ASSOCIATION BETWEEN MATERNAL DIETARY PATTERNS DURING PREGNANCY AND EARLY CHILDHOOD GROWTH OUTCOMES

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ABSTRACT

Chantel LeAnn Martin: Association between Maternal Dietary Patterns during Pregnancy and Early Childhood Growth Outcomes
(Under the direction of Anna Maria Siega-Riz)

Rates of childhood obesity have increased over the last few decades. Overweight and obesity during childhood is associated with obesity in adolescence and adulthood, as well as increased risk of immediate and long-term health consequences. Because the risk of child obesity may be programmed before birth, understanding the role of the fetal environment is imperative. Maternal diet quality during pregnancy is a modifiable factor that may influence the development of child obesity; however, few studies have examined this association.

We used data from the Pregnancy, Infection, and Nutrition study, a prospective, longitudinal pregnancy cohort, to examine the role of maternal dietary patterns during pregnancy on maternal cardiometabolic markers and child growth from birth to 36 months. Dietary patterns were derived using the Dietary Approaches to Stop Hypertension (DASH) diet and latent class analysis (LCA). Three dietary patterns emerged from LCA characterized by high intakes of: 1) hamburgers, hot dogs, bacon, French fries, fried chicken, white bread, and soft drinks; 2) some vegetables, fruit juice, refined grains, mixed dishes, processed meat, and empty calorie foods; and 3) fruits, vegetables, whole grains, low fat dairy, breakfast bars, and water. DASH scores were categorized into tertiles.

Using multivariable linear regression, we found that healthier diet quality (highest DASH tertile and Latent Class 3) was associated with lower insulin, insulin resistance, and triglyceride

levels compared to poorer diet quality (lowest DASH tertile and Latent Class 1). At 36 months, there was suggestion of a positive association between higher maternal DASH score and BMI z-score. Using linear mixed models, we found that, on average, children of mothers with a DASH diet score <28, representing poorer diet quality, had a higher weight-for-height z-score from birth to 36 months than children of mothers with a DASH diet score ≥28. We did not find evidence that maternal DASH score influenced the rate of childhood growth from birth to 36 months.

Our results support maternal diet quality as a modifiable behavioral factor that may be useful in intervention efforts to improve maternal cardiometabolic health during pregnancy and reduce the burden of childhood obesity.

To God and my family,
this would not be possible without you.

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LIST OF ABBREVIATIONS

AHEI	Alternate Healthy Eating Index
AIC	Akaike's Information Criteria
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DASH	Dietary Approaches to Stop Hypertension
HOMA-IR	Homeostasis Model for Assessment of Insulin Resistance
kcals	kilocalories
LCA	Latent Class Analysis
LGA	Large-for-gestational age
MET	Metabolic Equivalent
NHANES	National Health and Nutrition Examination Survey
NND	New Nordic Diet
PIN	Pregnancy, Infection, and Nutrition
RCT	Randomized Controlled Trial
SD	Standard Deviation
SGA	Small-for-gestational age
UNC	University of North Carolina
US	United States
USDA	United States Department of Agriculture
WHZ	Weight-for-Height z-score
WIC	Women, Infant, and Children

CHAPTER I: INTRODUCTION

Animal studies suggest that maternal overnutrition—defined as poor maternal diet quality, high maternal body mass index (BMI), and the presence of gestational diabetes—influences the development of offspring obesity by altering fetal energy regulation, appetite regulation, and adipocyte metabolism (1, 2). Despite this evidence from animal literature, the relationship is not well understood in human populations, where the focus is mainly on maternal BMI and gestational diabetes. Further, animal studies demonstrate that diet quality may play a more important role in offspring weight status than the intake of macronutrients and individual foods. Specifically, pregnant rats fed "high-fat" and "junk food" diets produced obese offspring (3-6). Unfortunately, there is limited research in humans to support animal findings about diet quality during pregnancy.

Analyses of dietary patterns have become useful in epidemiological studies aimed to investigate the overall quality of diet on health outcomes. Dietary patterns involve examination of the combinations of foods and nutrients eaten together, while allowing for the interaction and synergism between nutrients (7). Dietary patterns can be assessed using *a priori* score-based methods, based on dietary guidelines and recommendations, and *a posteriori* data-driven approaches using statistical methods (7, 8). These approaches translate at a population level making them ideal for public health interventions and applicable to clinical settings.

Although no epidemiological studies have examined the association between maternal dietary patterns during pregnancy and early childhood growth, studies on fetal growth outcomes suggest that maternal dietary patterns may have an impact. Additionally, randomized clinical

trials (RCTs) in pregnant women have shown the effectiveness of using healthy maternal dietary patterns in lowering women's glucose and lipid profiles; however, the results have limited generalizability (9-11).

This dissertation research utilized repeated anthropometric measures from the Pregnancy, Infection, and Nutrition (PIN) study, a longitudinal, prospective cohort, to expand existing literature by investigating the role of maternal dietary patterns on early childhood growth. Further, we explored whether maternal cardiometabolic markers during pregnancy could be an important biological mechanism for this association in humans.

Specifically, we investigated the following aims:

Aim 1. To examine the relationship between maternal dietary patterns and the following cardiometabolic markers during pregnancy: glucose, insulin, insulin resistance (HOMA-IR), triglycerides, and total cholesterol

Aim 2. To determine the association between maternal dietary patterns during pregnancy and early childhood growth outcomes from birth to 36 months

SubAim 2a: To investigate the effects of maternal dietary patterns on offspring weight status at 36 months, defined by BMI z-score

SubAim 2b: To investigate the effects of maternal dietary patterns on growth trajectory from birth to 36 months using linear mixed models

CHAPTER II: LITERATURE REVIEW

Childhood Obesity

Burden of Childhood Obesity

Obesity is one of the leading global public health issues. Worldwide, an estimated 45 million children are overweight or obese and another 92 million are at risk of becoming overweight (12). In the US, 16.9% of children and adolescents ages 2-19 years are classified as obese (age and sex specific BMI ≥95th percentile) (13). In the early childhood period, 8.4% of children 2-5 years of age are obese and 22.8% are overweight (age and sex specific BMI ≥85th percentile), while 8% of infants and toddlers <2 years of age are obese (13). Socioeconomically disadvantaged populations experience the highest rates of child obesity. Among children 2-5 years of age, the prevalence of obesity is 11.3% for non-Hispanic blacks and 16.7% for Hispanics compared to only 3.5% for non-Hispanic whites (13).

Overweight and obesity are the second leading behavioral causes of death in the US, only behind smoking (14). Studies indicate that these weight conditions during childhood have both short-term and long-term health consequences. Children living with obesity are more likely to be obese in adolescence and adulthood (15). In a previous study, children classified as overweight or obese in early childhood and adolescents were more likely to be obese as adults than children and adolescents who were normal weight (16). The growing rates of type 2 diabetes, metabolic syndrome, and atherosclerosis in children are attributed to the increased prevalence of childhood obesity (17). Additionally, childhood obesity precipitates subsequent

health conditions such as hypertension, ischemic heart disease, stroke, asthma, and even premature adult mortality (18-20). Childhood obesity also has psychosocial consequences. Studies indicate that obese children are more likely to suffer from negative self-confidence and self-esteem, poor socialization, and depression during childhood and adolescence (17, 18). Nationally, overweight and obesity costs more than $110 million dollars, with the direct medical expense of overweight and obesity comprising between 5-10% of US healthcare spending (21).

Measurement of Child Body Size

Obesity is defined as excess body fat, and ideally is based on a measure of body fat percentage or total fat mass (19). Unfortunately, measures of adiposity, such as dual energy x-ray absorptiometry and hydrostatic weighing, have limited practical use in epidemiological studies. Although direct measures would provide the most accurate measures of body composition, utilization of these instruments in large epidemiological is not cost-effective. Proxy measures of body fat are most widely used in epidemiological studies because of their low cost and noninvasiveness. The most frequently used measures to approximate body fat include BMI, weight, and waist circumference. Higher weight does not necessarily represent greater adiposity, as it includes muscle mass, bones, organs, and fat in the measure. Waist circumference provides a measure of central adiposity. BMI is a relative measure of excess weight-for-height, as indicated in the calculation (weight in kilograms/height in meters^2), and is most often used in epidemiological studies.

Estimation of body size in children requires special consideration to account for the natural growth patterns throughout childhood (22). Measures such as weight, height, and BMI are often converted to sex- and age-specific percentiles and z-scores to compare to a reference

population in children up to 19 years of age. Percentiles are used to classify children as overweight and obese, which are clinical definitions of excess body fat. A child is categorized as overweight when their value is greater than or equal to the 85th percentile and as obese when their value is greater than or equal to the 95th percentile. The use of these cutoffs minimizes misclassification and incorporates varying levels of health risks (23). Z-scores are calculated by taking the difference between the child's value and the mean value in the reference population divided by the standard deviation in the reference population. Several measures can be used for z-score calculation; however, BMI, weight-for-age, length-for-age, and weight-for-height are most commonly used. Our study utilized repeated measures of weight-for-height z-score to examine child growth and BMI z-score to examine weight status at 36 months in relation to maternal dietary patterns during pregnancy.

Proposed Biological Mechanism

In the early 1990s, David Barker hypothesized, based on available epidemiologic evidence, that the origins of adult chronic diseases began prior to birth (24). Barker's proposal became known as the fetal origins hypothesis, which acknowledged the importance of fetal life as a critical period for lifelong health. Given the recent rise in obesity rates, particularly among children and adolescents, researchers have become increasingly interested in understanding the role of the intrauterine environment on the origins of obesity (25-27). While obesity is a complex condition with biological, social, behavioral, and environmental determinants, identification of modifiable risk factors during fetal development could be vital in reducing the burden of childhood obesity. One potential mechanism that could explain a biological link between the fetal environment and child weight status is the overnutrition hypothesis. The

overnutrition hypothesis proposes that an intrauterine environment—characterized by poor maternal diet quality, high maternal body mass index (BMI), and the presence of gestational diabetes — alters fetal energy regulation, appetite regulation, and adipocyte metabolism, resulting in increased fetal/neonatal adiposity and subsequently high childhood and adult BMI (1, 2). Increased fetal concentrations of cardiometabolic markers are the proposed mechanistic link between maternal overnutrition and offspring BMI (**Figure 1**).

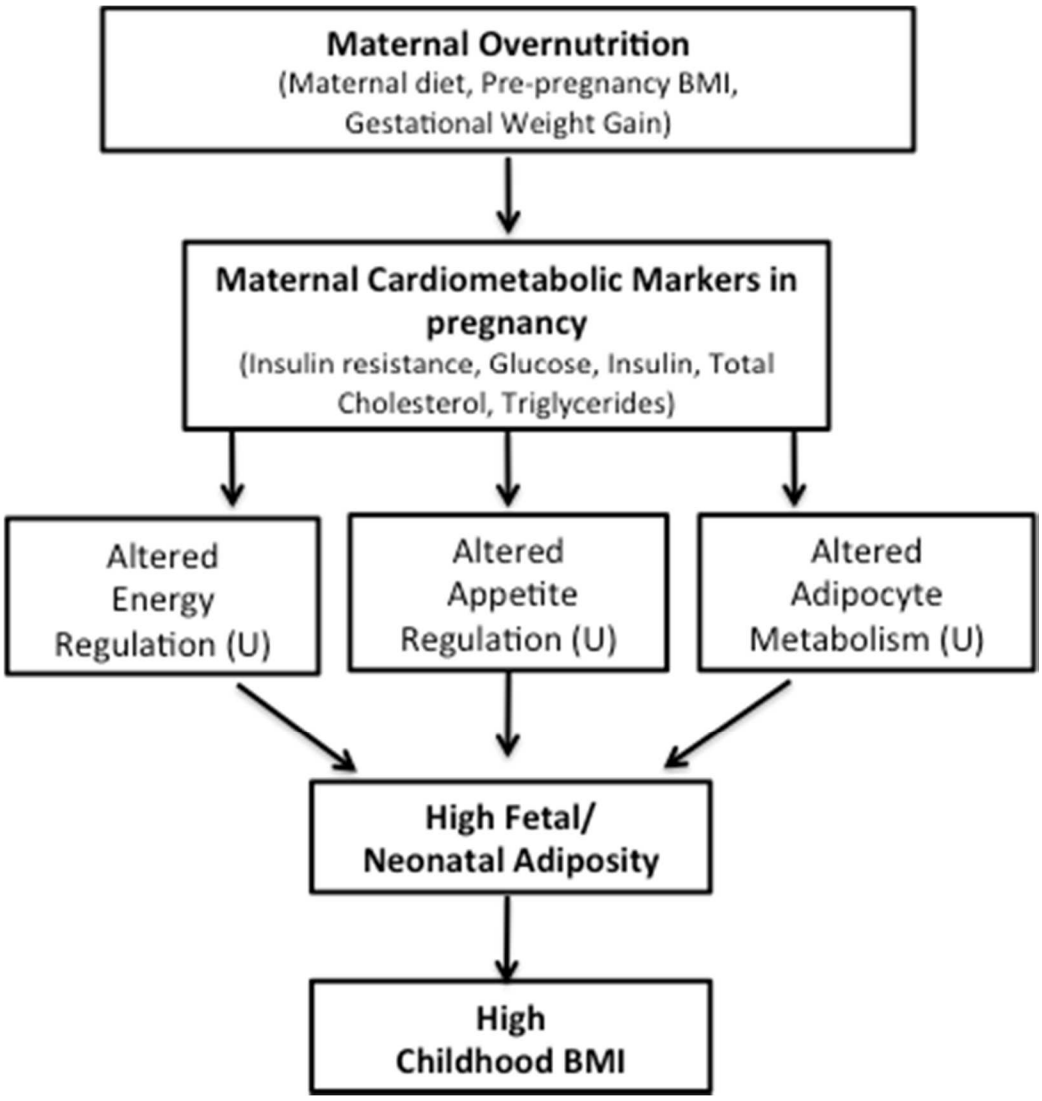


Figure 1. Potential biological pathways linking overnutrition to childhood obesity. Adapted from McMillen et al., 2006 and Dabelea et al., 2011. (1, 2)

Compelling research from experimental studies in animals shows that an intrauterine environment characterized by overnutrition may contribute to the programming of offspring obesity development. In pregnant rats, maternal overnutrition during gestation produced up-regulation of placental nutrient transport, influencing offspring hypothalamic appetite regulation and glucose homeostasis, resulting in greater adiposity later in life (28, 29). Pregnant rats fed high-fat chow experienced higher plasma triglyceride, insulin, leptin, and HOMA-IR levels compared to pregnant rats fed regular chow (29). Furthermore, pregnant rats fed high-calorie and/or high-fat diets during gestation also produced offspring with greater risk of obesity (3-6). Bayol et al. (4) found through experimentation that feeding pregnant Wister rats "cafeteria" diets, comprised of appetizing foods with a high fat and/or high sugar content, resulted in offspring with impaired skeletal muscle development and metabolic disorders (4). In a study examining the effects of maternal dietary lipid intake, independent of postnatal growth and nutrition, the offspring of mice fed high-fat diets during gestation accrued greater fat mass than offspring of mice fed low-fat diets, irrespective of maternal pre-pregnancy adiposity (6). While the maternal overnutrition hypothesis includes maternal BMI, gestational diabetes, and maternal diet, evidence supporting an association between maternal BMI and diabetes on offspring adiposity in human populations is more abundant in the literature (30-36). However, the role of maternal diet in the overnutrition hypothesis is less understood; hence the focus of this dissertation research.

Epidemiologic Evidence

Maternal diet and cardiometabolic markers during pregnancy

During pregnancy, maternal diet is associated with several maternal cardiometabolic markers. Maternal dietary glycemic index, a measure of the quality and quantity of

carbohydrates in the diet, is positively associated with plasma glucose levels and insulin sensitivity and insulin resistance indices (37, 38). In fact, pregnant women consuming a high glycemic carbohydrate diet during pregnancy experienced a 190% increase in blood glucose response compared to women consuming a low glycemic carbohydrate diet (39). Two previous RCTs during pregnancy demonstrated a beneficial effect of maternal diet on cardiometabolic markers. Among Iranian women with gestational diabetes, adherence to the Dietary Approaches to Stop Hypertension (DASH) eating plan during a 4-week study period resulted in lower fasting plasma glucose, serum insulin, HOMA-IR score, and total cholesterol, as well as improved glucose tolerance compared to women randomized to a control diet (10, 11). In addition, pregnant women randomized to a diet encouraging greater consumption of fish, low-fat meats and dairy products, oils, whole grains, fruits, vegetables, and legumes during pregnancy had lower total cholesterol levels compared to pregnant women in the control group (9). Further, higher maternal glucose, insulin resistance, and triglycerides levels during pregnancy are associated with higher birth weight (40-43), increased risk of large-for-gestational age (LGA) (40, 44), increased neonatal adiposity (45, 46), greater weight gain and adiposity in the first 12 months (41, 47), and increased risk of child obesity at 3 years of age (30).

