0.55,4.80)	0.38	1.71	(0.53,5.56)	0.37
Excessive II[d]	3.08	(1.28,7.39)	0.01	2.94	(1.19,7.27)	0.02

IRR, incidence risk ratio

[a]Model 1: Prepregnancy BMI models are adjusted for gestational age. Gestational weight gain models adjusted for prepregnancy BMI and gestational age.

[b]Model 2: Prepregnancy BMI models adjusted for Model 1 and maternal race/ethnicity, household income, prenatal smoking, education, marital status. Gestational weight gain models adjusted for Model 1 and maternal race/ethnicity, household income, prenatal smoking, education, marital status, prepregnancy diabetes.

[c]Reference is normal weight, there were no underweight women with obese children.

[d]Reference is inadequate/adequate weight gain because only 2 and 4 inadequate and adequate gainers, respectively, had obese children.

References

1. Whitaker RC. Predicting preschooler obesity at birth: The role of maternal obesity in early pregnancy. *Pediatrics*. 2004;114(1):e29-e36.

2. Reilly JJ, Armstrong J, Dorosty AR, et al. Early life risk factors for obesity in childhood: Cohort study. *Br Med J*. 2005;330(7504):1357.

3. Dubois L, Girard M. Early determinants of overweight at 4.5 years in a population-based longitudinal study. *Int J Obes*. 2006;30(4):610-617.

4. Li R, Jewell S, Grummer-Strawn L. Maternal obesity and breast-feeding practices. *Am J Clin Nutr*. 2003;77(4):931-936.

5. Li C, Kaur H, Choi WS, Huang TT, Lee RE, Ahluwalia JS. Additive interactions of maternal prepregnancy BMI and breast-feeding on childhood overweight. *Obes Res*. 2005;13(2):362-371.

6. Olson CM, Strawderman MS, Dennison BA. Maternal weight gain during pregnancy and child weight at age 3 years. *Matern Child Health J*. 2009;13(6):839-846.

7. Salsberry PJ, Reagan PB. Dynamics of early childhood overweight. *Pediatrics*. 2005;116(6):1329-1338.

8. Blair NJ, Thompson J, Black PN, et al. Risk factors for obesity in 7-year-old European children: The Auckland Birthweight Collaborative study. *Br Med J*. 2007;92(10):866-871.

9. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med*. 1997;337(13):869-873.

10. Siega-Riz AM, Herring AH, Carrier K, Evenson KR, Dole N, Deierlein A. Sociodemographic, perinatal, behavioral, and psychosocial predictors of weight retention at 3 and 12 months postpartum. *Obesity (Silver Spring)*. 2009;Dec(24):[Epub ahead of print].

11. Pan IJ, Daniels JL, Goldman BD, Herring AH, Siega-Riz AM, Rogan WJ. Lactational exposure to polychlorinated biphenyls, dichlorodiphenyltrichloroethane, and dichlorodiphenyldichloroethylene and infant neurodevelopment: An analysis of the Pregnancy, Infection, and Nutrition Babies study. *Environ Health Perspect*. 2009;117(3):488-494.

12. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Protocol 1999-2000. . http://www.cdc.gov.libproxy.lib.unc.edu/nchs/data/nhanes/meccomp.pdf.

13. Vidmar S, Carlin J, Hesketh K, Cole T. Standardizing anthropometric measures in children and adolescents with new functions for egen. *Stata J*. 2004;4(1):50-55.

14. Vahratian A, Zhang J, Troendle JF, Savitz DA, Siega-Riz AM. Maternal prepregnancy overweight and obesity and the pattern of labor progression in term nulliparous women. *Obstet Gynecol*. 2004;104(5, Part 1):943-951.

15. Siega-Riz AM, Adair LS, Hobel CJ. Institute of medicine maternal weight gain recommendations and pregnancy outcome in a predominantly Hispanic population. *Obstet Gynecol*. 1994;84(4, Part 1):565-573.

16. IOM (Institute of Medicine), NRC (National Research Council). *Weight Gain during Pregnancy: Reexamining the Guidelines.* Washington, DC: The National Academies Press; 2009.

17. Bodnar LM, Siega-Riz AM, Arab L, Chantala K, McDonald T. Predictors of pregnancy and postpartum haemoglobin concentrations in low-income women. *Public Health Nutr*. 2007;7(6):701-711.

18. Deierlein AL, Siega-Riz AM, Herring A. Dietary energy density but not glycemic load is associated with gestational weight gain. *Am J Clin Nutr*. 2008;88(3):693-699.

19. Proctor BD, Dalaker J, US Census Bureau, Current Population Reports, P60-219. Poverty in the United States: 2001. US Government Printing Office, Washington, DC, 2002.

20. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr*. 2003;3:6.

21. Rubin DB. Multiple imputation after 18 years. *Journal of the American Statistical Association*. 1996;91(434):473-489.

22. Rubin DB. *Multiple Imputation for Nonresponse in Sample Surveys.* New York: John Wiley & Sons, Inc.; 1987.

23. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48.

24. Pearl J. Causal diagrams for empirical research. *Biometrika*. 1995;82(4):669-688.

25. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol*. 2003;157(10):940-943.

26. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706.

27. Rogers W. Regression standard errors in clustered samples. *Stata Technical Bulletin*. 1993;13:19-23.

28. Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics*. 2000;56(2):645-646.

29. Wooldridge JM. *Econometric Analysis of Cross Section and Panel Data*. The MIT press; 2002.

30. Froot KA. Consistent covariance matrix estimation with cross-sectional dependence and heteroskedasticity in financial data. *Journal of Financial and Quantitative Analysis*. 1989;24(3):333-355.

31. Hull HR, Dinger MK, Knehans AW, Thompson DM, Fields DA. Impact of maternal body mass index on neonate birthweight and body composition. *Am J Obstet Gynecol*. 2008;198(4):416e1-e6.

32. Mesman I, Roseboom TJ, Bonsel GJ, Gemke RJ, van der Wal MF, Vrijkotte TGM. Maternal pre-pregnancy body mass index explains infant's weight and BMI at 14 months: Results from a multi-ethnic birth cohort study. *Br Med J*. 2009;94(8):587-595.

33. Stuebe AM, Forman MR, Michels KB. Maternal-recalled gestational weight gain, pre-pregnancy body mass index, and obesity in the daughter. *Int J Obes*. 2009;33(7):743-752.

34. Terry MB, Wei Y, Esserman D. Maternal, birth, and early-life influences on adult body size in women. *Am J Epidemiol*. 2007;166(1):5-13.

35. Stettler N, Tershakovec AM, Zemel BS, et al. Early risk factors for increased adiposity: A cohort study of African American subjects followed from birth to young adulthood. *Am J Clin Nutr*. 2000;72(2):378-383.

36. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. *Obstet Gynecol*. 2007;196(4):322.e1-322.e8.

37. Wrotniak BH, Shults J, Butts S, Stettler N. Gestational weight gain and risk of overweight in the offspring at age 7 y in a multicenter, multiethnic cohort study. *Am J Clin Nutr*. 2008;87(6):1818-1824.

38. Moreira P, Padez C, Mourao-Carvalhal I, Rosado V. Maternal weight gain during pregnancy and overweight in Portuguese children. *Int J Obes*. 2007;31(4):608-614.

39. Oken E, Rifas-Shiman SL, Field AE, Frazier AL, Gillman MW. Maternal gestational weight gain and offspring weight in adolescence. *Obstetrics & Gynecology*. 2008;112(5):999-1006.

40. Li C, Goran MI, Kaur H, Nollen N, Ahluwalia JS. Developmental trajectories of overweight during childhood: Role of early life factors. *Obesity*. 2007;15(3):760-771.

41. Mamun AA, O'Callaghan M, Callaway L, Williams G, Najman J, Lawlor DA. Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: Evidence from a birth cohort study. *Circulation*. 2009;119(13):1720-1727.

42. Schack-Nielsen L, Michaelsen KF, Gamborg M, Mortensen EL, Sørensen TIA. Gestational weight gain in relation to offspring body mass index and obesity from infancy through adulthood. *Int J Obes*. 2009;34(1):67-74.

43. Maffeis C, Micciolo R, Must A, Zaffanello M, Pinelli L. Parental and perinatal factors associated with childhood obesity in north-east Italy. *Int J Obes Relat Metab Disord*. 1994;18(5):301-305.

44. Fisch RO, Bilek MK, Ulstrom R. Obesity and leanness at birth and their relationship to body habitus in later childhood. *Pediatrics*. 1975;56(4):521-528.

45. Dietz WH. Critical periods in childhood for the development of obesity. *Am J Clin Nutr*. 1994;59(5):955-959.

46. Krebs NF, Jacobson MS, American Academy of Pediatrics Committee on Nutrition. Prevention of pediatric overweight and obesity. *Pediatrics*. 2003;112(2):424-430.

47. Brunner Huber LR. Validity of self-reported height and weight in women of reproductive age. *Matern Child Health J*. 2007;11(2):137-144.

48. Eisenmann JC, Heelan KA, Welk GJ. Assessing body composition among 3-to 8-year-old children: Anthropometry, BIA, and DXA. *Obes Res*. 2004;12(10):1633-1640.

CHAPTER VI

INFLUENCE OF PREPREGNANCY BODY MASS INDEX AND GESTATIONAL WEIGHT GAIN ON POSTNATAL GROWTH FROM BIRTH TO 3 YEARS

Abstract

Objective: To determine how prepregnancy BMI and gestational weight gain relate to changes in offspring weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length z-scores (WLZ) measured from birth to 3 years.

Subjects and Methods: Mother-infant pairs were recruited from the Pregnancy, Infection, and Nutrition Study, a prospective pregnancy cohort (2001-2005). Term infants with at least one measurement (weight or length) between birth and 3 years were included (n=476). Linear mixed effects regression models were used to estimate changes in child WAZ, LAZ, and WLZ between birth and 3 years associated with prepregnancy BMI and gestational weight gain defined by the 2009 Institute of Medicine recommendations.

Results: There were no significant differences in WAZ or LAZ at birth across categories of prepregnancy BMI; however, prepregnancy obesity was associated with a significant change in WAZ and prepregnancy overweight was associated with a significant change in LAZ between birth and 3 years. Prepregnancy overweight was associated with higher WLZ at birth and prepregnancy obesity was associated with a significant change in WLZ

across the study period. Significant differences in WAZ, LAZ, and WLZ at birth were observed across categories of gestational weight gain. Excessive weight gain≥200% of the recommended amount was associated with higher WAZ and WLZ at birth and significant changes in WAZ and LAZ across the study period compared to adequate weight gain.

Conclusions: Prepregnancy BMI and gestational weight gain differentially influenced the selected anthropometric outcomes at birth and their rates of change between birth and 3 years. Compared to lower categories of prepregnancy BMI and gestational weight gain, prepregnancy overweight and obesity and excessive weight gain ≥200% of the recommended amount were associated with higher predicted mean WAZ and WLZ that persisted across the study period.