Maternal diet and childhood growth outcomes

Several studies have examined the association between maternal diet and early childhood growth outcomes. This research has mainly focused on a single macronutrient or individual food in relation to fetal growth parameters (37, 48-56). The existing literature examining maternal diet during pregnancy and early childhood growth have produced mixed results, although suggestive of an association (57-61). In these studies, maternal diet was characterized by

composition of macronutrient intake, and only three of the five studies found an association. Higher intakes of sugar and higher glycemic index and glycemic load were associated with increased risk of child overweight/obesity at 5 years of age (57) and increased offspring fat mass at 4 and 6 years of age (60). Additionally, increased total *trans* fatty acid intake during the second trimester was positively associated with fetal growth z-score (54). Based on findings from the animal literature, diet quality may have more importance than intake of macronutrients and individual foods in relation to child growth outcomes; however, few studies have examined this in human populations.

Conventional analyses of individual foods and nutrients have several limitations (8, 62-65). Diet does not consist of foods and nutrients in isolation, but instead many foods and nutrients that are eaten in combination, which likely have interactive and synergistic effects on human health. Therefore, single effect of a nutrient may be too small to detect; however, the cumulative effects of many nutrients in a dietary pattern may be large enough to detect an association. Also, nutrient intakes are often associated with dietary patterns leading to confounded analyses in studies of single nutrients. Lastly, multiple analyses of single foods or nutrients may yield statistically significant results by chance because of the number of tests conducted. In lieu of single food and nutrient analyses, dietary patterns are commonly used in epidemiological studies as a measure of overall quality of the diet. Dietary patterns examine combinations of foods and nutrients eaten together allowing for assessment of the interaction and synergistic effects between nutrients on health. Dietary patterns can be assessed using *a priori* score-based methods, based on dietary guidelines and recommendations, and *a posteriori* data-driven approaches using statistical methods (7, 8). Previous studies have used both methods to

examine maternal dietary patterns in pregnancy; however, only in relation to fetal growth outcomes.

To date, five studies have utilized data-driven methods to examine the association between maternal dietary patterns, and fetal growth outcomes. In these studies, researchers most commonly used factor analysis to derive dietary patterns (66-70). Using data from the US Hispanic Health and Nutrition Examination Study, Wolff et al. (66) found in Mexican Americans a nutrient-dense pattern (fruits, vegetables, and low fat dairy) and a protein rich pattern (dairy desserts, low fat meats, and processed meats) were associated with increased birth weight, while a nutrient-dilute pattern (salty snacks, non-dairy, and sugar) was associated with decreased birth weight. In contrast, no association was found between an energy-rich pattern (bread, margarine, and nuts) and birth weight in a study among pregnant Dutch women (69). Healthier dietary patterns were associated with decreased odds of small-for-gestational age (SGA) in two separate studies (67, 68). In a cluster analysis among women participating in the Osaka Maternal and Child Health Study, the meat and eggs eating pattern and the wheat products eating pattern were associated with an increased odds of SGA (71).

Few studies have examined the association between maternal dietary patterns and child weight outcomes using score-based methods, in which all focused solely on fetal growth outcomes. Using the Alternate Healthy Eating Index (AHEI), a diet index examining intake of vegetables, fruit, nuts and soy, ratio of white meat to red meat, cereal fiber, *trans* fat, alcohol, and long-term multivitamin use, researchers showed that a higher AHEI score was associated with greater birth weight and lower odds of fetal growth restriction for weight and for head circumference (72). Hillesund et al., (2014) derived a New Nordic Diet (NND) score based on the following 10 components: meal pattern, Nordic fruits, root vegetables, cabbages, potatoes,

whole grain breads, oatmeal porridge, foods from wild countryside, milk, and water (73). A higher NND score compared to a lower NND score was associated with decreased odds of SGA and increased odds of LGA. In two separate studies, a Mediterranean-style Diet was associated with lower risk of fetal growth restriction (74) and lower placental weight and birth size (75).

Research Gaps

Together, animal and human studies offer some support of the overnutrition hypothesis as it relates to maternal diet. Previous research suggests an association between maternal diet quality and cardiometabolic markers during pregnant, as well as maternal diet quality and childhood anthropometric parameters. Dietary patterns provide an approach to measure overall quality, which is an advantage over single nutrient and food analyses. To our knowledge, no previous study has examined the role of maternal dietary patterns during pregnancy on early childhood growth patterns. In the studies that have assessed the association between maternal diet and childhood growth outcomes, methodological issues, such as limited generalizability, recall bias, and limited confounding control, restrict the interpretation of the findings. A recent systematic review and meta-analysis on the effects of dietary interventions on neonatal and infant outcomes demonstrated the need for more research to identify ideal maternal dietary intakes that optimize neonatal and infant anthropometric outcomes (76).

In addition, research literature on maternal dietary patterns and maternal cardiometabolic markers during pregnancy is scarce. Despite the indication of an association between maternal diet quality and cardiometabolic markers during pregnancy based on previous findings, we only found two studies that have examined the association using dietary patterns. In the two previous RCTs that used a score-based approach for dietary patterns, the studies encountered logistical

limitations such as small sample sizes, homogenous study populations, and women with gestational diabetes, which reduces generalizability.

Innovation and Significance

This dissertation research compares two separate approaches for assessing dietary patterns—*a priori* score-based and *a posteriori* data-driven. The Dietary Approaches to Stop Hypertension (DASH) eating plan is a score-based approach that examines the overall healthiness of the diet and has beneficial effects on components of the metabolic syndrome and metabolic profiles in pregnant women (10, 11). Additionally, the DASH dietary components are representative of the current Dietary Guidelines for Americans. We utilized latent class analysis (LCA) as the data-driven method in this dissertation research (77, 78). With LCA, women are categorized into mutually exclusive groups with similar eating habits.

Previous research on maternal diet and child growth outcomes has mainly focused on fetal growth and birth weight. Our study examines growth outcomes from birth through the first 36 months of life. It is well known that higher growth rates and adiposity during early infancy are associated with an increased risk of later development of overweight/obesity (79-82). The use of repeated measures in the first 36 months of life contributes to the scarce body of research on maternal diet and early childhood growth patterns.

This dissertation research has potential for significant public health impact. With over 30% of U.S. children and adolescents classified as overweight and 17% obese (13), maternal diet quality is a modifiable behavior that could have a role in childhood growth by influencing glucose and lipid metabolism during pregnancy. We utilized data from a longitudinal, prospective cohort study with rich prenatal and postnatal data. We examined maternal dietary

patterns in relation to maternal cardiometabolic markers during pregnancy and the following childhood growth outcomes: BMI z-score at 36 months of age and longitudinal changes in weight-for-height z-scores from birth to 36 months. Most crucially, this research study contributes to the understanding of one potential mechanism in the early origins of obesity that could inform future studies and interventions.

CHAPTER III: METHODS

The purpose of this dissertation was to determine the impact of maternal dietary patterns during pregnancy on maternal cardiometabolic markers and early childhood growth outcomes. We utilized data from the Pregnancy, Infection, and Nutrition (PIN) study. Multivariable linear regression and linear mixed effects regression were used to examine the specific aims. The following sections will detail the study design and population, data collection, and statistical analyses.

Study Design

To investigate the role of maternal dietary patterns on short-term cardiometabolic markers during pregnancy and early childhood growth, we conducted a secondary data analysis using data from the PIN study, a prospective longitudinal cohort study examining risk factors for preterm birth (83). Our first specific aim used data collected from women participating in the third cohort of the PIN study (PIN 3). Our second aim included eligible mother-child pairs from the PIN 3 study who participated in the follow-up studies at 3 and 12 months (PIN Postpartum) and 36 months (PIN Kids) postpartum. All PIN study protocols were reviewed and approved by the Institutional Review Boards of the School of Medicine at the University of North Carolina (UNC) at Chapel Hill. We provide details about each PIN study in the following section.

Study Population

PIN 3-Prenatal

For the PIN 3 study (2001-2005), women who were less than 20 weeks' gestation were recruited from private and public prenatal clinics at UNC Hospitals. Women were excluded if they were under 16 years of age, did not speak English, greater than 20 weeks' gestation, carrying multiple gestations, no telephone accessibility, or planned to continue care or deliver at a different site. Pregnant women who agreed to participate signed informed consent and provided basic demographic data to schedule the first telephone interview. Interviews were completed at 2 research clinic visits (15-20 weeks' gestation and 24-29 weeks' gestation), during 2 telephone interviews (17-22 weeks' gestation and 27-30 weeks' gestation), and following delivery at the hospital. Data collection via the telephone interviews and self-administered questionnaires solicited information on sociodemographic characteristics, psychosocial factors, dietary intake, physical activity, other health behaviors, medical history, and prior birth outcomes. Biological specimens were collected at the first and second research visits and the placenta was collected at delivery. Medical abstraction was conducted for information on reproductive history, gestational weight gain, pregnancy complications, medical lab values, and labor and delivery events. A total of 1,875 pregnant women (2,006 pregnancies) were enrolled into the prenatal component of the prenatal study.

PIN Postpartum

The PIN Postpartum study, which began in 2002, was a longitudinal study designed to examine factors related to postpartum weight retention. PIN Postpartum included home visits at 3 and 12 months postpartum. Mothers from PIN 3, who delivered a live birth after the

postpartum study recruitment period began, were eligible for participation in the follow-up study. Women who had a pregnancy loss, did not complete the first telephone interview, or delivered at a hospital other than UNC were not included. A total of 1,169 (62%) from the PIN 3 study were eligible to participate. Four hundred and eighty women were not included in the PIN Postpartum study for the following reasons: 24 had medical constraints, 153 were unreachable, 187 refused to participate, and 116 had timing or scheduling issues (**Figure 2**). A total of 689 (73%) eligible women agreed to participate and completed a 3-month interview. Women who became pregnant during the follow-up period (n=25) or moved outside of the catchment area or became unreachable (n=73) were excluded from participation in the 12-month visit. An additional 11 women requested to leave the study and 10 were excluded for other reasons, resulting in 550 mother-child pairs participating in the 12-month interview. During these home visits information on maternal socio-demographics, which may have changed since the prenatal period were collected, as were diet, smoking, vitamin/mineral supplement use, medications, health status, physical activity, neighborhood characteristics, psychosocial measures, and body image. Maternal weight and height were measured. For the child, information on breast or bottle-feeding, diet, anthropometry, illnesses and childcare were also collected. The study provided doctor cards to the mothers so that during pediatrician visits, a health care provider could record the child's weight and height.

PIN Kids

PIN Kids began in 2004 and followed-up with the index child at 36 months of age. Children were only able to participate in this study if their mothers participated in PIN 3 and PIN Postpartum studies and were a singleton birth with no major birth defects. Of the women

recruited to participate, there were 409 mother-child pairs who completed the 36-month visit (**Figure 2**). At the 36-month study visit, data were collected on child's diet, physical activity, hospitalizations, health status, and participation in childcare. PIN research staff measured the child's weight and height during the home visit. Updated socio-demographic information for the mother/household was also collected at this time.

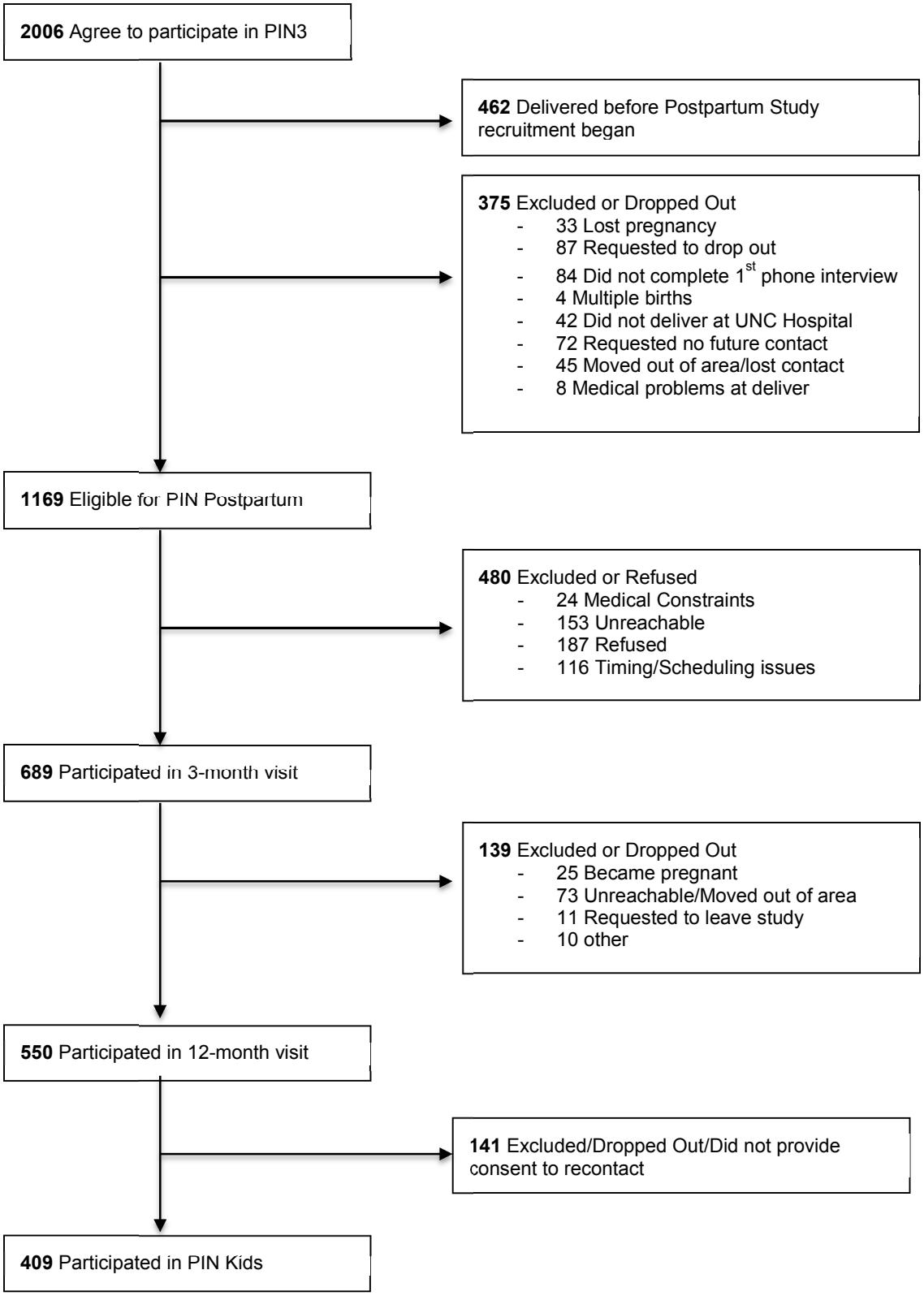


Figure 2. Flow chart of PIN studies that will be included in the proposed dissertation research

We examined distributions of select baseline maternal characteristics for PIN 3 mother-child pairs who were eligible but did not participate in PIN Postpartum (n=480) versus those who participated in PIN Postpartum (n=689). Eligible mothers who did not participate in the PIN Postpartum study were younger, had a higher pre-pregnancy BMI, and were more likely to be Black, unmarried, and had a lower education and household income than women participating in the PIN Postpartum study (**Appendix 1**). Similarly, we compared distributions of select baseline maternal characteristics for PIN Postpartum mother-child pairs who were eligible but did not participate in PIN Kids (n=280) versus those who did participate in PIN Kids (n=409). Women who participated in PIN Postpartum but not in PIN Kids were younger and more likely to be Black, unmarried, have lower education level and lower household income, and obese prior to pregnancy (**Appendix 2**).

Exposure Assessment

Maternal diet during pregnancy was collected at 26-29 weeks gestation with a self-administered, semi-quantitative, 119-item Block food frequency questionnaire (FFQ) to reflect dietary intake over the previous three months. Detailed information on the validity of the FFQ has been described elsewhere (77, 84, 85). Dietsys+Plus version 5.6 with an updated food composition table based on nutrient values from the National Health and Nutrition Examination Survey (NHANES) III and United States Department of Agriculture (USDA) 1998 nutrient databases were used to calculate daily energy intake in calories (kcals) and grams per day from the FFQ data.

Dietary patterns are primarily defined using the following methods: (1) *a priori* score-based approaches; (2) *a posteriori* data-driven approaches; and (3) self-selected diets such as

Vegan and Vegetarian. Our research focused on the score-based and data-driven methods. Score-based approaches are based on dietary recommendations or prior knowledge on the subject area (7). Individual's adherence to the score-based dietary pattern is estimated using a summary score. Data-driven approaches utilize statistical techniques, like factor and cluster analyses, to derive eating behaviors based on dietary data collected from diet assessment instruments. To characterize overall diet quality, the Dietary Approaches to Stop Hypertension (DASH) diet was used as the *a priori* method, while latent class analysis (LCA) was used as the *a posteriori* approach.

Method 1: Dietary Approaches to Stop Hypertension (DASH) diet.

The National Heart, Lung, and Blood Institute extensively promotes the DASH diet for prevention and treatment of hypertension based on results from the DASH randomized controlled trial (86). The DASH diet places emphasis on eight food components: fruits, vegetables, nuts and legumes, low fat dairy, whole grains, sodium, red and processed meat, sugar-sweetened beverages, and sodium (**Appendix 3**). We used a previously developed scoring algorithm, where individuals are scored based on their quintile of intake (87). Briefly, high intake of fruits, vegetables, nuts and legumes, low fat dairy, and whole grains were assigned one point for each quintile ranking (e.g. bottom quintile = 1 point, top quintile = 5 points). Sodium, red and processed meat, and sweetened beverages were reversed scored and the bottom quintile of intake received five points, while the top quintile received one point. Each component's score was summed to derive a total DASH adherence score for each participant, which could range from 8 (not adherent) to 40 (adherent).

Method 2: Latent Class Analysis (LCA)

We chose latent class analysis (LCA) as the data-driven approach to derive dietary patterns from the FFQ data, which classifies women into mutually exclusive groups. The methodology for deriving mutually exclusive groupings is described in full detail in previous studies (77, 78). The number of food items used to derive the latent classes were reduced from 119 to 105 due rarely consumed food items that were excluded (< 10%) and combining low-fat milks (skim, 1%, and 2%) into one group due to small cell counts. Because many of the food items had skewed distributions due to high prevalence of non-consumers, we used categories of intake were utilized. Food items with a high prevalence of consumption (non-consumption <10%; n=17 items), such as green beans and pizza, were dichotomized at the median. Food items with a low prevalence of consumption (non-consumption >70%; n=8), like grapefruit and whole milk, were dichotomized as consumed vs. non-consumed. The remaining food items (n=80) were categorized into three levels: non-consumers, below the median of consumption among consumers, and above the median of consumption among consumers. More details about the prevalence of food item consumption and categorization of food items is provided in **Appendix 4**. We fit 2-4 classes using energy-adjusted LCA models in Mplus 7.3 (88). The number of classes was selected based on the Lo-Mendell-Rubin likelihood ratio test (LRT) and women were classified into mutually exclusive classes according to their highest predicted probability of class membership (89).

Outcome Assessment

Maternal cardiometabolic markers

Maternal blood samples were collected at 24-29 weeks gestation (Mean: 27.2 ± 1.4 weeks; Range: 24.0-30.9 weeks). Maternal fasting glucose (mg/dL) was assayed by LINCO Research, Inc. using a standard hexokinase method. Fasting insulin (μU/mL) was assayed by LINCO Research, Inc. using the double antibody/PEG technique. Fasting cholesterol (mg/dL) and triglycerides (mg/dL) were assayed by LipoScience Inc. (Raleigh, NC) using nuclear magnetic resonance technique (NMR LipoProfile®). We estimated insulin resistance from fasting plasma glucose and insulin concentrations using the homeostasis model assessment for insulin resistance (HOMA-IR) and calculated using the following equation (90, 91):

$$\text{HOMA-IR} = \frac{\text{Fasting glucose (mg/dL)} \times \text{Fasting insulin (μU/mL)}}{405}$$

Child Anthropometrics

Child anthropometrics examined in this dissertation included: BMI z-score at 36 months of age and weight-for-height z-score (WHZ) from birth to 36 months of age. Child's birth weight and sex were collected from delivery records. The study provided doctor cards to the mothers so that during pediatrician visits, a health care provider could record the child's weight and height. We calculated the child's precise age at each measurement using the difference between the documented date of visit and the child's birth date. Trained PIN personnel measured children's standing height and weight at the 36-month in-home visit using stadiometers and scales according to the NHANES protocols (92).

WHZ for children from birth to 24 months were calculated using the 2006 World Health Organization (WHO) growth charts and for children 2 years of age and older using the 2000 CDC growth charts (22, 93). WHZ, a measure of relative weight, was used to examine child growth from birth to 36 months of age. BMI z-scores were calculated based on the 2000 Center for Disease Control and Prevention (CDC) growth charts to examine the association between maternal dietary patterns during pregnancy and child BMI z-score at 36 months of age.

Covariates

This section describes data collection and classification of covariates of interest. These variables have been divided into maternal and child variables.

Maternal variables

Maternal age

Maternal age at the time of recruitment was collected during the prenatal period. This factor was categorized as: 16-24, 25-29, 30-34, and ≥35 years.

Maternal race

Maternal race was based on mother's self-identified race and was dichotomized as non-black and black. Mother's also provided child's race/ethnicity.

Marital status

Marital status was based on cohabitation status and dichotomized as married/living with a partner and unmarried.

Gestational age at delivery

Gestational age was estimated from the first ultrasound measurement performed prior to 22 weeks' gestation (>90%); however, if an ultrasound was not performed prior to 22 weeks' gestation, then the date of last menstrual period was used.

Parity

Parity was defined based on the number of births prior to the index pregnancy at enrollment into the PIN3 study and was dichotomized as nulliparous and parous.

Household income

Household income was converted into percent of the poverty line by including the number of family members in the household based on the 2001 US Department of Health and Human Services Federal Poverty Guidelines (94) and cut-points were based on the Special Supplemental Nutrition Program for Women, Infant, and Children (WIC) eligibility guidelines: <185%, 185-350%, and >350%.

Maternal Education

The number of years of completed education was categorized as ≤Grade 12 (high school completion or less), Grades 13-16 (high school with some college), ≥Grade 17 (some post-college education).

Pre-pregnancy BMI

Pre-pregnancy BMI was based on height measured at either the first prenatal clinic visit or during the 3-month postpartum visit and self-reported pre-pregnancy weight. Missing pre-pregnancy weight was imputed based on measurements taken at the first prenatal care visit (95).

Maternal smoking status during pregnancy

Smoking status (smoker vs. nonsmoker) during the first six months of pregnancy was collected from self-administered questionnaires.

Child variables

Birth weight

Birth weight (grams) was collected from delivery logs. This variable was examined in the statistical analysis for Aim 2 to understand the influence on the associations between dietary patterns and child anthropometrics.

Infant diet

PIN Kids collected 2 dietary recalls to use for child dietary intake. We created DASH scores for children with available data at 36 months of age. At the 3- and 12-month PIN Postpartum interviews, data about breastfeeding were collected. Infant diet and duration of exclusive breastfeeding (months) were considered in analyses for Aim 2 to examine the influence of these factors on the exposure-outcome associations.

Statistical Analysis Plan

Descriptive statistics (means, standard deviations, frequencies, and percentages) were computed for selected baseline characteristics, exposures, and outcomes. Potential confounders were determined based on *a priori* review of the literature and directed acyclic graphs (96). Effect measure modification was assessed using likelihood ratio tests (LRT) with an *a priori* significance level set at p-value <0.15. A brief description of the statistical analyses conducted in each specific aim of this dissertation are provided below and detailed in their corresponding chapters:

Aim 1: To assess the relationship between maternal dietary patterns and the following maternal cardiometabolic markers during pregnancy: glucose, insulin, insulin resistance (HOMA-IR) triglycerides, and total cholesterol

To study the association between maternal dietary patterns during pregnancy and fasting glucose, insulin, HOMA-IR, triglycerides, and total cholesterol, we used multivariable linear regression. DASH diet scores and latent dietary classes were analyzed categorically, where Tertile 1 was the referent for DASH and Class 1 for LCA. We examined three models separately. First, we assessed the crude association between maternal dietary patterns and cardiometabolic markers. Second, we adjusted the crude model for maternal age, race, poverty level, parity, smoking status, physical activity, and energy intake. In a third model, we further adjusted for continuous pre-pregnancy BMI, to examine a potential confounding pathway between maternal dietary patterns and cardiometabolic markers during pregnancy (**Figure 1**).

AIM 2: To explore the effects of maternal dietary patterns in early pregnancy on early childhood growth outcomes from birth to 36 months of age

We used multivariable linear regression to examine the association between maternal dietary patterns and child BMI z-score at 36 months. In addition, we used linear mixed models to estimate child growth (WHZ), defined as intercept (birth) and slope (rate of change), from birth to 36 months in relation to maternal DASH score and latent dietary classes during pregnancy. Linear mixed models are used for continuous repeated outcome measures and can account for unbalanced data (varying number of repeated outcomes across children), unequal spacing of measurements across time, and the correlations between measurements within each child (97, 98). The mixed models were fit using restricted maximum likelihood for repeated measures, which accounts for the correlated measures at the different time points in the variance and covariance matrices. Children with at least one measurement were included in the analysis. Results from the DASH score analysis are provided in Chapter 3. Results from the LCA were not included in the manuscript, but are provided in Appendices 5-8. All analyses were performed using SAS version 9.3 (SAS Institute, Inc).

CHAPTER IV: MATERNAL DIETARY PATTERNS AND CARDIOMETABOLIC MARKERS DURING PREGNANCY

INTRODUCTION

Early life risk factors for childhood obesity have become a focus of epidemiologic research, as emerging evidence suggests that intrauterine exposures on the fetus can have effects on obesity development in childhood (25). During a typical pregnancy, several adaptations to metabolic profiles occur to sustain pregnancy and promote fetal growth and development (99, 100). Although elevated levels of metabolic markers are characteristic of a normal pregnancy, an intrauterine environment with profound insulin resistance and increased glucose, triglyceride, and cholesterol levels can result in higher birth weight, increased infant adiposity, and infant weight gain, and increased risk of subsequent childhood obesity (30, 40, 42, 43, 45-47, 101, 102).

Diet during pregnancy is a modifiable behavior that could influence offspring adiposity by optimizing levels of important cardiometabolic markers. While individual food and nutrient studies provide an understanding of biological mechanisms, dietary patterns offer a more holistic approach that can be applied to real world settings and, thus, public health interventions (8). Additionally, studies of dietary patterns can account for the interaction and synergistic effects of individual foods and nutrients on health outcomes.

Previous studies have used both score-based and data-driven approaches to investigate the relationship between diet patterns and cardiometabolic markers. Diet quality indices, like the Healthy Eating Index, Dietary Approaches to Stop Hypertension (DASH) diet, and the Mediterranean-style diet score, are score-based methods typically created based on dietary

guidelines and recommendations, whereas data-driven methods, such as factor analysis and latent class analysis (LCA), empirically derive patterns using the correlations of foods eaten together (8). Both randomized controlled trials (RCTs) and observational studies in healthy non-pregnant individuals have found associations between greater adherence to healthy dietary patterns, using the Mediterranean-style diet score and factor analysis, and lower glucose and lipid levels and decrease odds of insulin resistance (103-105). The influence of a healthy dietary pattern on metabolic markers in pregnant women is not as well established. Studies in pregnant women are limited to small sample sizes, racially and socioeconomically homogenous study populations, and analyses among pregnant women with gestational diabetes (9-11, 108).

To our knowledge, only one previous study has examined the effects of dietary patterns and cardiometabolic markers in a normal pregnant population. In this prospective study, the authors reported an inverse association between the Mediterranean-style diet score and maternal fasting glucose levels (106). Unfortunately, important cardiometabolic markers other than glucose were not assessed. Additionally, the Mediterranean-style diet is just one of many score-based diet quality indices used to assess the overall quality of diet in relation to health outcomes. Another score-based diet quality index is the DASH diet, which examines the overall healthiness of the diet and has been shown to positively impact components of the metabolic syndrome and metabolic profiles in pregnant women (10, 11). We used data from a prospective study of pregnant women to investigate the association between maternal dietary patterns and cardiometabolic markers during pregnancy using both a diet quality index and data-driven approach to define dietary patterns.

METHODS

Study design and population

We conducted a secondary analysis of data from the third cohort of the Pregnancy, Infection, and Nutrition (PIN3) study, which recruited women from private and public prenatal clinics at University of North Carolina (UNC) Hospitals (95). From January 1, 2001 to June 30, 2005, pregnant women who were ≤20 weeks' gestation, 16 years of age and older, carrying singleton gestation, had telephone accessibility, and were planning to continue care at the same clinic were recruited to participate in a prospective study of fetal growth and preterm delivery. A total of 1,875 pregnant women (2,006 pregnancies) were enrolled into the study, of which 1,352 women (1,442 pregnancies) had complete dietary information. Because it was possible for a woman to have multiple pregnancies during the PIN 3 study, we randomly selected one pregnancy per woman from those with complete dietary information to be included in this analysis (1,352 women = 1,352 pregnancies). Women provided written informed consent at recruitment and all procedures were reviewed and approved by the UNC Institutional Review Board.

Assessment of primary outcomes

Maternal blood specimens were collected at 24-29 weeks gestation. Using a standard hexokinase method, maternal fasting glucose (mg/dL) was assayed by LINCO Research, Inc. Fasting insulin (μU/mL) was assayed by LINCO Research, Inc. using the double antibody/PEG technique. Fasting cholesterol (mg/dL) and triglycerides (mg/dL) were assayed by LipoScience Inc. (Raleigh, NC) using nuclear magnetic resonance technique (NMR LipoProfile®). We estimated insulin resistance from fasting plasma glucose and insulin concentrations using the

homeostasis model assessment for insulin resistance (HOMA-IR) and calculated using the following equation (90, 91):

$$\text{HOMA-IR} = \frac{\text{Fasting glucose (mg/dL) x Fasting insulin (μU/mL)}}{405}$$

Assessment of primary exposures

Information on diet was collected at 26-29 weeks gestation using a self-administered, semi-quantitative, 119-item Block FFQ to assess dietary intake over the previous three months. Detailed information on the validity of FFQ has been described elsewhere (84). To calculate daily energy intake in kcals and grams per day from the FFQ data, we used Dietsys+Plus version 5.6 with an updated food composition table based on nutrient values from the NHANES III and USDA 1998 nutrient databases.

Dietary patterns

We examined dietary patterns using two different approaches, one score-based and another data-driven. Diet quality score-based methods define dietary patterns using established consensus reports (e.g. dietary guidelines or recommendations) and then assign scores at the individual level to reflect their adherence to the guidelines, whereas data-driven methods use statistical models to derive dietary patterns based on data collected from diet instruments (7). For the diet quality score-based approach, we assessed adherence to the DASH diet (86). The DASH scoring method was based on a previously developed approach, where participants received points based on their quintile of intake (87). High intake of fruits, vegetables, nuts and legumes, low fat dairy, and whole grains were assigned one point for each quintile ranking (e.g. lowest

quintile = 1 point, highest quintile = 5 points). Sodium, red and processed meat, and sweetened beverage intakes were reverse scored, where the lowest quintile of intake received five points, while the highest quintile of intake was assigned one point. Each component score was summed to derive a total DASH adherence score for each participant, which could range from 8 (not adherent) to 40 (adherent). We then divided DASH scores into tertiles for all analyses, where the highest tertile represented healthier diet quality.