Introduction

Pediatric obesity continues to be a major health epidemic among children in the United States and it is being documented as early as infancy. Recent studies show that the prevalence of ≥95th percentile of weight-for-recumbent length is 9.5% among infants and toddlers from birth to 2 years.[1] The prevalence of overweight/obesity (≥ 85th percentile) is 21.2% among children ages 2-5 years[1] and the rates among low income preschoolers are increasing.[2] Treatment of pediatric obesity is an arduous task, encompassing behavioral, social, and environmental factors[3]; therefore, the identification of modifiable risk factors to prevent the development of overweight and obesity during infancy and early childhood is of great importance.

Maternal prepregnancy body mass index (BMI) and gestational weight gain represent modifiable behavioral factors that are associated with offspring anthropometric outcomes[4,5]; however, there are relatively few studies that examine these associations using longitudinal data. Li et.al.[6] examined the role of early life factors on developmental overweight ($\geq 95^{th}$ percentile) trajectories in children from ages 2 to 12 years. Maternal overweight and obesity were associated with increased odds of both early onset overweight (defined as a consistent high probability of overweight status) and late onset overweight (defined as an initial high probability of overweight status at 2 years, low probability of overweight at 4-6 years, and high probability of overweight after 8 years); gestational weight gain ≥20.43 kg was only associated with increased odds of early onset overweight. These results suggest that there are potentially different underlying pathways for the development of pediatric obesity associated with these maternal exposures.

In the current study, we used data from a recent prospective pregnancy cohort and categorized prepregnancy BMI and gestational weight gain according to the 2009 Institute of Medicine guidelines. Our goal was to determine how prepregnancy BMI and gestational weight gain relate to offspring weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length z-scores (WLZ) from birth to 3 years of age. The use of longitudinal data allowed for an examination of how the associations between the selected maternal exposures and anthropometric outcomes differed and changed over time.

Methods

Study Population

Study subjects were women with singleton births who participated in the third cohort of the Pregnancy Infection and Nutrition study (PIN3), January 1, 2001- June 30, 2005. The recruitment protocols for the study have been documented previously.[7] Briefly, pregnant women who were at least 16 years of age at conception, English-speaking, prior to 20 weeks' gestation at recruitment, and receiving prenatal care from public and private clinics at the University of North Carolina (UNC) Hospitals were eligible for participation. Data collection throughout the prenatal period included socio-demographic characteristics, health behaviors, biological specimens, and medical chart abstraction for pre-existing and pregnancy complications as well as other outcomes.

In 2003, the PIN Postpartum study recruited eligible women from PIN3 (n=1169) and followed-up the index infant at 3 months (n=689) and 12 months (n=550) postpartum.[7] PIN Pediatric (beginning 2004) followed-up the index infant at 3 years (n=409). Data collected at the 3-month, 12-month, and 3-year home visits were similar to that collected during the prenatal period. Information on child anthropometric measurements was collected at the 12-month and 3 year visits (detailed in the following section). The PIN study protocols were reviewed and approved by the Institutional Review Boards of the School of Medicine at the University of North Carolina at Chapel Hill and Wake Medical Center.

We used data from the 550 mother-child pairs who participated at 12 months postpartum. Children with physician-diagnosed illnesses related to growth (n=3) and women with missing gestational weight gain or prepregnancy BMI (n=3) were excluded.

Due to potential differences in early growth patterns between preterm (gestational age <37 weeks) and term infants (gestational age ≥37 weeks), preterm infants were also excluded (n=68). The remaining 476 mother-child pairs had at least one anthropometric measurement (weight or length) between birth and 3 years and were included in the analyses.

We examined the distributions of selected baseline characteristics across mother-child pairs who were not included (n=693, pairs that were eligible for but did not participate in PIN Postpartum or excluded from the current analysis) and included (n=476) in the current analysis. In comparison to included mothers, those who were not included were more likely to be <30 years at conception, overweight/obese, black, not married, low education, low income, and smokers. They were also more likely to have excessive gestational weight gains ≥200% of the recommended amount and have infants with lower mean birthweight and gestational age. All other comparisons of characteristics were not significant.

Anthropometric Outcomes

Offspring anthropometric outcomes were weight-for-age (WAZ), length/height-for-age (LAZ), and weight-for-length/height z-scores (WLZ) between birth and 3 years. Infant birthweight (n=474) and sex (n=476) were abstracted from delivery logs (birth length was not available). Gestational age at birth was calculated from ultrasound measurements conducted prior to 22 weeks' gestation (up to 21 weeks, 6 days). If no ultrasound was performed or if it was not performed prior to the start of the 22nd week then the date of the last menstrual period was used. Other weights and lengths, with the

exception of the 3-year home visit measurements, were measured and recorded on doctor's cards during well-baby visits. Doctor's cards were provided to mothers by the PIN study staff. Mothers brought these cards to each pediatrician visit and the date of the visit and weight and length of the infant were recorded by medical staff. These cards were collected by the PIN staff at the 12-month home visit. The exact age of the infant at the time of each measurement was calculated by subtracting the infant's birth date from the date of the visit. We used the 15th of the month for infant measurements missing the day of the visit (n=14). We used the pediatrician recorded age for infant measurements when both the month and day of the visit were missing (n=64). At the 3-year home visit, children's heights and weights were measured by trained PIN staff using stadiometers and scales, respectively, according to National Health and Nutrition Examination Surveys (NHANES) protocols.[8]

All weights and lengths/heights were used to generate sex-specific WAZ, LAZ, and WLZ based on the 2000 Centers for Disease Control and Prevention/National Center for Health Statistics growth charts.[9] LAZ includes children's length-for-age z-scores from recumbent length measurements from doctor's cards and height-for-age z-scores from height measurements at the 3-year home visit. Similarly, WLZ includes children's weight-for-length z-scores and weight-for-height z-scores. All children (n=476) had at least one measurement (weight or length) between birth and 3 years. Measurements that corresponded to z-scores <-5 or >5 were considered implausible and not included in analyses (WAZ, n=0; LAZ, n=8; WLZ, n=7). There were 476 children contributing 3050 WAZ measurements (mean 6.4 measurements per child, range 1-11 measurements); 424 children contributing 2772 LAZ measurements (mean 6.5 measurements per child, range

1-11 measurements); and 422 children contributing 2679 WLZ measurements (mean 6.3 measurements per child, range 1-11 measurements).

Maternal Exposures

Maternal prepregnancy BMI (kg/m^2) was calculated using self-reported prepregnancy weight and measured height. For quality assurance, weight measurements at the first prenatal clinic visit (within 15 weeks' gestation) were compared to the self-reported prepregnancy weights to identify biologically implausible weight gains. Women with implausible values (n=14) had their prepregnancy weights imputed following previously published methods.[10,11] BMI was classified by the 2009 IOM recommendations[12]: underweight <18.5 kg/m^2; normal weight 18.5 to 24.9 kg/m^2; overweight 25.0 to 29.9 kg/m^2; and obese ≥30.0 kg/m^2.

Gestational weight gain was defined as the difference between the self-reported prepregnancy weight and last measured weight prior to delivery. The 2009 IOM recommendations[12] for total gain are: 12.5-18.0kg for underweight women; 11.5-16.0kg for normal weight women; 7.0-11.5kg for overweight women; and 5.0-9.0kg for obese women. An adequacy of gestational weight gain ratio (adequacy ratio) was calculated by dividing the observed weight gain by the expected weight gain according to the IOM recommendations, as described previously.[10,11,13,14]

Based on the 2009 IOM report we interpreted expected total first trimester weight gains as 2.0, 1.5, 1.0, and 0.5 kg for underweight, normal weight, overweight, and obese women, respectively. Mean expected rates of weight gain for the second and third trimesters are 0.49, 0.45, 0.30, and 0.24 kg/week for underweight, normal weight,

overweight, and obese women, respectively. The use of rates of weight gain adjusts for the fact that not all women have a weight measurement at the time of delivery. Cutoffs to determine inadequate, adequate, and excessive weight gains were based on ranges of adequacy ratios using the 2009 IOM total weight gain recommendations, as described previously.[11,13,14] The range of adequacy ratios defined as adequate weight gain for underweight, normal weight, overweight, and obese women were 0.82 to 1.18, 0.84 to 1.16, 0.76 to 1.24, and 0.71 to 1.29, respectively. Ratios below the lower value of the range were defined as inadequate weight gain and ratios above the upper value of the range were defined as excessive weight gain. Due to the large distribution of adequacy ratios within the excessive weight gain category, excessive weight gain was dichotomized at an adequacy ratio of 2.00, or 200%, to examine the effects of excessive weight gain within the upper adequacy ratios. Excessive I weight gain (n=213) was defined as an adequacy ratio greater than the upper value of the BMI-specific adequate range to 1.99. Excessive II weight gain (n=68) was defined as an adequacy ratio ≥2.00 (or ≥200% of the recommended amount).

Other Variables

Data concerning maternal prenatal smoking, household income, education, marital status, age at conception, race/ethnicity, pre-existing diabetes, and parity were collected from interviews during the prenatal period and categorized as shown in Table 11. Household income was expressed as percent of the poverty line and calculated using the 2001 U.S. Department of Health and Human Services Federal Poverty Guidelines[15]; a percentage ≤185% is the household income cut-off for the Special Supplemental

Nutrition Program for Women, Infants, and Children (WIC). Household income at the 3 month interview was used for women who were missing this information from the prenatal period (n=10).

Maternal glucose tolerance status was derived from universal screens that were conducted during the second trimester (mean gestational age ~27 weeks) on all women without pre-existing diabetes mellitus. Women with abnormal values on the screen were administered a 3-hour oral glucose tolerance test (OGTT) to confirm gestational diabetes (GDM). For this analysis, normal and impaired glucose tolerance (IGT) were defined as blood glucose <140 mg/dl and ≥140 on the universal screen, respectively. GDM was defined as having two abnormal values[16] on the OGTT or a GDM diagnosis by a physician listed on the medical record.

Statistical Analysis

Statistical analyses were performed using STATA 11 (College Station, TX). Means (standard deviations, SD) and frequencies were calculated for baseline characteristics in the population. Potential effect measure modifiers and confounders were identified a priori from a review of previous literature and causal diagrams.[17,18]

For longitudinal data analysis, child WAZ, LAZ, and WLZ were individually plotted over time between birth and 3 years to visually inspect the longitudinal pattern. The resulting graphs suggested a non-linear relation for WAZ but linear relations for LAZ and WLZ. Therefore, a quadratic term for child's age (child's age^2) was included in the WAZ models.

Linear mixed effects regression models[19-21] were fit using maximum restricted likelihood specified by the *xtmixed* function with an unstructured covariance pattern in STATA 11 (College Station, TX). These models were used to determine the effects of prepregnancy BMI and adequacy of gestational weight gain on changes in child WAZ, LAZ, and WLZ between birth and 3 years. The use of mixed models accounts for unbalanced data (unequal numbers of repeated measurements within children and irregular measurement times across children) and correlations of measurements within children. We included random intercepts and slopes for child's age at each measurement in the models to allow for child-specific intercepts and rates of overall growth. Interactions between the maternal exposures (prepregnancy BMI and adequacy of weight gain) with child's age were examined to determine whether associations between offspring anthropometric measurements and categories of maternal exposures varied over time. Due to potential differences in weight and length development by gestational age, we tested for an interaction between gestational age and child's age. We also tested for an interaction between prepregnancy BMI and weight gain adequacy. All fixed effects interaction terms were tested using Wald tests with an a priori significance p-value of <0.15. Full models for prepregnancy BMI and adequacy of gestational weight gain were adjusted for income (185-350% used as referent), education (grades 13-16 used as referent), race (non-black used as referent), smoking (nonsmoker used as referent), and marital status (married used as referent) using the categories shown in Table 11 and maternal height (centered at 65 inches) and gestational age (centered at 40 weeks). Gestational weight gain models were also adjusted for prepregnancy diabetes mellitus (no diagnosis used as referent) and prepregnancy BMI (centered at 23 kg/m^2).

Results

The mean (SD) prepregnancy BMI was 24.8 (6.3) kg/m^2; approximately, 32% of the women were overweight or obese. The mean (SD) gestational weight gain and adequacy of gestational weight gain ratio were 15.69 (5.62) kg and 1.41 (0.64), respectively. Fifty-nine percent of women had excessive gestational weight gains with 14.3% having weight gains that were ≥200% of the recommended amount (Table 11). The majority of women were white, 25-34 years of age at conception, married, college educated, non-smokers, and from high income households (Table 11). The mean (SD) infant birthweight and gestational age were 3435.9 (434.5) g and 39.2 (1.2) weeks, respectively.

Prepregnancy BMI and child anthropometric outcomes

Overall, children of underweight mothers had the lowest predicted mean WAZ, LAZ, and WLZ while children of overweight and obese mothers had the highest predicted mean values between birth and 3 years (Figures 3-5). There were no significant differences in WAZ or LAZ at birth across categories of prepregnancy BMI; however, prepregnancy obesity was associated with a significant change in WAZ (interaction of prepregnancy obesity and child's age) and prepregnancy overweight was associated with a significant change in LAZ (interaction of prepregnancy overweight and child's age) across the study period (Table 12). Beginning in early infancy through 3 years, predicted mean WAZ increased among infants of obese mothers and higher values were observed for infants of overweight and obese mothers across the study period (Figure 3). Predicted mean LAZ increased among infants of overweight mothers compared to infants of normal

weight mothers (Figure 4). Predicted mean WLZ increased between birth and 3 years across prepregnancy BMI categories (Figure 5). Prepregnancy overweight was associated with higher WLZ at birth and prepregnancy obesity was associated with a significant change in WLZ across the study period (interaction of prepregnancy obesity and child's age) (Table 12). Consistent with mean predicted WAZ (Figure 3), infants of obese mothers had higher mean predicted WLZ beginning in early infancy that increased over time despite having similar WLZ at birth as infants of normal weight mothers (Figure 5).

Gestational weight gain and child anthropometric outcomes

Predicted mean values of WAZ, LAZ, and WLZ were lowest among children of women with inadequate and adequate weight gain and highest among children of women with excessive II weight gain (Figures 6-8). Significant differences in WAZ, LAZ, and WLZ at birth were observed across categories of gestational weight gain (Table 13). Excessive II weight gain was associated with higher WAZ at birth and a significant change in WAZ across the study period (interaction of high excessive weight gain and child's age) compared to adequate weight gain (Table 13). Predicted mean WAZ for children of mothers with excessive II weight gain were higher and increased over time compared to children of mothers in the other weight gain categories (Figure 6). Excessive gestational weight gain was associated with higher LAZ at birth and excessive II weight gain was associated with a significant change in LAZ across the study period (Table 13). Predicted mean LAZ were highest and increased over time for children of mothers with excessive II weight gain (Figure 7). Excessive II weight gain was associated with higher WLZ at birth compared to adequate weight gain (Table 13). There were no significant

interactions between gestational weight gain categories and child's age. Predicted mean WLZ increased between birth and 3 years across the gestational weight gain categories with the highest values observed for children of women with excessive II weight gain (Figure 8). We did not find evidence of an interaction between prepregnancy BMI and adequacy of gestational weight gain for WAZ, LAZ, or WLZ.

Discussion

In this study we utilized longitudinal data analysis to determine how prepregnancy BMI and gestational weight gain relate to child anthropometric outcomes of WAZ, LAZ, and WLZ between birth and 3 years. We found that prepregnancy BMI and gestational weight gain differentially influence the selected anthropometric outcomes at birth and their rates of change between birth and 3 years. Compared to lower categories of prepregnancy BMI and gestational weight gain, prepregnancy overweight and obesity and excessive weight gain ≥200% of the recommended amount were associated with higher predicted mean WAZ and WLZ that persisted across the study period.

Positive associations for gestational weight gain with infant birthweight, ponderal index, and length[5] and for prepregnancy BMI with infant birthweight and ponderal index[22,23] have been reported. Infants of obese mothers have greater adiposity compared to those of normal BMI mothers[24,25] and this relationship may vary by gestational weight gain.[25] In a study by Sewell et.al.[25], observed increases in infant birthweight among overweight/obese women (BMI≥25 kg/m^2) were due to increases in infant fat mass but not lean body mass. Gestational weight gain was correlated with infant percent body fat in overweight/obese women while it was correlated with infant lean body mass but not

percent body fat in lean/average women (BMI<25 kg/m^2). In the current study, WAZ, LAZ, and WLZ at birth were similar across categories of prepregnancy BMI (with the exception of higher WLZ among infants of overweight women) but differed across categories of gestational weight gain. WAZ and LAZ at birth were significantly higher among infants of women with excessive I weight gain and WAZ and WLZ were significantly higher among infants of women with excessive II weight gain compared to infants of women with adequate weight gain. Though we did not find an interaction between prepregnancy BMI and gestational weight gain and we cannot comment on how our findings relate to differences in infant body composition, they suggest that prepregnancy BMI and gestational weight gain have distinctive influences on the relative size of infants at birth.

We also observed differences in rates of change of WAZ, LAZ, and WLZ from birth to 3 years between the maternal exposures. Prepregnancy obesity was associated with greater rates of increase in WAZ and WLZ from birth to 3 years compared to normal prepregnancy BMI such that these children had higher predicted mean WAZ and WLZ beginning in early infancy and across the study period. Excessive II weight gain was associated with greater rates of increase in WAZ and LAZ from birth to 3 years compared to adequate weight gain. The rate of increase in WAZ exceeded that in LAZ resulting in higher predicted mean WLZ from birth to 3 years in comparison to the other weight gain categories. Li et.al.[6] and Salsberry and Reagan[26] demonstrated persistent effects of prepregnancy BMI[6,26] and gestational weight gain ≥20.43kg[6] on risk of obesity at 2 years and continuing throughout childhood. In this study, we show that the effects of

prepregnancy BMI and gestational weight gain on child anthropometrics begin in infancy and persist through the early preschool years.

Previous studies revealed positive associations of prepregnancy BMI with early childhood weight outcomes[6,26-28] but there are fewer studies and less consistent evidence for associations of gestational weight gain with these outcomes.[6,29,30] In the current study, predicted mean WLZ increased between birth and 3 years across categories of prepregnancy BMI and gestational weight gain. However, compared to the lower categories of prepregnancy BMI and gestational weight gain, prepregnancy overweight/obesity and excessive II weight gain were associated with distinctly higher predicted mean WAZ and WLZ across the study period, with predicted mean WLZ approaching 1.5 at 3 years. Interestingly, excessive II weight gain and prepregnancy obesity appear to have different underlying pathways for the observed higher predicted mean WLZ. Excessive II weight gain but not prepregnancy obesity was associated with higher WAZ and WLZ at birth. Excessive II weight gain was also associated with changes in weight and length while prepregnancy obesity was associated only with changes in weight across the study period. Previous studies show that birthweight is positively associated with BMI later in life but this association is at least partly accounted for by changes in height and lean body mass rather than adiposity.[31-34] It is not clear whether this observation relates to differences in prepregnancy BMI and gestational weight gain exposures; further investigation is necessary to understand how maternal exposures correspond to distributions of fat and fat-free mass at birth and over time.

There is a growing amount of research dedicated to examining the effects of in utero exposures to overnutrition; in animal studies, prenatal maternal obesity and excess

nutrient intakes during pregnancy are linked to altered programming of appetite and metabolic regulators, obesity, and chronic disease risk factors in the offspring.[35-37] In humans, fetuses of obese women have increased levels of proinflammatory markers[38,39], cord blood leptin, and insulin resistance and infants have lower energy expenditures[40] and higher energy intakes[41] compared to those of normal weight women. Whether the current observations are attributable to an in utero programming effect, increased fetal growth and adiposity, and/or an obesogenic postnatal environment is unknown. Adiposity at birth[42], WLZ at birth and at 6 months[43], taller stature following rapid weight gain during infancy[44], and child height[45] are identified risk factors for later obesity. The current study and previous reviews[4,5] provide evidence for associations of some of these factors with prepregnancy BMI and/or gestational weight gain.

Our study must be interpreted within the context of several recognized limitations. First, the majority of the assessments of infant and child anthropometric measurements came from well-baby visits recorded on doctor's cards by medical staff. These measurements are subject to the inherent errors of clinical data because they were collected at multiple clinic sites and medical staffs were not trained using a standardized method. The number and timing of measurements also differed between children and we did not have measurements between ~18-35 months, which may have affected our ability to accurately model the changes in anthropometric outcomes over time. Second, as mentioned, WAZ, LAZ, and WLZ do not provide information on body composition, which limits our ability to determine how prepregnancy BMI and adequacy of weight gain relate to fat and fat-free mass development between birth and 3 years. Finally, the generalizability of the study population is limited because women in the sample had to

attend the participating prenatal clinics, meet eligibility criteria, and complete several years of postpartum follow-up interviews along with their offspring. There was also a disproportionate loss-to-follow-up of women among high risk groups. However, the exposure-disease relationship is not expected to differ across many of these factors and losses from high risk groups, such as prepregnancy obesity and excessive II weight gain, would likely have weakened the observed associations reported here.

Despite these limitations, our findings provide evidence for an influence of modifiable maternal factors on the development of offspring anthropometric outcomes in early life. This study highlights the need for future research to understand the implications of fetal exposure to prepregnancy obesity and excessive gestational weight gain ≥200% of the recommended amount for infant and childhood body composition, growth, and possibly later disease outcomes.