We chose LCA as the data-driven approach to derive dietary patterns, which classify women into mutually exclusive groups. The methodology for deriving mutually exclusive groupings is described in full detail in previous studies (77, 78). Here, the number of FFQ food items used to derive the latent classes was reduced from 119 to 105 due to excluding rarely consumed food items (< 10%) and combining low-fat milks (skim, 1%, and 2%) into one group due to small cell counts. Many of the food items had skewed distributions due to high prevalence of non-consumers; therefore, we used categories of intake. Food items with a high prevalence of consumption, such as green beans and pizza, (non-consumption <10%; n=17 items) were dichotomized at the median. Food items with a low prevalence of consumption, like grapefruit and whole milk, (non-consumption >70%; n=8) were dichotomized as consumed vs. non-consumed). The remaining food items (n=80) were categorized into three levels: non-consumers, below the median of consumption among consumers, and above the median of consumption among consumers. We fit energy-adjusted LCA models with 2-4 classes. The number of classes was selected based on the Lo-Mendell-Rubin likelihood ratio test (LRT) and women were classified into mutually exclusive classes according to their highest predicted probability of class membership (89).

Covariates

The following variables were evaluated as potential confounding factors of the maternal dietary patterns-cardiometabolic markers association based on extant literature and causal diagram analysis (96). At enrollment, women reported their age, race, marital status, parity, household income, education level, pre-pregnancy weight, smoking status, and physical activity. Age in years at time of conception was categorized into four categories: 16-24, 25-29, 30-34, and ≥35 years. Due to the small number of women self-identifying with a race/ethnicity other than "white" or "black", race was dichotomized as non-black and black. Marital status was based on cohabitation status and dichotomized as married or living with a partner and unmarried. Parity was defined based on the number of births prior to the index pregnancy at enrollment into the PIN3 study and was dichotomized as nulliparous and parous. Household income was converted to percent of poverty and categories were based on the Special Supplemental Nutrition Program for Women, Infant, and Children (WIC) eligibility guidelines: <185%, 185-350%, and >350% (94). This categorization was used because women with a household percentage <185% are eligible for WIC support. The number of years of completed education was categorized as ≤Grade 12 (high school completion or less), Grades 13-16 (high school with some college or college completion), ≥Grade 17 (some post-college education). Maternal pre-pregnancy BMI was calculated based on self-reported pre-pregnancy weight and height that was measured at the first clinic visit. BMI classifications followed the 2009 Institute of Medicine recommendations: underweight <18.5 kg/m^2; normal weight 18.5-24.9 kg/m^2; overweight 25.0-29.9 kg/m^2; and obese ≥30.0 kg/m^2. Smoking during pregnancy was dichotomized as non-smoker and smoker during the first six months of pregnancy, which was asked at 17-22 weeks and 27-30 weeks gestation. Lastly, physical activity during pregnancy was based on total metabolic equivalent

(MET) hours that were calculated from self-reported physical activity information at <20 weeks and 24-29 weeks gestation.

Statistical analysis

To avoid excluding women with missing covariate information from the analysis, we used data from the three months postpartum survey when possible for missing federal poverty level (n=12) and smoking status (n=9). In addition, we used multiple imputation methods to estimate values of other missing covariate data for maternal race (n=1), prenatal smoking (n=18), and federal poverty level (n=20). All covariates and outcomes discussed previously were included in the multiple imputation models (107). We used 10 iterations to produce 10 imputed datasets for regression analyses.

Of the 1,352 women included in this study, 569 had biomarker data for all cardiometabolic markers of interest (fasting glucose, insulin, total cholesterol, and triglycerides). We compared select baseline characteristics to determine whether women with data for all cardiometabolic markers (n=569) differed from women excluded (n=783). While those with complete biomarker data had a slightly lower mean ± SD pre-pregnancy BMI (25.3 ± 6.5 kg/m2 vs. 26.2 ± 7.3 kg/m2 for those excluded; (P<0.01)), all other comparisons of baseline characteristics were not statistically different. In addition, we further excluded women with pre-existing diabetes (n=12), chronic hypertension (n=34), or who had both conditions (n=10) because it is possible that these women had received preconception dietary advice for their conditions, which could have influenced their dietary habits during pregnancy, resulting in 513 women included in this analysis.

Frequencies and descriptive statistics were expressed as n (%) and means ± SDs, respectively. Cardiometabolic markers were examined for normality using the Shapiro-Wilk test and observation of box-plots. Those with skewed distributions were transformed using the natural log. Statistical significance was evaluated using χ^2 and Analysis of Variance (ANOVA) tests for categorical and continuous variables, respectively ($P<0.05$). We examined the correlation between continuous DASH score and nominal latent classes using Spearman correlation. To study the association between maternal dietary patterns during pregnancy and fasting glucose, insulin, HOMA-IR, triglycerides, and total cholesterol, we used multivariable linear regression. DASH diet scores and latent dietary classes were analyzed categorically, where Tertile 1 was the referent for the DASH diet and Class 1 for LCA. We examined three models separately. First, we assessed the crude association between maternal dietary patterns and cardiometabolic markers. Second, we adjusted the crude model for maternal age, race, poverty level, parity, smoking status, physical activity, and energy intake. In a third model, we further adjusted for continuous pre-pregnancy BMI, to examine a potential confounding pathway between maternal dietary patterns and cardiometabolic markers during pregnancy (**Figure 3**). Other covariates (maternal education and marital status) were tested as potential confounders, but were excluded because they did not meaningfully influence our estimates (change-in-estimate <10%). We further assessed the relationship between dietary patterns, maternal pre-pregnancy BMI, and cardiometabolic markers by calculating predicted means for each cardiometabolic marker, given the following profile: pregnant women 30-34 years of age who are non-Black, nulliparous, nonsmokers, 350% above federal poverty level, and median MET hours of 17.66 and median energy intake of 1994.9 kcal. All analyses were performed using SAS version 9.3 (SAS Institute, Inc. Cary, NC).

RESULTS

Three latent classes were identified from the LCA. Class 1 was characterized by high intake of hamburgers, hot dogs, French fries, fried chicken, white bread, bacon, and soft drinks. Class 2 was characterized by a high intake of some vegetables, refined grains, mixed dishes, meat, poultry, processed meat, salty snacks, sweets, some fast foods, and fruit juice. Class 3 included high intake of fruits, vegetables, whole grains, low fat dairy, breakfast bars, and water.

DASH scores ranged from 12 to 37 with a mean of 24.2 ± 5.1. A higher proportion of women were grouped into Latent Class 3, which represented a healthier dietary pattern, as compared to Latent Classes 1 and 2. Twenty-two percent (n=114) of the total sample was grouped into both DASH Tertile 3 and Latent Class 3. Continuous DASH score and latent classes were significantly correlated (ρ=0.50; p=<0.001). On average, women who were grouped into DASH Tertile 3 or Latent Class 3 were older and more likely to be non-Black and married **(Table 1)**. They also had a lower prevalence of pre-pregnancy obesity and smoking during pregnancy. These women were also more likely to have a high household income (>350% federal poverty level) and more than a college education (≥ Grade 17).

By definition, women with a DASH score in the highest tertile had a higher consumption of healthy food items (i.e. fruits, vegetables, whole grains, etc.) and lower intake of unhealthy foods (i.e. red meat, sweetened beverages, etc.) as compared to women with scores in the lower tertiles (**Table 2**). Similarly, women grouped into Latent Class 3 had higher mean intake of vegetables, whole grains, and low fat dairy, and lower intake of red meat and sweetened beverages than women in Latent Classes 1 and 2. For example, mean intake of vegetables among women grouped into Latent Class 3 was 2.6 ± 2.0 compared to 2.3 ± 1.7 for Latent Class 2 and 1.4 ± 1.4 for Latent Class 1, and mean intake of red meat was only 0.2 ± 0.2 for Latent

Class 3 compared to 0.6 ± 0.3 and 0.5 ± 0.8 for Latent Class 2 and 1, respectively. Saturated fat intake was also lower for women categorized into DASH Tertile 3 and Latent Class 1 as compared to women grouped into other categories.

In the multivariable analysis, an inverse association was observed between maternal dietary patterns and fasting glucose (**Table 3)**. In adjusted Model 2, a Latent Class 3 diet (characterized by high intake of fruits, vegetables, whole grains, low fat dairy, breakfast bars, and water) was associated with a significantly lower (β= -2.33, 95% CI: -4.17, -0.50) fasting glucose level compared to a Latent Class 1 diet (characterized by high intake of hamburgers, hot dogs, French fries, fried chicken, white bread, bacon, and soft drinks). There was suggestion that better adherence to the DASH diet was also associated with lower levels of maternal glucose (DASH Tertile 3 vs. Tertile 1 adjusted β= -1.01; 95% CI: -2.82, 0.81). When we further adjusted for pre-pregnancy BMI, the results were attenuated towards the null value. In contrast, there was indication of a positive association for adherence to a healthy dietary pattern (DASH Tertile 3 and Latent Class 3) and total cholesterol.

Table 4 presents the ratio of geometric means for log-transformed markers (fasting inulin, HOMA-IR, and triglycerides) according to DASH score tertile and latent dietary classes. As observed with fasting glucose, we found that adherence to a healthier dietary pattern was inversely associated with insulin, HOMA-IR, and triglyceride levels after adjustment for potential confounders. In adjusted Model 2, we found that women with a DASH score in Tertile 3 had 12-18% lower levels of insulin, HOMA-IR, and triglycerides compared to women with a DASH score in Tertile 1. The ratio of geometric mean for insulin, HOMA-IR, and triglycerides were 0.83 (95% CI: 0.74-0.94), 0.82 (95% CI: 0.72-0.94), and 0.88 (95% CI: 0.81-0.96), respectively. Similarly, compared to women categorized into Latent Class 1, women grouped

into Latent Class 3 had a 22% and 24% decrease in the geometric mean for maternal insulin and HOMA-IR, respectively. Additional adjustment for pre-pregnancy BMI slightly attenuated the results. Associations were similar after excluding pregnant women with daily energy intakes ±1st percentile (770 and 5010 kcals), ±2.5th percentile (995 and 4337 kcals), and ±5th percentile (1106 and 3668 kcals).

Figures 4-5 show the relationship between dietary patterns, pre-pregnancy BMI, and cardiometabolic markers for a given profile (pregnant women 30-34 years of age who are non-Black, nulliparous, nonsmokers, 350% above federal poverty level, and median MET hours of 17.7 and median energy intake of 1994.9 kcal). As found in the linear regression analyses, adherence to a healthy dietary pattern (DASH Tertile 3 and Latent Class 3) is related to lower predicted insulin, HOMA-IR, and triglyceride levels, independent of pre-pregnancy BMI. Predicted total cholesterol levels decreased as maternal pre-pregnancy BMI increased; however within each BMI category, adherence to the DASH diet was associated with lower total cholesterol, whereas the opposite was observed with the latent classes.

DISCUSSION

In this study, we found that adherence to a healthier dietary pattern during pregnancy was related to lower maternal insulin, HOMA-IR, and triglycerides. Similarly, a dietary pattern characterized by high intakes of fruits, vegetables, whole grains, low fat dairy, breakfast bars, and water using a data driven approach was associated with lower maternal glucose, insulin, HOMA-IR, and triglycerides. Associations were slightly attenuated upon further adjustment for pre-pregnancy BMI; however, several significant associations remained.

Epidemiological studies relating maternal dietary patterns to maternal cardiometabolic markers during pregnancy are sparse. We are aware of only four published studies that have examined dietary intake in relation to cardiometabolic markers during pregnancy (9-11, 108). Our findings of an association between healthy dietary patterns and fasting glucose, insulin, and HOMA-IR levels during pregnancy were generally consistent with results from a small RCT of women with gestational diabetes (10). In that study, women with diagnosed gestational diabetes randomized to the DASH diet at 24-28 weeks of gestation, as opposed to the control diet (40-55% energy as carbohydrates, 10-20% as proteins, 25-20% as fats), observed significant decreases in fasting glucose (-7.62 mg/dL vs. 3.68 mg/dL; P=0.02), insulin (-2.62 μIU/mL vs. 4.32 IU/mL; P=0.03), and HOMA-IR (-0.8 vs. 1.1; P=0.03) at the end of the four-week study period. Moreover, our results were consistent with those from a previous observational study that reported an inverse association between fruit and vegetable fiber intake during the second trimester and fasting glucose and HOMA-IR at 30 weeks gestation (108).

We found suggestion of an inverse association, though not statistically significant, between DASH score and total cholesterol levels after adjustment for all potential confounders including pre-pregnancy BMI, which is consistent with two previous RCTs (9, 11). Asemi et al. (2013) found that women with gestational diabetes randomized to the DASH diet experienced a reduction in total cholesterol as compared to women assigned to the control diet at the end of the four-week study period (-0.42 mmol/l vs. 0.31 mmol/l; P=0.01) (11). Similarly, women randomized to a cholesterol-lowering diet at 17-20 weeks gestation had significantly lower total cholesterol levels at 36 weeks gestation compared to women randomized into the usual diet group (9). We did not find any evidence of an association between latent class and total cholesterol.

Although the specific mechanisms to explain the suggested inverse associations between maternal dietary patterns and insulin, HOMA-IR, and triglyceride levels are unclear, the results are biologically plausible. The healthier dietary patterns (DASH Tertile 3 and Latent Class 3) are characterized by higher intakes of fruits, vegetables, and whole grains, which are rich sources of antioxidants, phytochemicals, vitamin C and dietary fiber, and may contribute to the protective associations seen in this study. Vitamin C and plasma ascorbic acid were previously found to be inversely associated with the risk of gestational diabetes (109). Furthermore, women in DASH Tertile 3 and Latent Class 3 had lower consumption of red and processed meats. High intakes of red and processed meats increase the risk of insulin resistance and gestational diabetes mellitus in previous research, possibly due to the high concentration of saturated fat, heme iron, and nitrosamines (110). In our study, women in DASH Tertile 3 and Latent Class 3 had significantly lower saturated fat intake than women in the other categories.

The use of dietary patterns is appealing in epidemiology as a measure of overall diet quality. Unlike single food and nutrient analyses, dietary patterns have the advantage of capturing the combinations of foods eaten together, which are more relevant in clinical and public health settings. Although both diet quality score-based and data-driven methods portray the overall diet, the methodologies of each approach result in different characterizations. Diet quality score-based methods, like the DASH diet used in this study, are based on dietary recommendations and guidelines, as well as substantive knowledge of dietary factors as they relate health outcomes (7) and as such are useful in quantifying the overall healthiness of the diet. Furthermore, they are easily reproducible making comparisons across study populations more feasible. Data-driven approaches, like cluster analysis and LCA, separate individuals into mutually exclusive groups based on the correlations of foods eaten together (7). One

disadvantage of data-driven methods is the difficulty in making comparisons across research studies, as the dietary patterns derived are often specific to the individual study sample (111, 112), which is why we consistently described the foods consumed in each pattern. By identifying the foods we could see similarities in the two dietary patterns and found similar results with the cardiometabolic markers, which speaks to the robustness of the association between dietary patterns and the outcomes examined.

Limitations of our study must be considered when interpreting the findings. Although we were able to adjust for several potential confounding factors, we cannot dismiss the possible influence of unmeasured confounding. Two potential confounders that we did not have information on were preconception dietary patterns and hormonal status during pregnancy. Dietary intake was assessed using a single FFQ administered at 26-29 weeks gestation to represent intake in the previous three months; however, we can assume based on the results of previous research that dietary patterns change minimally, if any, during pregnancy from the preconception period (113). Hormonal status during pregnancy plays an important role in the fluctuations of lipids and glucose levels during pregnancy (114-116). Maternal BMI may alter circulating concentrations of metabolic hormones during pregnancy, which, in turn, influence nutrient transport capacity (116). To further overcome this limitation, we included pre-pregnancy BMI in the fully adjusted regression analyses. Although pre-pregnancy BMI does not directly affect dietary patterns during pregnancy, and thus, does not meet the criteria of being considered a potential confounder, accounting for it in the analysis is important in isolating the association between maternal diet and cardiometabolic markers during pregnancy. By including pre-pregnancy BMI in the fully adjusted analyses, we account for possible variations in the maternal diet-cardiometabolic markers association that could be explained by preconception diet

and hormonal status. We also recognize the potential for residual confounding, as DASH scores in the bottom tertile were related to lower education and income levels, as well as higher proportions of pre-pregnancy obesity and smoking during pregnancy, while DASH scores in the top tertile were related to higher education and income levels and lower proportions of pre-pregnancy obesity and smoking during pregnancy. Lastly, women included in our study received prenatal care at a single University-based hospital system and resulted in a sample with high income and education, which may limit the generalizability of our study results.