Table 11. Distribution of Baseline Characteristics of Women and Children in the Pregnancy, Infection, and Nutrition Study (n=476)

Variable	N	Mean(SD[a])/Frequency,%
Age (years)	476	30.04 (5.37)
Age (years)	476	
16-24	78	16.39
25-29	133	27.94
30-34	176	36.97
35-47	89	18.70
Prepregnancy BMI (kg/m^2)	476	24.80 (6.30)
Prepregnancy BMI Category (kg/m^2)	476	
Underweight	24	5.04
Normal Weight	297	62.39
Overweight	82	17.23
Obese	73	15.34
Gestational Weight Gain (kg)	476	15.69 (5.62)
Adequacy of Gestational Weight Ratio	476	1.41 (0.64)
IOM Gestational Weight Gain Category	476	
Inadequate	57	11.97
Adequate	138	28.99
Excessive I	213	44.75
Excessive II	68	14.29
Race	476	
White/other	423	88.87
Black	53	11.13
Marital Status	476	

Married	399	83.82
Other	77	16.18
Education	476	
≤ Grade 12	63	13.24
Grades 13 -16	226	47.48
≥ Grade 17	187	39.29
Family Income (% Poverty)	475	
<185%	73	15.37
185-350%	94	19.79
>350%	308	64.84
Glucose Tolerance (excludes GDM and pre-DM)	431	104.06 (25.13)
Glucose Tolerance	454	
Normal	393	87.14
Impaired Glucose Tolerance	38	8.43
Gestational Diabetes	20	4.43
Pre-existing Diabetes Mellitus	476	
No	457	96.01
Yes	19	3.99
Parity	476	
Nulliparous	232	48.74
1 or More Births	244	51.26
Smoking in Months 1-6 of Pregnancy	460	
Yes	32	6.96
No	428	93.04
Infant Sex	476	
Male	247	51.89
Female	229	48.11
Infant Birthweight	474	3435.85 (434.51)

Infant Birthweight (g)	474	
<2500	6	1.27
2500-<3000	54	11.39
3000-<3500	228	48.1
3500-<4000	136	28.69
≥4000	50	10.55
Gestational Age (weeks)	476	39.18 (1.17)

[a]SD, standard deviation

Table 12. Full[a] linear mixed models of the association between categories of maternal prepregnancy BMI and offspring weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length z-scores (WLZ) between birth and 3 years in the Pregnancy, Infection, and Nutrition Study.

	WAZ (n=459)				LAZ (n=414)				WLZ (n=412)			
	β	95% CI		p	B	95% CI		p	β	95% CI		p
Intercept	0.13	-0.18	0.44	0.42	0.26	-0.09	0.61	0.14	-0.08	-0.50	0.34	0.72
Underweight	-0.16	-0.49	0.17	0.35	-0.05	-0.38	0.28	0.77	-0.09	-0.52	0.34	0.70
Overweight	0.16	-0.04	0.36	0.12	-0.13	-0.33	0.08	0.23	0.33	0.06	0.60	0.02
Obese	-0.02	-0.24	0.20	0.85	-0.02	-0.27	0.22	0.86	-0.03	-0.35	0.29	0.84
Child's Age	-0.61	-0.81	-0.40	<0.001	-0.09	-0.15	-0.04	<0.001	0.24	0.18	0.30	<0.001
Underweight x Child's Age	-0.36	-1.02	0.31	0.29	-0.05	-0.21	0.12	0.59	-0.18	-0.39	0.03	0.09
Overweight x Child's Age	0.24	-0.16	0.65	0.24	0.13	0.03	0.23	0.01	0.03	-0.10	0.16	0.96
Obese x Child's Age	0.73	0.28	1.18	0.001	0.04	-0.08	0.15	0.52	0.21	0.06	0.36	0.01
Child's Age^2	0.20	0.14	0.26	<0.001	—	—	—	—	—	—	—	—
Underweight x Child's Age^2	0.10	-0.10	0.30	0.32	—	—	—	—	—	—	—	—
Overweight x Child's Age^2	-0.05	-0.17	0.07	0.42	—	—	—	—	—	—	—	—
Obese x Child's Age^2	-0.19	-0.32	-0.06	0.005	—	—	—	—	—	—	—	—
Gestational Age[b]	0.25	0.19	0.31	<0.001	0.21	0.14	0.27	<0.001	-0.01	-0.09	0.06	0.70
Gestational Age[b] x Child's Age	-0.33	-0.46	-0.20	<0.001	-0.06	-0.10	-0.03	<0.001	—	—	—	—
Gestational Age[b] x Child's Age^2	0.09	0.05	0.12	<0.001	—	—	—	—	—	—	—	—

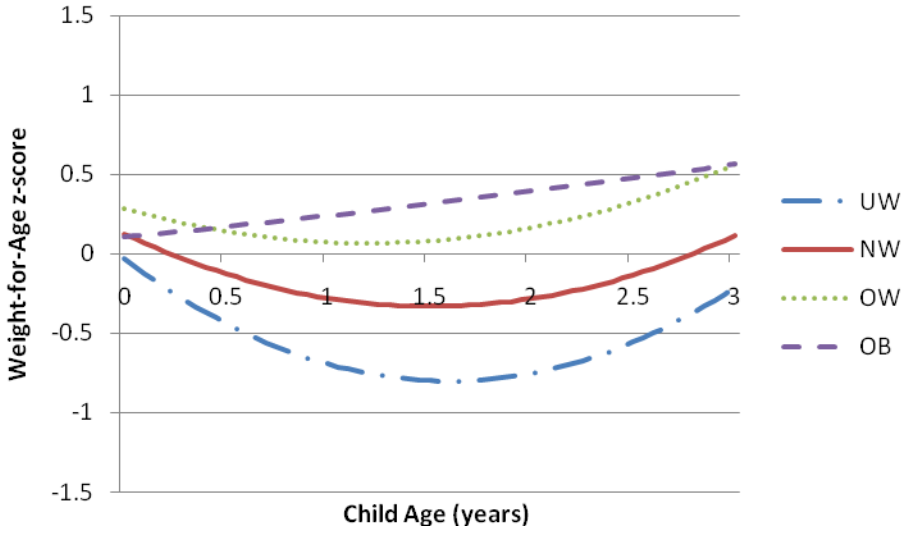
[a]Full models are adjusted for variables listed in table as well as income, education, race, smoking, marital status, and maternal height (centered at 65 inches). Reference is normal prepregnancy BMI.
[b]Gestational age is centered at 40 weeks.

Table 13. Full[a] linear mixed models of the association between categories of adequacy of gestational weight gain and offspring weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length z-scores (WLZ) between birth and 3 years in the Pregnancy, Infection, and Nutrition Study.

	WAZ (n=459)				LAZ (n=414)				WLZ (n=412)			
	β	95% CI		p	B	95% CI		p	β	95% CI		p
Intercept	-0.09	-0.53	0.36	0.70	0.32	-0.18	0.82	0.21	-0.49	-1.09	0.12	0.12
Inadequate	-0.08	-0.32	0.16	0.50	0.09	-0.16	0.33	0.49	-0.13	-0.41	0.36	0.38
Excessive I	0.17	0.00	0.34	0.05	0.19	0.02	0.37	0.03	0.16	0.04	0.36	0.11
Excessive II	0.28	0.04	0.53	0.02	0.16	-0.10	0.41	0.23	0.50	0.20	0.80	0.001
Child's Age	-0.72	-1.00	-0.44	<0.001	-0.11	-0.18	-0.04	<0.001	0.24	0.18	0.30	<0.001
Inadequate x Child's Age	0.17	-0.33	0.68	0.50	0.03	-0.10	0.16	0.64	—	—	—	—
Excessive I x Child's Age	0.29	-0.07	0.64	0.11	0.04	-0.05	0.33	0.37	—	—	—	—
Excessive II x Child's Age	0.62	0.14	1.10	0.01	0.13	0.01	0.25	0.03	—	—	—	—
Child's Age^2	0.23	0.15	0.31	<0.001	—	—	—	—	—	—	—	—
Inadequate x Child's Age^2	-0.03	-0.18	0.12	0.69	—	—	—	—	—	—	—	—
Excessive I x Child's Age^2	-0.08	-0.18	0.03	0.14	—	—	—	—	—	—	—	—
Excessive II x Child's Age^2	-0.16	-0.30	-0.02	0.03	—	—	—	—	—	—	—	—
Gestational Age[b]	0.26	0.19	0.32	<0.001	0.21	0.14	0.27	<0.001	-0.01	-0.09	0.06	0.70
Gestational Age[b] x Child's Age	-0.33	-0.46	-0.20	<0.001	-0.06	-0.10	-0.03	<0.001	—	—	—	—
Gestational Age[b] x Child's Age^2	0.09	0.05	0.12	<0.001	—	—	—	—	—	—	—	—

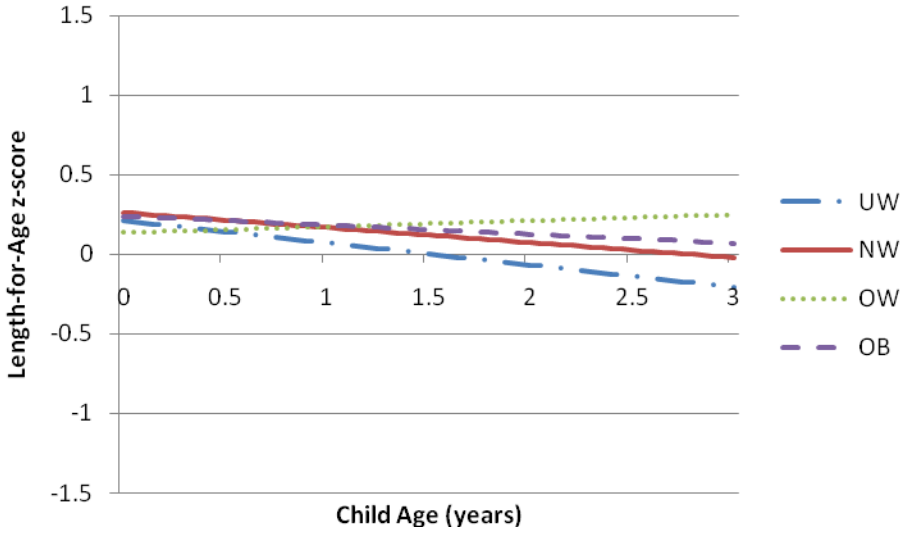
[a]Full models are adjusted for variables listed in table as well as income, education, race, smoking, marital status, prepregnancy diabetes mellitus, prepregnancy BMI (centered at 23 kg/m^2), and maternal height (centered at 65 inches). Reference is Adequate weight gain.
[b]Gestational age is centered at 40 weeks.