CONCLUSIONS

Our study documents a relationship between maternal dietary patterns and cardiometabolic markers during pregnancy. A higher diet quality was associated with lower maternal glucose, insulin, HOMA-IR, and triglyceride levels, which are important factors for later offspring health. These findings have important implications, as early prenatal visits are critical times to make recommendations for healthy dietary habits during pregnancy. Ideally, these conversations would begin prior to pregnancy. Future studies with a larger sample size in a more diverse population are needed to confirm the findings of this study. Furthermore, large intervention studies investigating the effect of healthy dietary patterns on cardiometabolic markers would be useful to overcome biases related to observational studies. In summary, for a favorable metabolic profile, pregnant women may be advised to eat a dietary pattern that is consistent with the DASH diet as well as the Dietary Guidelines for Americans that emphasize high intakes of fruits, vegetables, whole grains, low fat dairy, nuts and legumes.

Table 1. Distribution of maternal characteristics by DASH score tertile or latent dietary class, Pregnancy, Infection, and Nutrition (PIN) study, (n=513)

Variable[A]	DASH			LCA[B]		
	Tertile 1 (n= 186)	Tertile 2 (n=182)	Tertile 3 (n=145)	Class 1 (n=150)	Class 2 (n=163)	Class 3 (n=200)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age (years)						
16-24	70 (37.6)	35 (19.2)	11 (7.6)	58 (38.7)	49 (30.1)	9 (4.5)
25-29	50 (26.9)	60 (33.0)	35 (24.1)	52 (34.7)	40 (24.5)	53 (26.5)
30-34	44 (23.7)	61 (33.5)	72 (49.7)	27 (18.0)	53 (32.5)	97 (18.5)
35-47	22 (11.8)	26 (14.3)	27 (18.6)	13 (8.7)	21 (12.9)	41 (20.5)
Race						
Non-Black	135 (72.6)	158 (86.8)	137 (95.1)	111 (74.0)	125 (76.7)	194 (97.5)
Black	51 (27.4)	24 (13.2)	7 (4.9)	39 (26.0)	38 (23.3)	5 (2.5)
Marital status						
Married	114 (61.3)	150 (82.4)	133 (91.7)	91 (60.7)	118 (72.4)	188 (94.0)
Unmarried	72 (38.7)	32 (17.6)	12 (8.3)	59 (39.3)	45 (27.6)	12 (6.0)
Family income (% federal poverty level)						
<185%	61 (43.3)	25 (14.5)	9 (6.4)	45 (33.6)	39 (24.4)	11 (5.6)
185-350%	40 (22.5)	42 (24.4)	26 (18.4)	29 (21.6)	46 (28.8)	33 (42.0)
>350%	77 (43.3)	105 (61.1)	106 (75.2)	60 (44.8)	75 (46.9)	153 (54.5)
Education						
≤Grade 12	61 (32.8)	30 (16.5)	7 (4.8)	55 (36.7)	36 (22.1)	7 (3.5)
Grade 13 - 16	91 (48.9)	97 (53.2)	56 (38.6)	72 (48.0)	88 (54.0)	84 (42.0)
≥ Grade 17	34 (18.3)	55 (30.2)	82 (56.2)	23 (15.3)	39 (23.9)	109 (54.5)
Pre-pregnancy BMI, mean ± SD	27.5 ± 7.9	25.3 ± 5.8	22.8 ± 4.1	27.6 ± 8.0	26.7 ± 6.8	22.7 ± 3.5
Pre-pregnancy BMI Category (kg/m^2)						
Underweight	6 (3.2)	14 (7.7)	6 (4.1)	10 (6.7)	6 (3.7)	10 (5.0)
Normal weight	82 (44.1)	92 (50.6)	115 (79.3)	60 (40.0)	76 (46.6)	153 (76.5)
Overweight	48 (25.8)	41 (22.5)	15 (10.3)	35 (23.3)	40 (24.5)	29 (14.5)
Obese	50 (26.9)	35 (19.2)	9 (6.2)	45 (30.0)	41 (25.2)	8 (4.0)
Parity						
Nulliparous	80 (43.0)	83 (45.6)	98 (67.6)	63 (42.0)	72 (44.2)	126 (63.0)
Parous	106 (57.0)	99 (54.4)	47 (32.4)	87 (58.0)	91 (55.8)	74 (37.0)
Smoking status during pregnancy						
No	141 (80.1)	161 (91.5)	137 (97.2)	113 (80.7)	132 (84.6)	194 (98.5)
Yes	35 (19.9)	15 (8.5)	4 (2.8)	27 (19.3)	24 (15.4)	3 (1.5)

[A] All tests of differences in maternal characteristics by DASH and LCA patterns were statistically significant based on chi-square tests (P-values <0.001)

[B]Class 1: high consumption of hamburgers, hot dogs, French fries, fried chicken, white bread, bacon, and soft drinks. Class 2: high consumption of vegetables, refined grains, mixed dishes, red and processed meat, poultry, salty snacks, sweets, some fast foods, and fruit juice. Class 3: high consumption of fruits, vegetables, whole grains, low fat dairy, breakfast bars, and water

Table 2. Distribution of maternal dietary factors and cardiometabolic markers (mean + SD) by DASH score tertile or latent dietary classes

Variable	DASH				LCA[A]			
	Tertile 1 (n= 186)	Tertile 2 (n=182)	Tertile 3 (n=145)		Class 1 (n=150)	Class 2 (n=163)	Class 3 (n=200)	
Dietary factors								
DASH score[B]	18.7 ± 2.7	24.9 ± 1.4	30.2 ± 1.9	**	21.1 ± 4.4	22.3 ± 4.2	28.0 ± 3.6	**
Fruits (svg/d)	4.0 ± 3.3	4.5 ± 2.6	4.9 ± 2.6	*	3.7 ± 3.0	5.3 ± 3.3	4.2 ± 2.3	**
Vegetable (svg/d)	1.3 ± 1.2	2.3 ± 1.6	3.2 ± 2.2	**	1.4 ± 1.4	2.3 ± 1.7	2.6 ± 2.0	**
Nuts and legumes (svg/d)	0.2 ± 0.3	0.3 ± 0.3	0.4 ± 0.3	**	0.2 ± 0.2	0.4 ± 0.3	0.3 ± 0.3	**
Whole grains (svg /d)	0.4 ± 0.6	1.1 ± 1.5	1.5 ± 1.0	**	0.7 ± 1.7	0.9 ± 0.9	1.3 ± 0.9	**
Low fat dairy (svg /d)	1.2 ± 1.7	2.4 ± 2.1	3.7 ± 2.3	**	1.5 ± 2.0	1.9 ± 2.2	3.4 ± 2.2	**
Red meat (svg /d)	0.6 ± 0.7	0.4 ± 0.3	0.2 ± 0.2	**	0.5 ± 0.8	0.6 ± 0.3	0.2 ± 0.2	**
Sweetened beverages (svg /d)	3.8 ± 3.1	2.1 ± 2.2	0.9 ± 1.2	**	3.3 ± 3.6	3.2 ± 2.3	1.1 ± 1.2	**
Sodium (mg/d)	2925 ± 1193	2807 ± 1246	2626 ± 899		2217 ± 1052	3518 ± 1222	2573± 814	**
Energy intake (kcal/d)	2287 ± 964	2126 ± 859	1999 ± 623	*	1878 ± 914	2692 ± 869	1907 ± 504	**
Saturated fat	29.9 ± 14.0	26.3 ± 12.0	22.7 ± 8.5	**	23.9 ± 13.4	34.2 ± 12.3	22.4 ± 7.7	**
% energy from carbohydrates	54.3 ± 7.2	54.2 ± 7.5	56.2 ± 6.7	*	55.4 ± 8.5	53.9 ± 6.1	55.1 ± 6.9	
% energy from protein	13.1 ± 2.3	14.6 ± 2.5	15.4 ± 2.4	**	13.4 ± 2.7	13.7 ± 2.0	15.4 ± 2.5	**
% energy from fat	34.1 ± 5.7	33.5 ± 6.1	31.6 ± 5.6	**	33.1 ± 6.9	34.3 ± 4.9	32.4 ± 5.6	*
Cardiometabolic markers								
Glucose (mg/dL)	79.1 ± 7.7	78.5 ± 7.4	78.4 ± 7.4		79.5 ± 8.4	78.8 ± 7.7	78.0 ± 6.6	
Insulin (mg/dL)[C]	17.1 ± 1.7	15.4 ± 1.6	12.9 ± 1.6	**	17.4 ± 1.7	16.8 ± 1.6	12.7 ± 1.6	**
HOMA-IR[C]	3.3 ± 1.8	3.0 ± 1.7	2.5 ± 1.7	**	3.4 ± 1.8	3.3 ± 1.7	2.4 ± 1.6	**
Total Cholesterol (mg/dL)	241.3 ± 46.6	244.1 ± 43.5	250.8 ± 49.8		237.5 ± 46.3	239.7 ± 46.5	254.9 ± 45.2	*
Triglycerides (mg/dL)[C]	159.3 ± 1.5	158.6 ± 1.5	151.9 ± 1.4		153.1 ± 1.5	159.7 ± 1.5	157.7 ± 1.5	

**$P<0.0001$; *$P<0.05$

[A]Class 1: high consumption of hamburgers, hot dogs, French fries, fried chicken, white bread, bacon, and soft drinks. Class 2: high consumption of vegetables, refined grains, mixed dishes, red and processed meat, poultry, salty snacks, sweets, some fast foods, and fruit juice. Class 3: high consumption of fruits, vegetables, whole grains, low fat dairy, breakfast bars, and water

[B]DASH score ranges: Tertile 1 (12-22); Tertile 2 (23-27); Tertile 3 (28-37)

[C]Values represent geometric means of log-transformed outcomes

Table 3. Linear regression analysis for fasting glucose and total cholesterol according to DASH score tertile and latent dietary classes in 513 pregnant women, Pregnancy, Infection, and Nutrition (PIN) Study, 2001-2005

	Unadjusted Model 1[A]	Adjusted Model 2[B]	Adjusted Model 3[C]
	β (95% CI)	β (95% CI)	β (95% CI)
Glucose (mg/dL)[D]			
DASH score			
Tertile 1	--	--	--
Tertile 2	-0.56 (-2.10, 0.97)	-0.77 (-2.37, 0.83)	-0.23 (-1.75, 1.28)
Tertile 3	-0.72 (-2.36, 0.91)	-1.01 (-2.82, 0.81)	0.29 (-1.46, 2.04)
LCA patterns[E]			
Class 1	--	--	--
Class 2	-0.77 (-2.43, 0.90)	-1.01 (-2.86, 0.84)	-0.63 (-2.39, 1.12)
Class 3	-1.57 (-3.16, 0.02)	**-2.33 (-4.17, -0.50)**	-0.85 (-2.64, 0.92)
Cholesterol (mg/dL)[D]			
DASH score			
Tertile 1	---	---	---
Tertile 2	2.73 (-6.79, 12.25)	-4.50 (-14.07, 5.07)	-5.93 (-15.45, 3.59)
Tertile 3	9.48 (-0.63, 19.60)	0.57 (-10.34, 11.49)	-2.93 (-13.95, 8.08)
LCA patterns			
Class 1	---	---	---
Class 2	2.22 (-7.99, 12.44)	-0.05 (-11.15, 11.16)	-0.98 (-12.03, 10.07)
Class 3	**17.36 (7.60, 27.11)**	9.25 (-1.77, 20.27)	5.58 (-5.63, 16.79)

[A]Variables with skewed distributions were natural log (LN) transformed. To facilitate interpretation, back transformation (geometric mean change) values are provided which are calculated by exponentiating the regression coefficients and because of log(a/b)= log(a) – log(b)

[B]Unadjusted Model 1 represents crude association.

[C]Adjusted Model 2: maternal age, race, poverty level, smoking status, physical activity, parity, and energy intake.

[D]Adjusted Model 3: Model 2 plus pre-pregnancy BMI.

[E]Class 1: high consumption of hamburgers, hot dogs, French fries, fried chicken, white bread, bacon, and soft drinks. Class 2: high consumption of vegetables, refined grains, mixed dishes, red and processed meat, poultry, salty snacks, sweets, some fast foods, and fruit juice. Class 3: high consumption of fruits, vegetables, whole grains, low fat dairy, breakfast bars, and water

DASH: Dietary Approaches to Stop Hypertension, LCA: latent class analysis; HOMA-IR: homeostasis model of assessment for insulin resistance

Table 4. Ratio of geometric mean[A] for fasting insulin, HOMA-IR, and triglycerides (outcomes with skewed distributions) according to DASH score tertile and latent dietary classes in 513 pregnant women, Pregnancy, Infection, and Nutrition (PIN) Study, 2001-2005

	Unadjusted Model 1[B]	Adjusted Model 2[C]	Adjusted Model 3[D]
	Ratio of Geometric Mean (95% CI)[D]	Ratio of Geometric Mean (95% CI)	Ratio of Geometric Mean (95% CI)
Insulin			
DASH score			
Tertile 1	--	--	--
Tertile 2	**0.90 (0.81, 1.00)**	0.94 (0.85, 1.05)	0.99 (0.90, 1.09)
Tertile 3	**0.76 (0.68. 0.84)**	**0.83 (0.74, 0.94)**	0.93 (0.84, 1.04)
LCA patterns[E]			
Class 1	--	--	--
Class 2	0.97 (0.87, 1.08)	0.95 (0.84, 1.07)	0.98 (0.88, 1.10)
Class 3	**0.73 (0.66, 0.81)**	**0.78 (0.69, 0.88)**	**0.89 (0.80, 0.99)**
HOMA-IR			
DASH score			
Tertile 1	--	--	--
Tertile 2	0.90 (0.79, 1.00)	0.93 (0.83, 1.05)	0.98 (0.89, 1.09)
Tertile 3	**0.75 (0.66, 0.84)**	**0.82 (0.72, 0.94)**	0.94 (0.83, 1.06)
LCA patterns			
Class 1	--	--	--
Class 2	0.96 (0.85, 1.08)	0.94 (0.82, 1.07)	0.96 (0.85, 1.08)
Class 3	**0.72 (0.64, 0.80)**	**0.76 (0.66, 0.87)**	**0.88 (0.78, 1.00)**
Triglycerides			
DASH score			
Tertile 1	--	--	--
Tertile 2	0.99 (0.92, 1.08)	0.95 (0.88, 1.02)	0.96 (0.89, 1.03)
Tertile 3	0.95 (0.88, 1.03)	**0.88 (0.81, 0.96)**	**0.90 (0.82, 0.98)**
LCA patterns			
Class 1	--	--	--
Class 2	1.04 (0.96, 1.14)	1.04 (0.96, 1.14)	1.05 (0.96, 1.15)
Class 3	1.03 (0.95, 1.12)	0.96 (0.88, 1.05)	0.99 (0.91, 1.08)

[A]Variables with skewed distributions were natural log (LN) transformed. To facilitate interpretation, back transformation (geometric mean change) values are provided which are calculated by exponentiating the regression coefficients and because of log(a/b)= log(a) – log(b)
[B]Unadjusted Model 1 represents crude association.
[C]Adjusted Model 2: maternal age, race, poverty level, smoking status, physical activity, parity, and energy intake.
[D]Adjusted Model 3: Model 2 plus pre-pregnancy BMI.
[E]Class 1: high consumption of hamburgers, hot dogs, French fries, fried chicken, white bread, bacon, and soft drinks. Class 2: high consumption of vegetables, refined grains, mixed dishes, red and processed meat, poultry, salty snacks, sweets, some fast foods, and fruit juice. Class 3: high consumption of fruits, vegetables, whole grains, low fat dairy, breakfast bars, and water
DASH: Dietary Approaches to Stop Hypertension, LCA: latent class analysis; HOMA-IR: homeostasis model of assessment for insulin resistance

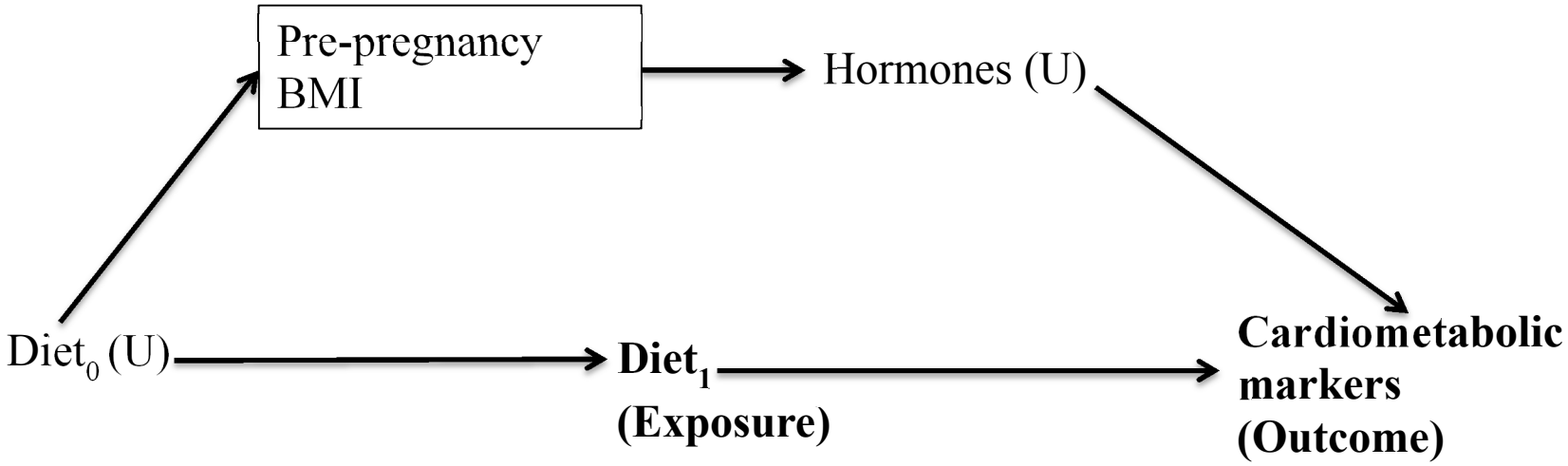


Figure 3. A simplified conceptual model of the dietary pattern-cardiometabolic markers association and adjustment for pre-pregnancy BMI

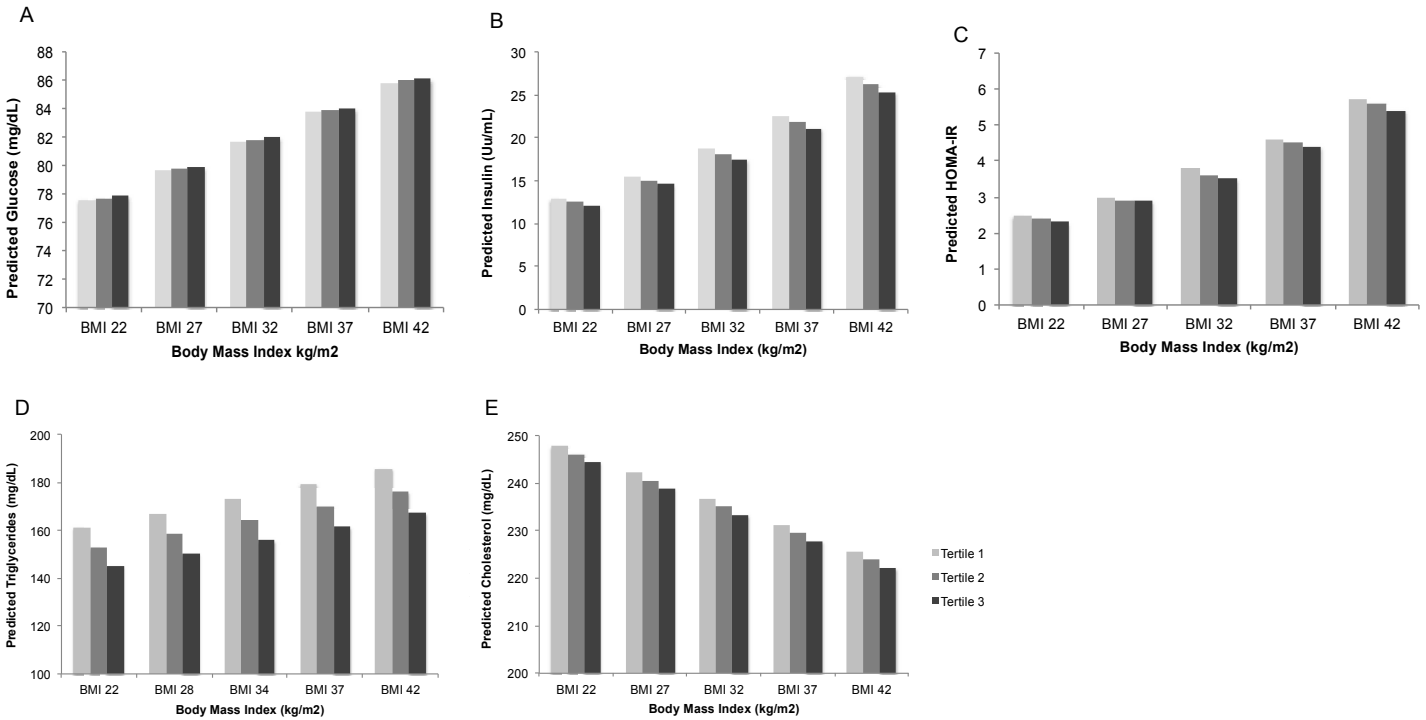


Figure 4. Predicted mean level for fasting A) Glucose, B) Insulin, C) HOMA-IR, D) Triglycerides, and E) Cholesterol according to DASH score tertile for women at varying pre-pregnancy BMI levels in the (PIN) study (n=513). Predicted means adjusted for maternal age, race, parity, smoking status during pregnancy, % poverty level, physical activity (median), and energy intake (median)

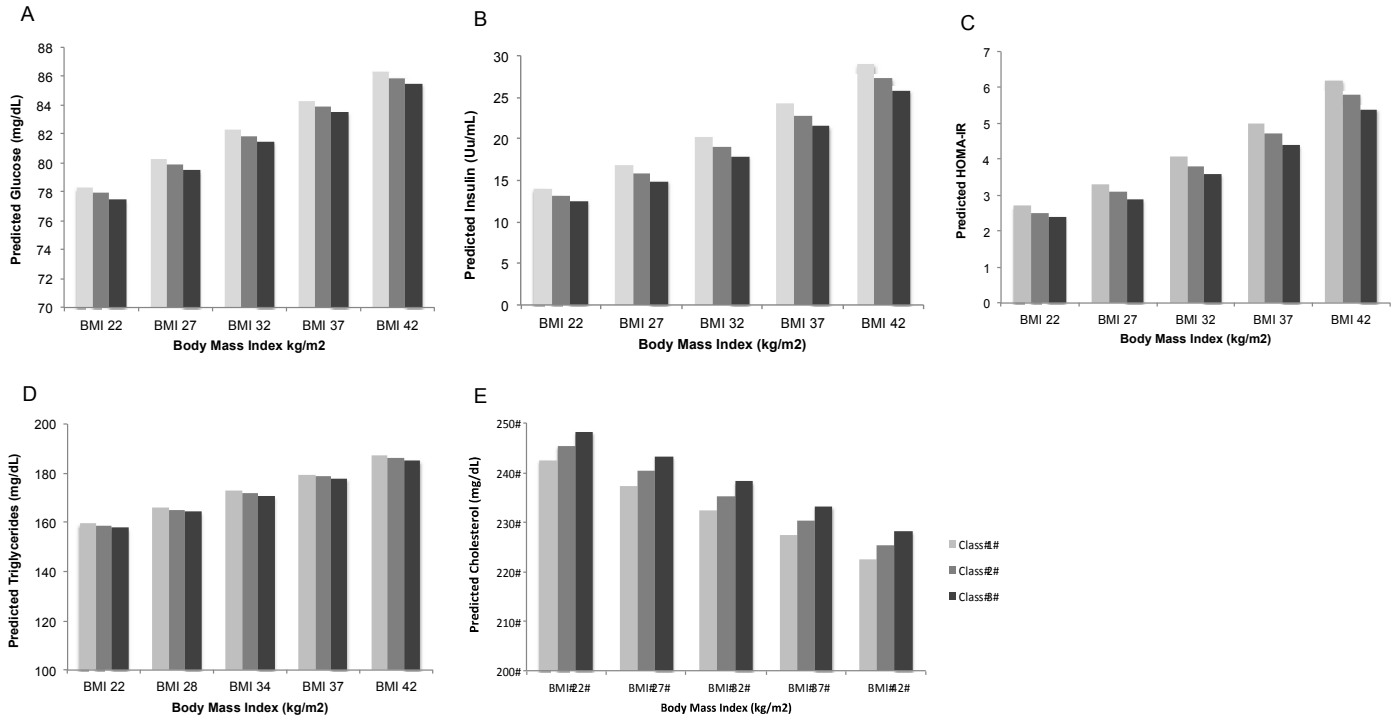


Figure 5. Predicted mean level for fasting A) Glucose, B) Insulin, C) HOMA-IR, D) Triglycerides, and E) Cholesterol according to latent class for women at varying pre-pregnancy BMI levels in the (PIN) study (n=513). Predicted means adjusted for maternal age, race, parity, smoking status during pregnancy, % poverty level, physical activity (median), and energy intake (median)

CHAPTER V: MATERNAL DIETARY PATTERNS DURING PREGNANCY AND CHILD GROWTH FROM BIRTH TO 36 MONTHS

INTRODUCTION

Early childhood obesity continues to be a major public health concern in the United States. The most recent national estimates indicate that the prevalence of child overweight/obesity is nearly 23% among children 2-5 years of age (13). In a child's first two years of life, the prevalence of obesity is more than 8% (13). Overweight and obesity during childhood increases the likelihood of obesity later in life and the risk of obesity-related chronic conditions (15, 19, 117). Identifying early-life risk factors can have important implications for prevention strategies because the development of adipocytes – the cells that regulate fat mass—begins during fetal development (118).

Maternal diet during pregnancy is the primary source of energy and nutrients needed for fetal growth and development (119), and therefore a potential modifiable factor for intervention. Previous cohort studies examining the effect of maternal diet during pregnancy on offspring adiposity have provided inconclusive results (57-59, 120). These studies mainly focused on the intake of a single macronutrient or an individual food during pregnancy, and the effect may be too small to detect (7). Alternatively, evidence from animal studies suggests that diet quality may be of more importance than intake of macronutrients and individual foods during pregnancy in relation to offspring weight status, as pregnant rats fed "high-fat" and "junk food" diets

produced obese offspring (3-6). However, there is limited research in humans to support animal findings about diet quality during pregnancy.

Assessment of dietary patterns has become useful in epidemiological studies that aim to examine the impact of overall diet quality on health outcomes. Analysis of dietary patterns includes examination of combinations of foods and nutrients eaten together allowing for assessment of interactions between nutrients. Dietary patterns can be assessed using *a priori* score-based methods, based on dietary guidelines and recommendations, and *a posteriori* data-driven approaches using statistical methods (7, 8). Studies of dietary patterns have provided important insights into the role of diet quality during pregnancy on offspring birth weight. However, to our knowledge, no study has examined the relation between maternal dietary patterns and early childhood growth patterns. A recent systematic review and meta-analysis on the effects of dietary interventions on neonatal and infant outcomes demonstrated the need for more research to identify ideal maternal dietary intakes that optimize neonatal and infant anthropometric outcomes (76).

In our study, we sought to investigate the association between a score-based dietary pattern, based on adherence to the Dietary Approaches to Stop Hypertension (DASH) diet, and child growth outcomes using data from a prospective cohort study. The main objective was to examine how overall maternal diet quality during pregnancy relates to offspring weight status at 36 months of age and the change in weight status over time from birth to 36 months.

METHODS

Study design and population

We used data from the Pregnancy, Infection, and Nutrition (PIN) study. Pregnant women, less than 20 weeks' gestation, were recruited from public and private clinics at the University of North Carolina (UNC) Hospitals into the third cohort of PIN (PIN 3) from January 2001-June 2005 and followed to delivery (n=2,006). Women who were at least 16 years of age, English-speaking, and planning to continue receiving prenatal care from the UNC clinics were eligible to participate. The PIN Postpartum study began in 2002 and was a prospective cohort study of eligible women from PIN 3 (n=1,169) that followed-up the index child at 3 months (n=688) and 12 months (n=550) postpartum. PIN Kids began in 2004 and followed-up eligible children born in the last two years of the PIN 3 study through 36 months of age.

Data were collected using self-administered questionnaires and telephone interviews during the prenatal period, including a food frequency questionnaire (FFQ) to collect dietary information. In-home visits were conducted at 3,12, and 36 months postpartum to collect information on the mother and child's health and behaviors, as well as to measure weight and height. All PIN study protocols and procedures were reviewed and approved by the Institutional Review Board of the UNC School of Medicine.

For this investigation, we used data from the mother-child pairs who participated in the 12 months postpartum interviews. A total of 521 children provided at least one anthropometric measurement (height or weight). We excluded children who were born preterm (n=59) and who did not have maternal prenatal dietary information (n=25). We further excluded 7 mother-child pairs who were missing prenatal covariate information (pre-pregnancy body mass index (BMI),

n=1, maternal race, n=1, smoking status during pregnancy, n=2, and household income level, n=3). Our final analytical sample included 430 mother-child pairs.

Outcome Assessment

We abstracted child's birthweight and sex from delivery records. Child's weight and height were recorded by medical staff during pediatrician visits and provided to mothers doctor cards supplied by the PIN study. We calculated the child's precise age at each measurement using the difference between the documented date of visit and the child's birth date. Trained research staff measured children's standing height and weight at the 36-month home visit using stadiometers and scales according to the NHANES protocols (92).

We computed weight-for-height z-scores (WHZ) for children from birth to 24 months using the 2006 WHO growth charts and for children 2 years and older using the 2000 CDC growth charts (22, 93). Z-scores are used to account for sex differences and variation in the ages at the time of measurement. WHZ is a measure of relative weight and was used as the outcome to examine child growth from birth to 36 months of age. We excluded measurements considered extreme values (<-5 or >5 for WHO; <-4 or >5 for CDC) from the analysis (n=10). The 430 children included in the analysis contributed 3,154 measurements (mean = 5 measurements per child; range = 1-15 measurements). We calculated body mass index (BMI) z-scores based on the 2000 CDC growth charts to examine the association between maternal dietary patterns during pregnancy and child BMI z-score at 36 months of age for children with available in-home measurements (n=276).

Exposure assessment

Maternal diet during pregnancy was collected at 26-29 weeks gestation using a self-administered, semi-quantitative, 119-item Block FFQ to assess dietary intake over the prior three months. Detailed information on the validity of the FFQ has been described elsewhere (84). Dietsys+Plus version 5.6 with an updated food composition table based on nutrient values from the NHANES III and USDA 1998 nutrient databases were used to calculate daily energy intake in kcals and grams per day from the FFQ data.

We examined dietary patterns based on adherence to the DASH diet. Briefly, the DASH diet is comprises eight food components: fruits, vegetables, nuts and legumes, low fat diary, whole grains, sodium, red and processed meat, and sugar-sweetened beverages. The scoring algorithm for the DASH diet is based on a previously developed approach, where participants are scored based on their quintile of intake (87). High intake of fruits, vegetables, nuts and legumes, low fat dairy, and whole grains were assigned one point for each quintile ranking (e.g. bottom quintile = 1 point, top quintile = 5 points). Sodium, red and processed meat, and sweetened beverage intakes were reverse scored, where the bottom quintile of intake received five points and the top quintile received one point. Each component score was summed to derive a total DASH adherence score for each participant, which could range from 8 (not adherent) to 40 (adherent).