Figure 3. Predicted mean child weight-for-age z-scores (WAZ) from birth to 3 years associated with prepregnancy BMI categories based on the 2009 IOM recommendations in the Pregnancy, Infection, and Nutrition Study (n=459).[a]



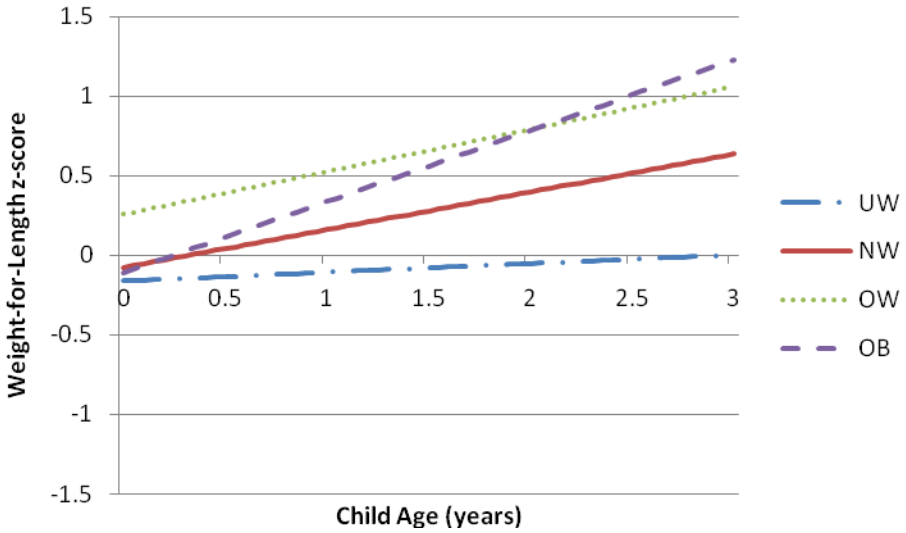
Legend: UW=underweight; NW=normal weight; OW=overweight; OB=obese
[a]Predicted mean child WAZ from birth (age 0 years) to 3 years are based on the full linear mixed model for WAZ displayed in Table 12.

Figure 4. Predicted mean child length-for-age z-scores (LAZ) from birth to 3 years associated with prepregnancy BMI categories based on the 2009 IOM recommendations in the Pregnancy, Infection, and Nutrition Study (n=414).[a]



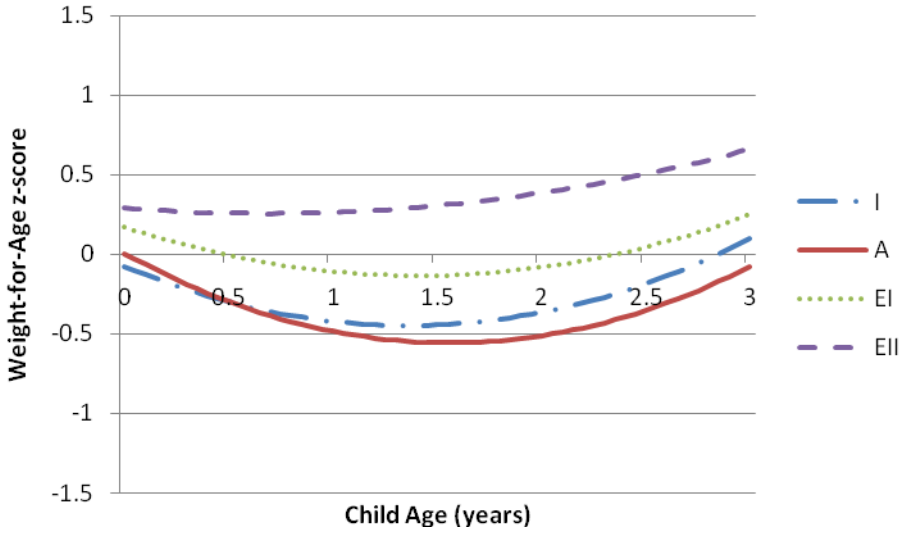
Legend: UW=underweight; NW=normal weight; OW=overweight; OB=obese
[a]Predicted mean child LAZ from birth (age 0 years) to 3 years are based on the full linear mixed model for LAZ displayed in Table 12.

Figure 5. Predicted mean child weight-for-length z-scores (WLZ) from birth to 3 years associated with prepregnancy BMI categories based on the 2009 IOM recommendations in the Pregnancy, Infection, and Nutrition Study (n=412).[a]



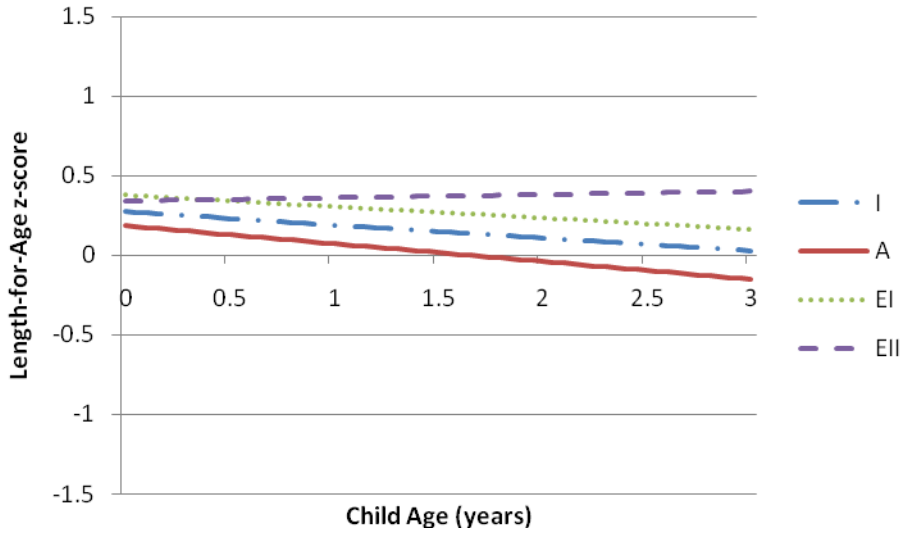
Legend: UW=underweight; NW=normal weight; OW=overweight; OB=obese
[a]Predicted mean child WLZ from birth (age 0 years) to 3 years are based on the full linear mixed model for WLZ displayed in Table 12.

Figure 6. Predicted mean child weight-for-age z-scores (WAZ) from birth to 3 years associated with gestational weight gain categories based on the 2009 IOM recommendations in the Pregnancy, Infection, and Nutrition Study (n=459).[a]



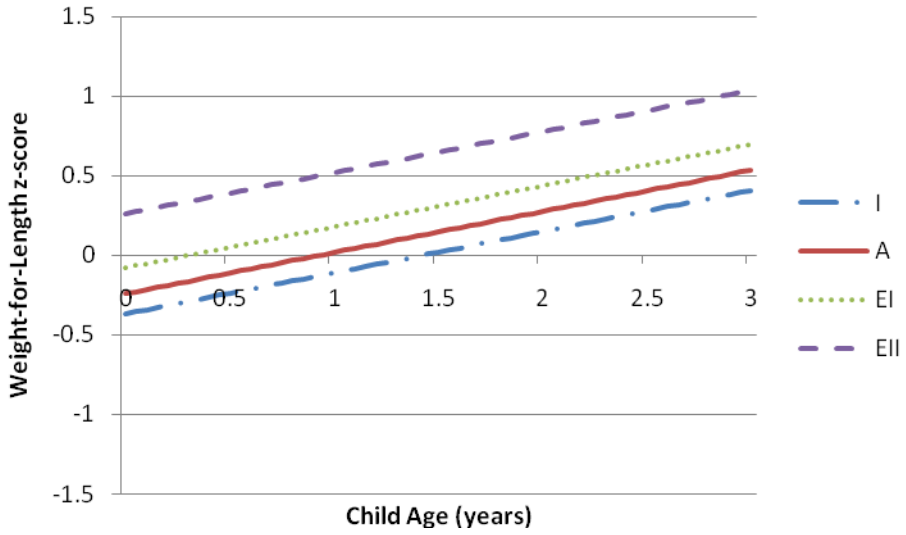
Legend: I=inadequate; A=adequate; EI=excessive I; EII=excessive II
[a]Predicted mean child WAZ from birth (age 0 years) to 3 years are based on the full linear mixed model for WAZ displayed in Table 13.

Figure 7. Predicted mean child length-for-age z-scores (LAZ) from birth to 3 years associated with gestational weight gain categories based on the 2009 IOM recommendations in the Pregnancy, Infection, and Nutrition Study (n=414).[a]



Legend: I=inadequate; A=adequate; EI=excessive I; EII=excessive II
[a]Predicted mean child LAZ from birth (age 0 years) to 3 years are based on the full linear mixed model for LAZ displayed in Table 13.

Figure 8. Predicted mean child weight-for-length z-scores (WLZ) from birth to 3 years associated with gestational weight gain categories based on the 2009 IOM recommendations in the Pregnancy, Infection, and Nutrition Study (n=412).[a]



Legend: I=inadequate; A=adequate; EI=excessive I; EII=excessive II
[a]Predicted mean child WLZ from birth (age 0 years) to 3 years are based on the full linear mixed model for WLZ displayed in Table 13.

References

1. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007-2008. *JAMA*. 2010;303(3):242-249.

2. Sharma AJ, Grummer-Strawn LM, Dalenius K, et al. Obesity prevalence among low-income, preschool-aged children—United States, 1998–2008. *MMWR Morb Mortal Wkly Rep*. 2009;58(28):769-773.

3. Latzer Y, Edmunds L, Fenig S, et al. Managing childhood overweight: Behavior, family, pharmacology, and bariatric surgery interventions. *Obesity*. 2009;17(3):411-423.

4. Catalano P, Ehrenberg H. The short-and long-term implications of maternal obesity on the mother and her offspring. *BJOG*. 2006;113(10):1126-1133.

5. Viswanathan M, Siega-Riz AM, Moos MK, et al. Outcomes of maternal weight gain. *Evidence report/technology assessment*. 2008;168:1-223.

6. Li C, Goran MI, Kaur H, Nollen N, Ahluwalia JS. Developmental trajectories of overweight during childhood: Role of early life factors. *Obesity*. 2007;15(3):760-771.

7. Siega-Riz AM, Herring AH, Carrier K, Evenson KR, Dole N, Deierlein A. Sociodemographic, perinatal, behavioral, and psychosocial predictors of weight retention at 3 and 12 months postpartum. *Obesity (Silver Spring)*. 2009;Dec(24):[Epub ahead of print].

8. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Protocol 1999-2000. http://www.cdc.gov.libproxy.lib.unc.edu/nchs/data/nhanes/meccomp.pdf.

9. Kuczmarski R, Ogden C, Grummer-Strawn L, et al. CDC Growth Charts: United States. *Adv Data*. 2000(314):1.

10. Vahratian A, Zhang J, Troendle JF, Savitz DA, Siega-Riz AM. Maternal prepregnancy overweight and obesity and the pattern of labor progression in term nulliparous women. *Obstet Gynecol*. 2004;104(5, Part 1):943-951.

11. Siega-Riz AM, Adair LS, Hobel CJ. Institute of medicine maternal weight gain recommendations and pregnancy outcome in a predominantly Hispanic population. *Obstet Gynecol*. 1994;84(4, Part 1):565-573.

12. IOM (Institute of Medicine), NRC (National Research Council). *Weight Gain during Pregnancy:Reexamining the Guidelines*. Washington, DC: The National Academies Press; 2009.

13. Bodnar LM, Siega-Riz AM, Arab L, Chantala K, McDonald T. Predictors of pregnancy and postpartum haemoglobin concentrations in low-income women. *Public Health Nutr*. 2007;7(6):701-711.

14. Deierlein AL, Siega-Riz AM, Herring A. Dietary energy density but not glycemic load is associated with gestational weight gain. *Am J Clin Nutr*. 2008;88(3):693-699.

15. Proctor BD, Dalaker J, US Census Bureau, Current Population Reports, P60-219. Poverty in the United States: 2001, U.S. Government Printing Office, Washington, DC. 2002.

16. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol*. 1982;144(7):768-773.

17. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48.

18. Pearl J. Causal diagrams for empirical research. *Biometrika*. 1995;82(4):669-688.

19. Harville DA. Maximum likelihood approaches to variance component estimation and to related problems. *Journal of the American Statistical Association*. 1977;72(358):320-338.

20. Ware JH. Linear models for the analysis of longitudinal studies. *American Statistician*. 1985:95-101.

21. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38(4):963-974.

22. Nohr EA, Timpson NJ, Andersen CS, Davey Smith G, Olsen J, Sørensen TI. Severe obesity in young women and reproductive health: The Danish National Birth cohort. *PLoS One*. 2009;4(12):e8444.

23. Bhattacharya S, Campbell DM, Liston WA, Bhattacharya S. Effect of body mass index on pregnancy outcomes in nulliparous women delivering singleton babies. *BMC Public Health*. 2007;7:168. 10.1186/1471-2458-7-168.

24. Hull HR, Dinger MK, Knehans AW, Thompson DM, Fields DA. Impact of maternal body mass index on neonate birthweight and body composition. *Am J Obstet Gynecol*. 2008;198(4):416e1-e6.

25. Sewell MF, Huston-Presley L, Super DM, Catalano P. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. *Obstet Gynecol*. 2006;195(4):1100-1103.

26. Salsberry PJ, Reagan PB. Dynamics of early childhood overweight. *Pediatrics*. 2005;116(6):1329-1338.

27. Whitaker RC. Predicting preschooler obesity at birth: The role of maternal obesity in early pregnancy. *Pediatrics*. 2004;114(1):e29-e36.

28. Mesman I, Roseboom TJ, Bonsel GJ, Gemke RJ, van der Wal MF, Vrijkotte TGM. Maternal pre-pregnancy body mass index explains infant's weight and BMI at 14 months: Results from a multi-ethnic birth cohort study. *Br Med J*. 2009;94(8):587-595.

29. Olson CM, Strawderman MS, Dennison BA. Maternal weight gain during pregnancy and child weight at age 3 years. *Matern Child Health J*. 2009;13(6):839-846.

30. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. *Obstet Gynecol*. 2007;196(4):322.e1-322.e8.

31. Yliharsila H, Kajantie E, Osmond C, Forsen T, Barker DJP, Eriksson JG. Body mass index during childhood and adult body composition in men and women aged 56-70 y. *Am J Clin Nutr*. 2008;87(6):1769-1775.

32. Baird J, Osmond C, MacGregor A, Snieder H, Hales C, Phillips D. Testing the fetal origins hypothesis in twins: The Birmingham twin study. *Diabetologia*. 2001;44(1):33-39.

33. Loos RJF, Beunen G, Fagard R, Derom C, Vlietinck R. Birth weight and body composition in young women: A prospective twin study. *Am J Clin Nutr*. 2002;75(4):676-682.

34. Allison D, Paultre F, Heymsfield S, Pi-Sunyer F. Is the intra-uterine period really a critical period for the development of adiposity? *Int J Obes*. 1995;19(6):397-402.

35. Chen H, Simar D, Lambert K, Mercier J, Morris MJ. Maternal and postnatal overnutrition differentially impact appetite regulators and fuel metabolism. *Endocrinology*. 2008;149(11):5348-5356.

36. Muhlhausler BS, Adam CL, Findlay PA, Duffield JA, McMillen IC. Increased maternal nutrition alters development of the appetite-regulating network in the brain. *FASEB J*. 2006;20(8):1257-1259.

37. Howie GJ, Sloboda DM, Kamal T, Vickers MH. Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet. *Exp Physiol*. 2009;587(4):905-915.

38. Bugatto F, Fernández-Deudero Á, Bailén Á, Fernández-Macías R, Hervías-Vivancos B, Bartha JL. Second-trimester amniotic fluid proinflammatory cytokine levels in normal and overweight women. *Obstet Gynecol*. 2010;115(1):127-133.

39. Challier JC, Basu S, Bintein T, et al. Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. *Placenta*. 2008;29(3):274-281.

40. Rising R, Lifshitz F. Lower energy expenditures in infants from obese biological mothers. *Nutr J*. 2008;7:15. 10.1186/1475-2891-7-15.

41. Rising R, Lifshitz F. Relationship between maternal obesity and infant feeding-interactions. *Nutr J*. 2005;4:17.

42. Catalano PM, Farrell K, Thomas A, et al. Perinatal risk factors for childhood obesity and metabolic dysregulation. *Am J Clin Nutr*. 2009;90(5):1303-1313.

43. Taveras EM, Rifas-Shiman SL, Belfort MB, Kleinman KP, Oken E, Gillman MW. Weight status in the first 6 months of life and obesity at 3 years of age. *Pediatrics*. 2009;123(4):1177-1183.

44. Akaboshi I, Haraguchi Y, Mizumoto Y, Kitano A, Kan H. Taller stature after postnatal rapid weight gain in early infancy predicts overweight status at age 3. *Acta Pædiatrica*. 2008;97(10):1460-1464.

45. Stovitz SD, Hannan PJ, Lytle LA, Demerath EW, Pereira MA, Himes JH. Child height and the risk of young-adult obesity. *Am J Prev Med*. 2010;38(1):74-77.

CHAPTER VII

CONCLUSION

The purpose of the current research was to determine how the modifiable maternal behavioral factors of prepregnancy BMI and gestational weight gain influence offspring anthropometric outcomes between birth and 3 years. Our specific aims were to determine how prepregnancy BMI and adequacy of gestational weight gain relate to: 1) infant WAZ, LAZ, and WLZ at 6 months and rapid infant weight gain between birth and 6 months; 2) child BMI z-scores and risk of overweight/obesity at 3 years; 3) child WAZ, LAZ, and WLZ from birth to 3 years.

The following sections review the findings from this research and acknowledge its strengths and limitations. Public health implications and directions for future research are discussed.

Summary of Key Findings

Taken collectively, our findings suggest that prepregnancy BMI and gestational weight gain, based on the 2009 IOM guidelines, are positively associated with offspring anthropometric outcomes measured within the first 3 years of life. The results identified three key findings: 1) Prepregnancy BMI and gestational weight gain differentially influence child WAZ, LAZ, and WLZ at birth and at 6 months, and their rates of change from birth to 3 years. 2) Children of overweight and obese mothers have higher WAZ and

WLZ beginning in infancy through 3 years and are at greater risk of being overweight or obese at 3 years compared to children of women with normal BMI. 3) Excessive gestational weight gain is associated with changes in WAZ, LAZ, and WLZ from birth to 3 years. Children of mothers with excessive weight gain (that does not exceed 200% of the recommendations) have higher WAZ and LAZ at birth and at 6 months and higher BMI z-scores at 3 years compared to children of women with adequate weight gain, but changes in weight and length appear to be proportional. Children of mothers with excessive weight gain ≥200% of the recommendations have changes in weight that exceed those in length; they have higher WAZ and WLZ from birth through 3 years and are at greater risk of obesity at 3 years compared to children of mothers with adequate weight gain.

Review of Aims

In Chapter IV we examined the associations between infant WAZ, LAZ, and WLZ at 6 months as well as rapid infant weight gain between birth and 6 months with the selected maternal exposures. We found that while both prepregnancy BMI and gestational weight gain were positively associated with WAZ, only gestational weight gain was associated with LAZ at 6 months. Prepregnancy overweight and obesity and excessive weight gain ≥200% of the IOM recommended amount were associated with increased WLZ. These results suggest that the relative body size of infants at 6 months differs by maternal exposure. Risk estimates for rapid infant weight gain, a measure of infant growth rate, increased across maternal exposure categories, but none were statistically significant in the full models.

In Chapter V, we examined the associations between child BMI at 3 years and the selected maternal exposures. Prepregnancy overweight and obesity were associated with higher child BMI z-scores and increased risks of BMI≥85th and ≥95th percentiles compared to normal prepregnancy BMI. Excessive gestational weight gains were associated with higher child BMI z-scores but only excessive weight gain ≥200% of the IOM recommendations was associated with an increased risk of BMI≥95th percentile compared to inadequate/adequate weight gain.

Lastly in Chapter VI, we utilized longitudinal data analysis to examine the influence of prepregnancy BMI and gestational weight gain on child WAZ, LAZ, and WLZ between birth and 3 years. Our results suggest that prepregnancy BMI and gestational weight gain differentially influence the selected anthropometric outcomes and their rate of change from birth to 3 years. At birth, regression estimates of WAZ, LAZ, and WLZ were similar across categories of prepregnancy BMI (with the exception of higher WLZ among neonates of overweight women) whereas, WAZ and LAZ were higher among women with excessive weight gain and WAZ and WLZ were significantly higher among women with excessive weight gain ≥200% of the recommendations compared to women with adequate weight gain. Prepregnancy obesity was associated with greater rates of increase in WAZ and WLZ from birth to 3 years compared to normal prepregnancy BMI. Excessive weight gain ≥200% of the recommendations was associated with greater rates of increase in WAZ and LAZ from birth to 3 years compared to adequate weight gain. Compared to the lower categories of prepregnancy BMI and gestational weight gain, prepregnancy overweight and obesity and excessive

weight gain ≥200% of the recommendations were associated with distinctly higher mean predicted values of WAZ and WLZ that persisted across the study period.

Study Strengths

The PIN study is a contemporary, prospective, longitudinal pregnancy cohort that reflects recent trends in pediatric and maternal obesity and excessive gestational weight gains. The study collected measurements of gestational weight gain and child weights and lengths/heights at various time points between birth and 3 years. It also included collection of key covariates such as sociodemographic characteristics, prenatal smoking, maternal glucose tolerance status, and infant feeding behaviors, which allowed for appropriate adjustment for confounders in the statistical models.

There is limited research that examines and contrasts the relationships of prepregnancy BMI and gestational weight gain with infant postnatal growth or using longitudinal measurements; therefore, our studies are valuable contributions to the current literature. Prepregnancy BMI and gestational weight gain were categorized using the most recent IOM guidelines released in May 2009, which are specific for maternal prepregnancy BMI. These guidelines are used by healthcare professionals to advise women about appropriate gestational weight gains. Our research evaluated these guidelines with respect to child anthropometric development and provides clinicians with results that they can easily interpret and communicate to their patients.