Covariates

We considered the following covariates, all of which women reported during the prenatal period—age, race, marital status, parity, household income, education level, gestational age at delivery, pre-pregnancy BMI, and smoking status. Age, in years, at time of conception was

categorized: 16-24, 25-29, 30-34, and ≥35 years. Race was dichotomized as non-black and black due to the small number of women self-identifying with a race/ethnicity other than "white" or "black". Marital status was based on cohabitation status and dichotomized as married/living with a partner and unmarried. Parity was defined based on the number of births prior to the index pregnancy and was dichotomized as nulliparous and parous. Household income was converted to percent of the poverty line based on the 2001 US Department of Health and Human Services Federal Poverty Guidelines and cut points were based on the Special Supplemental Nutrition Program for Women, Infant, and Children (WIC) eligibility guidelines: <185%, 185-350%, and >350% (94). If prenatal household income information was missing, we used household income data collected at the 3-month interview (n= 7). The number of years of completed education was categorized as ≤ Grade 12 (high school completion or less), Grades 13-16 (high school with some college), ≥ Grade 17 (some post-college education). Gestational age was estimated from the first ultrasound measurement performed prior to 22 weeks' gestation; however, if an ultrasound was not performed prior to 22 weeks' gestation, then the date of last menstrual period was used. Pre-pregnancy BMI was based on height measured at the first prenatal clinic visit and self-reported pre-pregnancy weight. Missing pre-pregnancy weight was imputed using weight at the first prenatal care visit (95). Smoking status (smoker vs. nonsmoker) during the first six months of pregnancy was collected from self-administered questionnaires. Smoking information at the 3-month interview was used when information was missing for the prenatal period (n= 7).

Statistical Analysis

We calculated baseline mean and standard deviation (SD) for continuous variables and frequency and percentages for categorical variables, to describe the baseline characteristics of the study population. DASH adherence scores were divided into tertiles (Teritle 1: 12-23; Tertile 2: 24-27; Tertile 3: 28-35) for descriptive analyses. We subsequently created a dichotomous DASH score variable (<28 vs. ≥28) due to similarities in dietary intake between Tertile 1 and Tertile 2. Potential confounders were determined *a priori* from the research literature and directed acyclic graphs (DAG) analysis (96).

We used multivariable linear regression to examine the association between maternal DASH adherence and child BMI z-score at 36 months of age. We first adjusted models for maternal race, education, poverty level, marital status, and smoking status during pregnancy. We further examined the influence of maternal pre-pregnancy BMI by subsequently including it in the adjusted models.

Linear mixed models were used to estimate child growth (WHZ), defined as intercept (birth) and slope (rate of change) from birth to 36 months of age in relation to maternal DASH score during pregnancy. We used linear mixed models, because they are used for continuous repeated outcome measures and can account for unbalanced data (varying number of repeated outcomes across children), unequal spacing of measurements across time, and the correlations between measurements within each child (97, 98). Children with at least one measurement were included in the analysis. Age (in years) represented the unit of time. We included a polynomial term for the time variable to take into account the non-linear change in WHZ over time. We found that the quadratic (age-squared), not cubic (age-cubed), provided better model fit. We included random effects at the individual level for the intercept, linear age term, and quadratic

age term to allow both the intercept and slope to vary between individuals. We used Akaike's Information Criteria (AIC) to determine the best-fit model. We further examined interactions to determine whether the associations between maternal dietary patterns and child WHZ varied over time by including an interaction term for binary DASH score and child's age. The AIC was used to test the fixed effects for the interaction terms. All analyses were performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

Baseline characteristics

Sixty-five percent (n=281) of the mothers had a DASH adherence score in the bottom 67th percentile (**Table 5**). The mean (SD) gestational age at delivery and birthweight were 39 (1) weeks and 3438 (522) grams, respectively. The majority of mothers were non-Black, married, from high-income households, college educated, and nonsmokers. The mean (SD) pre-pregnancy BMI was 24 (6). At 36 months of age, the mean (SD) child BMI z-score was 0.28 (1.01), 20% were overweight/obese (BMI ≥85th percentile), and 6% were obese (BMI ≥95th percentile).

As we expected, mothers with DASH scores less than 28 had significantly lower reported intake of fruits, vegetables, nuts and legumes, whole grains, and low fat dairy than women with scores ≥28, while intake of red meat, sweetened beverages, and sodium and energy intake were higher (**Table 6**). We also found that percent energy intake from fat was higher, while percent energy intake from carbohydrates and protein was lower for mothers with scores <28 compared to mothers with scores ≥28.

BMI z-score at 36 months of age

In the multivariable linear regression models, mothers with lower DASH scores, <28, had children with a significantly higher BMI z-scores at 36 months of age compared to mothers with higher DASH scores, ≥28 (β=0.30; 95% CI: 0.05-0.55; **Table 7**). After adjustment for potential confounders, the association shifted towards the null (β=0.11; 95%CI: -0.15-0.37). Associations were similar after excluding pregnant women with daily energy intakes ±2.5th percentile (1083 and 3813 kcals).

Changes in WHZ over time

On average, children of mothers with a lower DASH score had a higher WHZ compared to children of mothers with a higher DASH score (β=0.19; 95% CI: 0.04, 0.34; **Table 8**, Model 2). Adjustment for maternal pre-pregnancy BMI slightly attenuated the results (β=0.15; 95% CI: -0.01, 0.30). Predicted mean WHZ for children of mothers with a DASH score <28 was consistently higher than children of mothers with a DASH score ≥28 (**Figure 6**). We did not find evidence of an interaction between maternal DASH score and child's age. Adjustment for maternal age, gestational weight gain, child and maternal physical activity, and exclusive breastfeeding did not noticeably change estimates, so we did not include these factors in our final models.

DISCUSSION

In this prospective cohort study, we observed a difference in child growth outcomes in relation to the DASH diet during pregnancy. To our knowledge, this is the first study to use dietary pattern methodology to explore the association between maternal diet quality during

pregnancy and growth patterns in early childhood. On average, children of mothers with a lower DASH score, less than 28, had higher mean WHZ from birth to 36 months than children of mothers with a higher DASH score, greater than or equal to 28. Predicted offspring WHZ was consistently higher for mothers with a DASH score <28 compared with mothers with a DASH score ≥28. Associations were similar, but weaker, for BMI z-score at 36 months of age. We did not find evidence of an interaction between maternal DASH score and child's age, which indicates that the rate of change in WHZ does not differ in the first 36 months of life by maternal DASH score. Overall, our findings suggest that fetal exposure to a poor diet quality during pregnancy may contribute to the development of offspring overweight/obesity, independent of maternal sociodemographics.

Observational studies of maternal diet during pregnancy demonstrate a link to offspring adiposity during infancy and childhood nutrients (37, 48-56). However, many of these studies focus on macronutrient intake. Our findings are consistent with studies examining the early childhood period. In a study of Irish mother-child pairs, Murrin et al., (2013) found significantly higher odds of child overweight/obesity at 5 years of age with higher maternal sugar intake in the first trimester compared to lower intakes (Q5 vs. Q1: 4.57; 95% CI: 1.01-20.69) (57). Furthermore, a previous study demonstrated the importance of the quality and quantity of carbohydrates during pregnancy, using the glycemic index (GI) and glycemic load (GL), in the development of early childhood obesity (60). Results from Southampton Women's Survey showed that maternal dietary GI and GL were associated with increased offspring fat mass at 4 and 6 years of age (60).

Our results extend findings from animal studies suggesting a biological link between maternal diet composition during gestation and offspring early life weight status. It is possible

that fetal exposure to maternal overnutrition during gestation influences offspring appetite regulators and metabolic profiles resulting in increased adiposity later in life (1, 29). Experimental studies in animal models show that high-fat and high-energy diets during gestation produced offspring with greater fat mass, fat distribution, and greater risk of obesity (3, 4, 6).

Our findings are consistent with previous studies showing an association between maternal diet during pregnancy and fetal growth. Using fetal ultrasound to measure fetal body composition, authors found a positive association between fetal abdominal visceral area throughout gestation and maternal protein and protein:carbohydrate ratio (121). Similarly, Knudsen et al., (2013) found that higher maternal dietary glycemic load during the second trimester was associated with increased risk of delivering a LGA baby (48). Rodriguez-Bernal et al. (2010), utilized the Alternate Healthy Eating Index-Pregnancy (AHEI), a score-based method, to examine the association between maternal diet quality and fetal growth outcomes among women and newborns participating in a Spanish cohort study (72). These authors reported a positive association between AHEI score and birth weight.

Data-driven approaches to dietary patterns have also supported an association with birth outcomes. Two previous studies using factor analysis found that healthier dietary patterns during pregnancy were associated with reduced odds of having a small-for-gestational (SGA) baby. Knudsen et al. (2008) reported a 25% decrease in odds of delivering a SGA baby for women consuming a diet high in fruits, vegetables, fish, and poultry compared to a diet with high intake of high-fat dairy, refined grains, processed and red mat, animal fat, potatoes, and sweets (67). Similarly, Thompson et al., (2009) reported lower odds of SGA for women with high intakes of fruits, vegetables, and dairy (68). Additionally, in a cohort study among Japanese pregnant women using cluster analysis, higher odds of SGA for weight were found among women

consuming a diet characterized by high intake of bread, confectioneries, fruit and vegetable juice, and soft drinks compared to women with diets high in rice, potatoes, nuts, pulses, fruits, vegetables, fish, shellfish, sea products, and miso soup (71). Weight status at birth and in early childhood is an established risk factor for development of obesity and our results along with previous research provide evidence of an association between maternal dietary patterns during pregnancy and early life adiposity.

Our results must be interpreted in light of study limitations. First, WHZ and BMI z-scores, which are commonly used as proxies, are not direct measures of body composition. WHZ measurements were collected during pediatrician visits by medical staff. As with all studies using information previously collected by medical staff without standardized collection protocols, measurement error of weight and height cannot be overlooked. Although the prospective cohort design allowed for adjustment of many confounding factors, the effect of unmeasured confounders on study results cannot be ignored. The loss to follow-up experienced from birth to 36 moths postpartum resulted in a lower proportion of women from high-risk groups, which likely weakened the associations observed in this study. Additionally, the loss to follow up limited our sample size and possible detection of some associations that may have existed. Lastly, the generalizability of our study population is limited because women were mainly well-educated, white, and had high income levels, leading to a lower prevalence of pregnant women with unhealthy dietary patterns (122).

CONCLUSIONS

Despite these limitations, our findings further advance our knowledge of the influence of diet quality during pregnancy on offspring weight status in early childhood. The results suggest

that poor adherence to the DASH diet is associated with early childhood growth and BMI. Further investigations in larger, more diverse longitudinal studies are warranted to confirm and extend our study's findings.

Table 5. Select maternal and child characteristics: Means (SD) and percentages in the Pregnancy, Infection, and Nutrition study, (n=430)

Variable	**N**	**Mean (SD)/ %**
Maternal age at conception (years)	430	30.3 (5.1)
Age (years)		
16-24	59	14
25-29	123	29
30-34	167	39
35-47	81	19
Race		
Non-Black	394	92
Black	36	8
Marital status		
Married	372	87
Unmarried	58	13
Federal poverty level		
<185%	58	13
185-350%	80	19
>350%	292	68
Education		
≤Grade 12	43	10
Grade 13 - 16	211	49
≥ Grade 17	176	41
Pre-pregnancy BMI	430	24.4 (6.1)
Pre-pregnancy BMI Category (kg/m^2)		
Underweight	23	5
Normal weight	281	65
Overweight	72	17
Obese	54	13
Parity		
0	213	50
≥1	217	50
Smoking status during pregnancy		
No	393	91
Yes	37	9
DASH score tertile		
<28	281	65
≥28	149	35
Gestational age at delivery (weeks)	430	39.2 (1.2)
Infant sex		
Male	218	51
Female	212	49

Table 6. Dietary and energy intake according to DASH score tertiles, Pregnancy, Nutrition, and Infection study (n=430)

Variable	DASH score[A]	
	<28 (n=281)	**≥28** (n=149)
Dietary factors		
Fruits (svg/d)	4.0 (2.7)	4.8 (2.5)**
Vegetable (svg/d)	1.9 (1.5)	2.9 (1.8)**
Nuts and legumes (svg/d)	0.3 (0.3)	0.4 (0.2)**
Whole grains (svg /d)	0.8 (1.3)	1.4 (1.0)**
Low fat dairy (svg /d)	2.1 (2.0)	4.1 (2.2)**
Red meat (svg /d)	0.5 (0.6)	0.2 (0.2)**
Sweetened beverages (svg /d)	2.5 (2.6)	1.0 (1.1)**
Sodium (mg/d)	2902 (1122)	2643 (786)*
Energy intake (kcal/d)	2194 (869)	1999 (485)*
% energy from carbohydrates	54 (7)	56 (6)**
% energy from protein	14 (2)	15 (2)**
% energy from fat	34 (6)	31 (5)**

***P*<0.01; **P*<0.05 T-test

[A]DASH score ≥28 represents the top 33rd percentile.

Table 7. Association between maternal DASH diet score during pregnancy and child BMI z-score at 36 months of age in Pregnancy, Infection, and Nutrition study excluding preterm births (n=276)

	Model 1[A]	Model 2[B]	Model 3[C]
DASH score			
<28	**0.30 (0.05-0.55)**	0.17 (-0.08-0.43)	0.11 (-0.15-0.37)
≥28	---	---	---

[A]Model 1 represents crude association

[B]Model 2 adjusts for maternal age, race, education, poverty level, smoking status during pregnancy, and marital status

[C]Model 3 adjusts for Model 2 variables and pre-pregnancy BMI

Table 8. Linear mixed model results of the association between DASH adherence score and child weight-for-height z-score from birth to 36 months of age, Pregnancy, Infection, and Nutrition study (n=430)

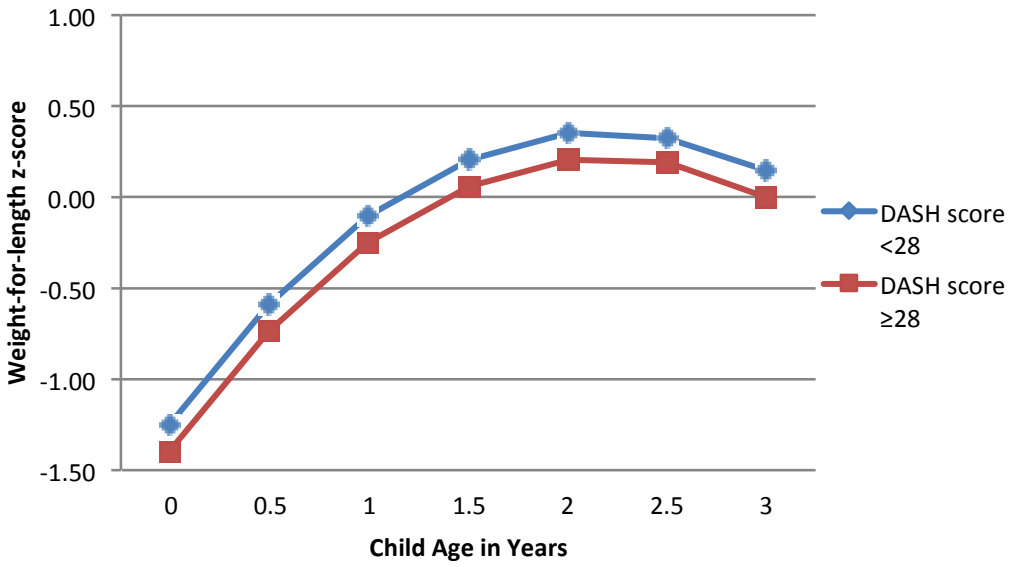
	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)
Intercept	-1.23 (-1.36, -1.11)	-1.34 (-1.65, -1.02)	-1.39 (-1.71, -1.08)
Exposure			
DASH score <28	0.23 (0.08, 0.37)	0.19 (0.04, 0.34)	0.15 (-0.01, 0.30)
DASH score ≥ 28	---	---	---
Time			
Age (years)	1.48 (1.34, 1.61)	1.47 (1.34, 1.61)	1.47 (1.34, 1.61)
Age*Age (years)	-0.34 (-0.42, -0.25)	-0.34 (-0.42, 0.26)	-0.34 (-0.42, -0.26)

Model 1 adjusts for child age

Model 2 adjusts for maternal race, education at recruitment, poverty level, marital status and smoking status during pregnancy

Model 3 adjusts for Model 2 variables and pre-pregnancy BMI

Figure 6. Predicted child weight-for-height z-score from birth to 36 months of age according to DASH adherence score in the Pregnancy, Infection, and Nutrition study (n=430)*



*Predicted means adjusted for maternal race, education, poverty level, marital status, smoking status during pregnancy, and pre-pregnancy BMI

CHAPTER VI: CONCLUSIONS

The purpose of this dissertation was to advance current knowledge about the relationship between maternal diet quality, defined using dietary patterns, and early childhood growth outcomes. In addition, we sought to determine the possibility of cardiometabolic markers during pregnancy as a potential biological mechanism. The following section summarizes the key study findings, details the study's strengths of limitations, discusses the public health significance, and directions for future research.