We examined the effects of prepregnancy BMI and gestational weight gain on anthropometric outcomes at various time points between birth and 3 years. The age interval of birth to 6 months has been identified as a critical window in infancy associated

with an increased risk of future overweight/obesity development[1-4] and high systolic blood pressure at 3 years.[5] Additionally, childhood overweight during the preschool years is a predictor of later obesity that tracks into adolescence and adulthood.[6] Child BMI z-score ≥95th percentile has a sensitivity of 88% and a specificity of 94% to predict high body fat percentage[7] and BMI z-score ≥85th percentile is useful for identifying excess fat in children[8] as well as predicting future weight status and disease risk.[9]

Study Limitations

There are several recognized limitations of this research, many of which were discussed in the previous chapters and are reviewed here. First, the generalizability of the PIN study population is narrow given the fact that women in the sample had to receive care from the participating prenatal clinics, meet eligibility criteria for the PIN Study, and complete several years of postpartum follow-up interviews along with their offspring. In a prospective cohort design, the greatest concern is selective loss to follow-up[10], with bias resulting if those who remain in the study experience a different exposure-outcome relationship than those who are lost. Although it is unlikely that the relationships between child anthropometric outcomes and prepregnancy BMI or gestational weight gain were modified by unknown factors related to inclusion in the study, we were able to indirectly evaluate this by comparing the baseline characteristics between included and excluded mother-offspring pairs across the PIN studies. Losses from high risk groups, such as obese or women with excessive weight gain ≥200% of the recommendations may have weakened the observed associations reported here.

Second, with the exception of birthweight and the 3 year measurements, infant anthropometric measurements came from well-baby visits recorded on doctors' cards, which mothers returned to study staff at the 12-month visit. These measurements are subject to the inherent errors related to measurements made in the clinical setting since they were collected at multiple clinic sites and medical staffs were not trained using a standardized measurement method. Additionally, birth length was not collected, the number of measurements and ages at which they were assessed differed for the children, and many mothers did not return the cards.

Third, anthropometric measurements are not direct measures of adiposity. WAZ, LAZ, and WLZ provide estimates of infant body size relative to the U.S. reference population. Child BMI is a measure of excess weight rather than excess fat. Direct measurements, such as dual-energy x-ray absorpiometry, are preferred.

Fourth, despite the fact that women were enrolled in PIN 3 during early pregnancy, enrollment within the first month of pregnancy is rare and therefore a self-reported measure of prepregnancy weight was used in the analyses. Since prepregnancy weight is used in the calculation of prepregnancy BMI (height was measured) and gestational weight gain, misclassification of women with regards to the child outcomes may have occurred. Women of reproductive ages have a tendency to under-estimate their weights and overestimate their heights.[11] This type of error would result in an underestimation of prepregnancy BMI and an overestimation of total gestational weight gain.

Lastly, due to the observational nature of our data, we cannot entirely exclude the possibility that important unknown confounders were neglected in the data collection and

analysis or that adjustment for confounders was incomplete, which is a concern for all observational studies.

Public Health Implications

Pediatric obesity is a national health epidemic with nearly one third of children and adolescents being overweight or obese.[12] Recently, First Lady Michelle Obama launched a multi-faceted nationwide campaign, which focuses on healthy eating and physical activity, to eliminate pediatric obesity in one generation. However, results from animal and human studies suggest that the prenatal environment, specifically exposure to increased maternal nutrition via prepregnancy obesity and/or excess nutrient intakes during gestation, plays an important role in the development of overweight and obesity beginning in utero. In the current research, we found that prepregnancy BMI and gestational weight gain, based on the 2009 IOM guidelines, are positively associated with postnatal growth measured within the first 3 years of life. We also found that excessive gestational weight gain ≥200% of the recommendations and prepregnancy overweight/obesity similarly influenced child WAZ and WLZ between birth and 3 years and risk of obesity at 3 years.

Our results emphasize the need for preconceptional counseling and intervention efforts that target lowering BMI before women begin trying to get pregnant and inform women about the importance of achieving adequate gestational weight gains during pregnancy. Such interventions may also have the added benefit of improving the postnatal environment by altering maternal behaviors related to pediatric obesity, including infant/child nutrition, sleeping, and physical activity/screen-watching

behaviors.[13] Considering that nearly half of pregnancies are unplanned[14] and many women do not obtain prenatal care within the first trimester[15,16], intervention efforts may be challenged in their ability to target prepregnancy BMI, especially among high-risk populations; however, our research suggests that promotion of adequate gestational weight gains, regardless of prepregnancy BMI, during the prenatal period is still important for preventing pediatric obesity.

Besides organized interventions within communities and health care organizations, women's health care providers play a central role in monitoring prepregnancy BMI status and educating women about appropriate gestational weight gains. Due to their consistent contact with women before, during, and after pregnancy, health care providers are in the unique position to provide women with guidance and resources regarding physical activity, nutrition, and psychological counseling services. Programs and strategies to inform health care providers about the importance of implementing the 2009 IOM guidelines for normal prepregnancy BMI and adequate gestational weight gain in their daily practices are necessary.

Directions for Future Research

Further investigation is necessary to better understand the influence of maternal prepregnancy BMI and gestational weight gain on the development of overweight and obesity, as well as chronic disease risk factors, in infants and children. We identified four directions for future research:

1) *Precise measurements of gestational weight gain*. Gestational weight gain reflects maternal tissue, fat, and fluid expansion as well as fetal and placental mass.

Previous studies reported positive associations for birthweight with maternal body water[17], fat-free mass[18], and pattern of gestational weight gain.[19] To understand the underlying biology of the association between gestational weight gain and offspring anthropometric outcomes, it is necessary to have precise measurements of the components of gestational weight gain. Gestational weight gain is also reflective of energy intakes and expenditure during pregnancy. Evidence from animal and human studies suggests that maternal diet macronutrient composition may be associated with offspring anthropometric and disease outcomes.[20-24] Considering that food sources and dietary patterns in the United States have changed over the past several decades[25-27], future studies should also address the effects of maternal diet on offspring outcomes and determine how they relate to gestational weight gain.

2) *Precise measurements of infant/child body composition.* The majority of studies that investigated associations between child anthropometric outcomes and maternal exposures, including the current studies, did not have information on infant/child body composition. As mentioned, anthropometric measurements are not direct measures of adiposity. We reported differential influences of prepregnancy BMI and gestational weight gain on WAZ, LAZ, and WLZ between birth and 3 years. Gestational weight gain was associated with WAZ and LAZ while prepregnancy BMI was associated only with WAZ; however, excessive weight gain≥200% of the recommendations and prepregnancy overweight/obesity were associated with higher WAZ and WLZ between birth and 3 years and increased risk of obesity at 3 years. Precise measurements of fat and fat-free mass

are needed to understand how they relate to our findings for WAZ, LAZ, and WLZ at birth and over time.

3) *Distinction of prenatal vs. postnatal exposures.* Our research addressed the total effects of prepregnancy BMI and gestational weight gain on offspring outcomes. Previous research indicates that prepregnancy BMI and gestational weight gain may be associated with offspring anthropometric outcomes due to influences on fetal growth and body composition; metabolic, appetite, and hormonal programming; and the postnatal environment. Since prepregnancy BMI is likely to be highly correlated with BMI in the postnatal period, the observed associations between prepregnancy BMI and child anthropometrics may partly reflect the effects of maternal BMI and its related environmental factors (such as child diet and physical activity) in the postnatal period. Similarly, although gestational weight gain models were adjusted for prepregnancy BMI, it is possible that maternal behaviors related to gestational weight gain remain in the postnatal period as well. In our causal models, we were able to adjust for many prenatal confounders that would pervade into the postnatal period, such as household income and education. We also performed additional analyses with adjustments for birthweight z-scores and infant feeding behaviors. However, longitudinal analyses that include data collection prior to pregnancy throughout early childhood are needed to help distinguish prenatal and postnatal effects.

4) *Utilization of recent cohorts that reflect current trends in maternal and pediatric obesity as well as excessive gestational weight gains.* As discussed in the *Background and Significance* section, there is a need for studies that examine the

associations between maternal exposures and offspring anthropometrics/adiposity using recent cohorts. Previous studies that used historical cohorts may have lacked adequate variation or power in their study populations to detect significant associations. In our pregnancy cohort using data collected 2001-2008, approximately 30% of women were overweight or obese, 14% of women had excessive weight gain ≥200% of the recommendations, and 22% of children were overweight/obese at 3 years. These high percentages of maternal and pediatric obesity as well as excessive weight gain≥200% of the recommendations highlight the need for studies that examine associations within higher classes of obesity and over ranges of excessive weight gain.

There is also a need for more research on this topic in general, notably for gestational weight gain exposure. We identified four studies that examined the relationship between gestational weight gain and offspring weight outcomes during infancy or the preschool years.[28-31] Only one of these studies reported a positive association; Oken et.al.[31] found that compared to children of women with inadequate weight gains, children of women with adequate and excessive gains had significantly higher BMI z-scores and were more likely to be obese (≥95th percentile) at 3 years. We did not replicate this finding in our research; however, we did find that excessive weight gain ≥200% of the IOM recommendations is associated with risk of obesity at 3 years.

We also found that excessive weight gain ≥200% of the recommendations but not excessive weight gain below this threshold is associated with disproportionately higher WAZ than LAZ, resulting in higher WLZ between birth

and 3 years. This suggests that lumping women with excessive weight gains into a single category for statistical analyses may be problematic for estimating associations of gestational weight gain and offspring anthropometrics, especially risks of child overweight and obesity. Considering the suggested implications of gestational weight gain for infant and child outcomes and the fact that it is a modifiable behavior, future studies using improved methodology are required to confirm our results as well as inform preconception/prenatal intervention and policy efforts.

References

1. Ekelund U, Ong K, Linne Y, et al. Upward weight percentile crossing in infancy and early childhood independently predicts fat mass in young adults: The Stockholm Weight Development Study (SWEDES). *Am J Clin Nutr*. 2006;83(2):324-330.

2. Botton J, Heude B, Maccario J, Ducimetiere P, Charles MA. Postnatal weight and height growth velocities at different ages between birth and 5 y and body composition in adolescent boys and girls. *Am J Clin Nutr*. 2008;87(6):1760-1768.

3. Dennison BA, Edmunds LS, Stratton HH, Pruzek RM. Rapid infant weight gain predicts childhood overweight. *Obesity*. 2006;14(3):491-499.

4. Chomtho S, Wells JCK, Williams JE, Davies PSW, Lucas A, Fewtrell MS. Infant growth and later body composition: Evidence from the 4-component model. *Am J Clin Nutr*. 2008;87(6):1776-1784.

5. Belfort MB, Rifas-Shiman SL, Rich-Edwards J, Kleinman KP, Gillman MW. Size at birth, infant growth, and blood pressure at three years of age. *J Pediatr*. 2007;151(6):670-674.

6. Krebs NF, Jacobson MS, American Academy of Pediatrics Committee on Nutrition. Prevention of pediatric overweight and obesity. *Pediatrics*. 2003;112(2):424-430.

7. Reilly JJ, Dorosty AR, Emmett PM. Identification of the obese child: Adequacy of the body mass index for clinical practice and epidemiology. *Int J Obes*. 2000;24(12):1623-1627.

8. Field AE, Laird N, Steinberg E, Fallon E, Semega-Janneh M, Yanovski JA. Which metric of relative weight best captures body fatness in children? *Obesity*. 2003;11(11):1345-1352.

9. Field AE, Cook NR, Gillman MW. Weight status in childhood as a predictor of becoming overweight or hypertensive in early adulthood. *Obes Res*. 2005;13(1):163.

10. Hunt JR, White E. Retaining and tracking cohort study members. *Epidemiol Rev*. 1998;20(1):57-70.

11. Brunner Huber LR. Validity of self-reported height and weight in women of reproductive age. *Matern Child Health J*. 2007;11(2):137-144.

12. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007-2008. *JAMA*. 2010;303(3):242-249.

13. Anderson SE, Whitaker RC. Household routines and obesity in US preschool-aged children. *Pediatrics*. 2010;125(3):420-428.

14. Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. *Perspectives on Sexual and Reproductive Health*. 2006;38(2):90-96.

15. Martin JA, Hamilton BE, Sutton PD, et al. Births: Final data for 2005. *National vital statistics reports*. 2007;56(6):1-104.

16. Alexander GR, Kogan MD, Nabukera S. Racial differences in prenatal care use in the United States: Are disparities decreasing? *Am J Public Health*. 2002;92(12):1970-1975.

17. Lederman SA, Paxton A, Heymsfield SB, Wang J, Thornton J, Pierson RN. Maternal body fat and water during pregnancy: Do they raise infant birth weight? *Obstet Gynecol*. 1999;180(1):235-240.

18. Mardones-Santander F, Salazar G, MD PR, Villarroel L. Maternal body composition near term and birth weight. *Obstetrics & Gynecology*. 1998;91(6):873-877.

19. Abrams B, Selvin S. Maternal weight gain pattern and birth weight. *Obstetrics & Gynecology*. 1995;86(2):163-169.

20. Watson PE, McDonald BW. The association of maternal diet and dietary supplement intake in pregnant New Zealand women with infant birthweight. *Eur J Clin Nutr*. 2009:1-10.

21. Scholl TO, Chen X, Khoo CS, Lenders C. The dietary glycemic index during pregnancy: Influence on infant birth weight, fetal growth, and biomarkers of carbohydrate metabolism. *Am J Epidemiol*. 2004;159(5):467-474.

22. Clapp JF. Maternal carbohydrate intake and pregnancy outcome. *Proc Nutr Soc*. 2007;61(01):45-50.

23. Howie GJ, Sloboda DM, Kamal T, Vickers MH. Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet. *Exp Physiol*. 2009;587(4):905-915.

24. Bayol SA, Simbi BH, Stickland NC. A maternal cafeteria diet during gestation and lactation promotes adiposity and impairs skeletal muscle development and metabolism in rat offspring at weaning. *J Physiol (Lond)*. 2005;567(3):951-961.

25. Piernas C, Popkin BM. Snacking increased among US adults between 1977 and 2006. *J Nutr*. 2010;140(2):325-332.

26. Duffey KJ, Popkin BM. Shifts in patterns and consumption of beverages between 1965 and 2002. *Obesity*. 2007;15(11):2739-2747.

27. Nielsen SJ, Popkin BM. Patterns and trends in food portion sizes, 1977-1998. *JAMA*. 2003;289(4):450-453.

28. Ay L, Van Houten VAA, Steegers EAP, et al. Fetal and postnatal growth and body composition at 6 months of age. *J Clin Endocrinol Metab*. 2009;94(6):2023-2030.

29. Whitaker RC. Predicting preschooler obesity at birth: The role of maternal obesity in early pregnancy. *Pediatrics*. 2004;114(1):e29-e36.

30. Olson CM, Strawderman MS, Dennison BA. Maternal weight gain during pregnancy and child weight at age 3 years. *Matern Child Health J*. 2009;13(6):839-846.

31. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. *Obstet Gynecol*. 2007;196(4):322.e1-322.e8.

APPENDIX

Table

Table 1. Comparison of distributions of selected baseline characteristics of PIN 3 mother-infant pairs who were eligible but did not participate in PIN Postpartum (n=480) and those who participated in PIN Postpartum (n=689).

	Eligible but did not participate in PIN Postpartum (n=480)		Participated in PIN Postpartum (n=689)		(480 vs. 689)
Variable	**N**	**Mean (SD)/ Frequency**	**N**	**Mean (SD)/ Frequency**	***P* value**
Age (years)	480	28.7 (5.8)	689	29.5 (5.5)	0.02
Age (years)	480		689		
16-24	118	24.6	132	19.2	
25-29	136	28.3	195	28.3	0.10
30-34	148	30.8	250	36.3	
35-47	78	16.3	112	16.3	
Prepregnancy BMI (kg/m^2)	469	26.4 (7.4)	687	25.36 (6.8)	0.01
Prepregnancy BMI Category (kg/m^2)					
Underweight	25	5.3	33	4.8	
Normal Weight	229	48.8	399	58.1	0.01
Overweight	97	20.7	133	19.4	
Obese	118	25.2	122	17.8	
Gestational Weight Gain (kg)	467	14.78 (6.3)	684	15.45 (6.0)	0.07
Adequacy of Gestational Weight Gain	467	1.47 (0.8)	684	1.46 (0.7)	0.76
Gestational Weight Gain	467		684		
Inadequate	63	13.5	83	12.1	
Adequate	111	23.8	180	26.3	0.56
Excessive I	206	44.1	306	44.7	
Excessive II	87	18.6	115	16.8	
Race	480		688		
Non-Black	358	74.6	586	85.2	<0.001

Black	122	25.4	102	14.8	
Marital Status	480		689		
Married	329	68.5	554	80.4	<0.001
Other	151	31.5	135	19.6	
Education	480		689		
≤ Grade 12	115	24.0	118	17.1	
Grades 13 -16	228	47.5	323	46.9	0.003
≥ Grade 17	137	28.5	248	36.0	
Family Income (% Poverty)	455		667		
<185%	117	25.7	123	18.4	
185-350%	88	19.3	136	20.4	0.01
>350%	250	55.0	408	61.2	
Glucose Tolerance	423	103.5 (1.2)	608	104.4 (1.0)	0.54
Glucose Tolerance	442		640		
Normal	388	87.8	559	87.3	
Impaired Glucose Tolerance	38	8.6	51	8.0	0.67
Gestational Diabetes	16	3.6	30	4.7	
Pre-existing Diabetes Mellitus	479		687		
No	460	96.0	656	95.5	0.77
Yes	19	4.0	31	4.5	
Parity	480		689		
Nulliparous	221	46.0	334	48.5	0.44
1 or More Births	259	54.0	355	51.5	
Smoking in Months 1-6 of Pregnancy	424		653		
No	362	85.4	601	92.0	0.001
Yes	62	14.6	52	8.0	

Infant Sex	480		689		
Male	237	49.4	371	53.8	0.14
Female	243	50.6	318	46.2	
Infant Birthweight	480	3280.3 (780.2)	689	3332.6 (677.5)	0.22
Infant Birthweight (g)	480		689		
<2500	47	9.8	49	7.1	
2500-<3000	85	17.7	103	15.0	
3000-<3500	173	36.0	290	42.1	0.15
3500-<4000	132	27.5	180	26.1	
≥ 4000	43	9.0	67	9.7	
Gestational Age (weeks)	480	38.2 (2.4)	689	38.6 (2.2)	0.02
Term Birth	480		689		
Term	410	85.4	602	87.4	0.34
Preterm	70	14.6	87	12.6	

Table 2. Comparison of distributions of selected baseline characteristics of PIN Postpartum mother-infant pairs who participated in PIN Pediatric (n=409) and those who were eligible but did not participate in PIN Pediatric (n=280).

	Participated at 36 months (n=409)		Participated in PINPost (3 or 12m) but did not at 36 months (n=280)		(409 vs. 280)
Variable	**N**	**Mean(SD)/ Frequency,%**	**N**	**Mean (SD)/ Frequency,%**	**p**
Age (years)	409	30.2 (5.2)	280	28.4 (5.8)	<0.001
Age (years)	409		280		
16-24	60	14.7	72	25.7	0.002
25-29	124	30.3	71	25.4	
30-34	149	36.4	101	36.1	
35-47	76	18.6	36	12.9	
Prepregnancy BMI (kg/m^2)	408	25.0 (6.7)	279	25.90 (7.0)	0.09
Prepregnancy BMI Category (kg/m^2)	408		279		
Underweight	18	4.4	15	5.4	
Normal Weight	256	62.8	143	51.3	0.02
Overweight	73	17.9	60	21.5	
Obese	61	15.0	61	21.9	
Gestational Weight Gain (kg)	408	15.8 (6.2)	276	15.0 (5.8)	0.11
Adequacy of Gestational Weight Gain	408	1.5 (0.8)	276	1.5 (0.7)	0.67
Gestational Weight Gain (IOM Category)	408		276		

Inadequate	53	13.0	30	10.8	
Adequate	105	25.7	75	27.2	0.69
Excessive I	186	45.6	120	25.2	
Excessive II	64	15.7	51	18.5	
Race	408		280		
White/other	366	89.7	220	78.6	<0.001
Black	42	10.3	60	21.4	
Marital Status	409		280		
Married	355	86.8	199	71.1	<0.001
Other	54	13.2	81	28.9	
Education	409		280		
≤ Grade 12	47	11.5	71	25.4	
Grades 13 -16	208	50.9	115	41.1	<0.001
≥ Grade 17	154	37.7	94	33.6	
Family Income (% Poverty)	401		266		
<185%	53	13.2	70	26.3	
185-350%	76	19.0	60	22.6	<0.001
>350%	272	67.8	136	51.1	
Glucose Tolerance	381	107.68 (26.9)	254	104.96 (27.0)	0.21
Glucose Tolerance	385		255		
Normal	336	87.3	223	87.5	

Impaired Glucose Tolerance	32	8.3	19	7.5	0.85
Gestational Diabetes	17	4.4	13	5.1	
Pre-existing Diabetes Mellitus	409		278		
No	388	94.9	268	96.4	0.45
Yes	21	5.1	10	3.6	
Parity	409		280		
Nulliparous	202	49.4	132	47.1	0.59
1 or More Births	207	50.6	148	52.9	
Smoking in Months 1-6 of Pregnancy	399		254		
Yes	370	92.7	231	90.9	0.46
No	29	7.3	23	9.1	
Infant Sex	409		280		
Male	221	54.0	150	53.6	0.94
Female	188	46.0	130	46.4	
Infant Birthweight	409	3358.8 (720.5)	280	3294.3 (608.6)	0.22
Infant Birthweight (g)					
<2500	24	5.9	25	8.9	
2500-<3000	61	14.9	42	15.0	
3000-<3500	186	45.5	104	37.1	0.03
3500-<4000	93	22.7	87	31.1	
≥ 4000	45	11.0	22	7.9	

Gestational Age (weeks)	409	38.6 (2.1)	280	38.4 (2.3)	0.16
Term Birth	409		280		
Term	359	87.8	243	86.8	0.73
Preterm	50	12.2	37	13.2	