SUMMARY OF FINDINGS

In the first specific aim, we examined the association between second trimester maternal dietary patterns, measured using the DASH diet and LCA, and cardiometabolic markers at 24-29 weeks gestation. Specifically, we examined maternal glucose, insulin, HOMA-IR, total cholesterol, and triglycerides. We found that pregnant women in the highest tertile of the DASH diet, which represents healthier diet quality, had lower insulin, HOMA-IR, and triglyceride levels compared to women in the lowest tertile of the DASH diet score. The ratio of geometric mean for insulin, HOMA-IR, and triglycerides were 0.83 (95% CI: 0.74-0.94), 0.82 (95% CI: 0.72-0.94), and 0.88 (95% CI: 0.81-0.96), respectively. Additionally, using LCA, we found that a dietary pattern characterized by high intake of fruits, vegetables, whole grains, low fat dairy, breakfast bars, and water was associated with lower glucose, insulin, and HOMA-IR levels compared to a diet consisting of high intake of hamburgers, hot dogs, French fries, fried chicken,

white bread, bacon, and soft drinks. Pre-pregnancy BMI attenuated the results was an important confounding factor to consider.

In the second specific aim, we examined the association between maternal DASH diet and child anthropometric measurements between birth and 36 months of age. We utilized the longitudinal nature of the PIN study to examine repeated measures of WHZ in the 36 months of life. We found evidence that exposure to lower maternal DASH score, representing poorer diet quality, during the second trimester was associated with higher WHZ from birth to 36 months, compared to higher DASH score (β=0.19; 95% CI: 0.04, 0.34). Further adjustment for pre-pregnancy BMI slightly reduced the association (β=0.15; 95% CI: -0.01, 0.30). Suggestion of an association was found between low maternal DASH score and BMI z-score at 36 months of age (β=0.11; 95% CI: -0.15-0.37). We did not find evidence of an interaction between maternal DASH diet score and WHZ, indicating that maternal DASH score during pregnancy does not influence the rate of change in WHZ in the first 36 months of life.

Overall, our findings offer some support of the overnutrition hypothesis, which proposes that poor maternal diet during pregnancy is related to elevated cardiometabolic markers leading to high fetal/neonatal BMI and subsequently high childhood BMI (1). We demonstrated that lower DASH score, indicative of poor diet quality, was associated with higher WHZ. Although not statistically significant, predicted WHZ was consistently higher for children of mothers with a lower DASH score compared to higher DASH score from birth to 36 months of age. Furthermore, we found that better maternal diet quality during pregnancy could be a mitigating factor by reducing levels of cardiometabolic markers during pregnancy, which are also related to increased offspring adiposity in observational studies (30, 40, 42-44, 46, 47, 101, 102, 123).

STUDY LIMITATIONS

Our research study has several limitations that were previously discussed in the preceding chapters and are revisited here. First, all dietary information relied on self-report. As with all dietary assessment instruments, there is the potential for misreporting. The PIN FFQ was validated in previous PIN cohorts against 24-hour dietary recalls (84). We also examined the robustness of our findings against extreme reported energy intakes by excluding the $\pm 2.5^{th}$ and $\pm 5^{th}$ percentiles for reported daily energy intake and found no noticeable changes in our results.

Second, although WHZ and BMI z-scores are commonly used as proxies, they are not direct measures of child body composition. WHZ is an estimate of infant body size relative to the U.S. reference population. The CDC and WHO growth data are based on repeated cross-sectional measurements, which do not adequately account for child growth. Child BMI z-score is also based on a U.S. reference population and is only a measure of excess weight instead of fat mass. Direct measurements, such as dual-energy x-ray absorptiometry (DEXA), are preferential, yet impracticable for large epidemiologic research.

Third, WHZ measurements were collected on doctor's cards provided by the PIN study that medical staff used to record weight and height measurements during pediatrician visits. As with all studies using information previously collected by medical staff without standardized collection protocols, measurement error of weight and height cannot be overlooked. The birth weights and heights were collected from delivery logs and trained PIN personnel collected the 36-month measurements according to study protocols.

Fourth, the loss-to-follow up from birth to 36 months postpartum limited our sample size, which may have impacted our ability to detect some associations that may have existed. We were only able to include 276 mother-child pairs at 36 months of age, which limited our ability

to examine child overweight (≥85th percentile) and obese (≥95th percentile) outcomes. However, we were able to investigate the relationship using BMI z-score, which did show suggestion of an association.

Fifth, the loss to follow-up experienced from the prenatal to postpartum period resulted in a lower proportion of women from high-risk groups. In a separate study using dietary data from the PIN study, women with lower income and education levels were likely to have lower DASH diet scores (122). In addition, the risk of child overweight and obesity is higher in lower socioeconomic classes (124, 125). The lower prevalence of women from high-risk groups likely weakened the associations observed in our study. In addition, the findings of our study has limited generalizability to disadvantaged populations, as the majority of our study sample was white, well-educated, and had high household income.

Lastly, although we were able to take advantage of the rich data available in this prospective cohort study and adjust for several potential confounding factors, we cannot dismiss the possible influence of unmeasured confounding. This is not unique to our study, as this is a concern of all observational studies.

STUDY STRENGTHS

The PIN study is a longitudinal, prospective pregnancy cohort with mother-child follow-up data through 36 months postpartum. The study collected measurements of child weight and height at several time points between birth and 36 months of age. Dietary intakes were collected using calibrated FFQ to reflect the intakes during the second trimester. Because of the multiple interviews during the prenatal and the postnatal period, the study also had information available on key prenatal variables such as sociodemographic characteristics, smoking status, and pre-

pregnancy BMI, which allowed for appropriate adjustment of potential confounders for the total effect of maternal dietary patterns on offspring weight status.

The study utilized novel methods to examine maternal dietary patterns during pregnancy using the DASH diet and LCA. While previous studies of maternal diet and child weight status have mainly focused on individual foods and nutrients (37, 48-56), dietary patterns capture the overall quality of the diet by examining the combinations of foods and nutrients eaten together and allowing for assessment of interaction and synergistic effects between nutrients on health outcomes.

Research is limited on the impact of maternal dietary patterns on cardiometabolic markers during pregnancy and early childhood weight status. Our study adds a valuable contribution to the research literature. Maternal dietary intake was collected at 26-29 weeks gestation to reflect early pregnancy and blood samples were collected at 24-29 weeks gestation. This allowed for a prospective analysis of the association. In addition, because of the longitudinal nature of the PIN study we were able to utilize the repeated measurements of child weight and height to determine the relationship between maternal diet quality during pregnancy and early childhood growth.

PUBLIC HEALTH IMPLICATIONS

Childhood overweight and obesity are significant problem in the United States. With over 30% of U.S. children and adolescents being overweight and 17% obese (13), the observed findings between maternal dietary patterns during pregnancy and child weight status in early childhood could have sizable public health impact. Our main hypothesis posited that maternal overnutrition, defined as poor diet quality in our study, was associated with early

childhood weight status through increased levels of important cardiometabolic markers during pregnancy (1). In our second specific aim, we observed evidence of an association between lower maternal DASH diet score in the second trimester and offspring WHZ in the first 36 months of life. Our first specific aim demonstrated that healthier maternal dietary patterns during pregnancy were associated with lower glucose, insulin, HOMA-IR, and triglycerides. This offers support of a potential mechanistic link between maternal diet during pregnancy and early childhood weight status.

Our primary hypothesis was based on fetal concentrations of metabolic markers; however, it is impossible to collect this data in epidemiologic studies. Therefore, maternal concentrations served as a proxy. Several observational studies have reported higher offspring anthropometrics as a result of increased maternal cardiometabolic marker concentrations in pregnancy (30, 40, 42, 43, 45-47, 101, 102), which suggests the potential to reduce the risk of early childhood overweight and obesity through improving maternal cardiometabolic profiles during pregnancy. Our results contributes to a growing body of research evidence implying that maternal diet quality during pregnancy may influence offspring weight status and emphasizes the potential impact of dietary counseling and interventions on maternal health during pregnancy and subsequently offspring anthropometrics.

Currently, there is limited research on prenatal dietary patterns that extend into early childhood and includes secondary outcomes such as maternal cardiometabolic markers. RCTs have examined the effects of dietary interventions on maternal cardiometabolic markers during pregnancy. One RCT found that the DASH diet during pregnancy was effective in improving glucose and lipid profiles of women during pregnancy, but was only for a 4-week period and was conducted among women with gestational diabetes (10, 11). A recently published systematic

review and meta-analysis found only three studies that have evaluated the effects of dietary interventions on infant weight outcomes (76), where only one found an association with infant weight and height in the first year of life (126). However, this study lacked generalizability, as the participants were nutritionally at-risk. If future research confirms the results of our study, interventions during pregnancy with a focus on maternal diet quality could have significant public health impact.

In addition to intervention efforts, healthcare providers offer a unique opportunity for promoting healthy diet quality. While preconception dietary counseling is ideal for intervening and counseling, our findings indicate that prenatal counseling could also be beneficial. Health care providers are in constant contact with women, especially during pregnancy, providing a unique opportunity for educating on the importance of following current dietary recommendations. For example, pregnant women may be advised to eat a dietary pattern that is consistent with the DASH diet, which aligns with the current Dietary Guidelines for Americans, that emphasizes high intakes of fruits, vegetables, whole grains, low fat dairy, and nuts and legumes for healthier pregnancy and offspring outcomes. Efforts to inform health care providers of these dietary recommendations are warranted.

DIRECTION OF FUTURE RESEARCH

As previously mentioned, limited research is available that examines the influence of overall maternal diet quality during pregnancy on short-term maternal health and long-term child adiposity. Further investigations in large, diverse cohorts are necessary to understand the association between maternal dietary patterns during pregnancy and early childhood weight status. We have identified the following areas for future research:

1) *Direct Measures of child adiposity*

Anthropometric measurements are commonly used in large epidemiologic research because of their cost-efficiency and practical use. Our study, like many previous studies, did not have information on direct measures of child adiposity like body fat, and instead utilized anthropometric measurements to investigate the association between child weight status and prenatal dietary patterns. As discussed previously, anthropometric measures only serve as a proxy for child adiposity. Future studies using direct measures of body fat are needed.

2) *Disentangle effects of fetal exposures*

During the pregnancy period, the fetus is exposed to multiple factors, including pre-pregnancy BMI, gestational weight gain, environmental pollutants, and maternal smoking, which could be influential in the development of child obesity. In analyses of maternal diet during pregnancy and child weight status, many of the factors mentioned above are not actual confounding factors, as they are on the causal pathway from the exposure to the outcome. Our study focused on the total effects, so these prenatal exposures were not included in the multivariable models. Future studies that examine the direct and indirect effects between maternal dietary patterns and child weight status, accounting for the previously mentioned fetal exposures, are necessary.

3) *Examination of prenatal vs. postnatal effects*

As previously mentioned, our study focused solely on the total effect of maternal dietary patterns on offspring growth outcomes. Since maternal diet during pregnancy is highly correlated with postpartum maternal diet, it is possible that the observed associations found

in our study may partially reflect the shared effects of the postnatal environment. In our models, we attempted to overcome the issue of the shared environment by adjusting for prenatal socioeconomic factors that extend into the postnatal period, such as household income and education level. We also performed additional analyses that further adjusted for child birthweight, child physical activity, and child dietary intake. Ideally, future studies will collect data beginning in the preconception period and continue into childhood to differentiate between the effects of the prenatal and postnatal period.

APPENDIX I: COMPARISON OF ELIGIBLE PIN POSTPARTUM STUDY PARTICIPANTS AND NON-PARTICIPANTS

Comparison of select maternal characteristics at baseline for eligible PIN 3 mother-child pairs who participated in PIN Postpartum (n=689) vs. those who did not participate in PIN Postpartum (n=480)

	PIN Postpartum participants (n=689)	Did not participate in PIN Postpartum (n=480)	*P*-value
Age at enrollment, mean (SD)	30 (6)	29 (6)	0.02
Race, %			
Black	15	25	<0.001
Non-Black	85	75	
Marital status, %			
Married	80	68	<0.001
Unmarried	20	32	
Education Level, %			
≤Grade 12	17	24	
Grade 13-16	47	48	0.003
≥Grade 17	36	28	
Household income, %			
<185%	18	26	
185-350%	20	19	0.01
>350%	61	55	
Pre-pregnancy BMI (kg/m^2), mean (SD)	25 (7)	25 (7)	0.01
Pre-pregnancy BMI (kg/m^2) category, %			
Underweight	5	5	
Normal weight	58	49	0.01
Overweight	19	21	
Obese	18	25	

APPENDIX II: COMPARISON OF ELIGIBLE PIN KIDS STUDY PARTICIPANTS AND NON-PARTICIPANTS

Comparison of select maternal characteristics at baseline for eligible PIN Postpartum mother-child pairs who participated in PIN Kids (n=409) vs. those who did not participate PIN Kids (n=280)

	PIN Kids participants (n=409)	Did not participate in PIN Kids (n=280)	*P*-value
Age at enrollment, mean (SD)	30 (5)	28 (6)	<0.001
Race, %			
Black	10	21	<0.001
Non-Black	90	79	
Marital status, %			
Married	87	71	<0.001
Unmarried	13	29	
Education Level, %			
≤Grade 12	11	25	
Grade 13-16	51	41	<0.001
≥Grade 17	38	34	
Household income, %			
<185%	13	26	
185-350%	19	23	<0.001
>350%	68	51	
Pre-pregnancy BMI (kg/m^2), mean (SD)	25 (7)	26 (7)	0.09
Pre-pregnancy BMI (kg/m^2) category, %			
Underweight	4	5	
Normal weight	63	51	0.02
Overweight	18	22	
Obese	15	22	

APPENDIX III: DASH SCORING APPROACH

The scoring criteria used to calculate DASH diet scores for women included in this study (87).

Scoring Criteria for the DASH Diet		
Component	***Foods***	***Scoring Criteria***
Fruits	All fruits and fruit juices	Q1 = 1 point Q2 = 2 points Q3 = 3 points Q4 = 4 points Q5 = 5 points
Vegetables	All veg. except potatoes and legumes	
Nuts and Legumes	Nuts and peanut butter, dried beans, peas, tofu	
Low fat dairy	Skim milk, yogurt, cottage cheese	
Whole Grains	Brown rice, dark breads, cooked cereal, popcorn, etc.	
Sodium	Sum of sodium content of all foods in FFQ	Reverse scoring: Q1 = 5 points Q2 = 4 points Q3 = 3 points Q4 = 2 points Q5 = 1 point
Red and processed meats	Beef, pork, lamb, deli meats, hot dogs, bacon, etc.	
Sweetened beverages	Carbonated and noncarbonated sweetened beverages	

APPENDIX IV: FOOD ITEM CATEGORIZATION FOR LATENT CLASS ANALYSIS

Food item	No consumption %	≥ Median %	>Median %
Vitamin C fruits			
Oranges or tangerines	27.2	44.7	28.2
Grapefruit[1]	73.9		
Other fruits			
Apples or pears	12.8	44.5	42.8
Bananas	13.9	55.3	30.8
Peaches or apricots	42.8	36.6	20.9
Cantaloupe	35.9	36.8	27.5
Watermelon	53.5	26.9	20.6
Strawberries	20.6	45.9	33.8
Canned fruit	28.4	45.9	26.0
Other fruits	11.1	48.0	41.1
Vegetables			
Green beans or peas[2]		56.1	34.8
Corn[2]		46.7	43.6
Cabbage or coleslaw	41.3	32.6	26.3
Green salad[2]		47.1	41.1
White potatoes (baked or mashed)[2]		54.2	38.8
Other vegetables	26.3	45.3	27.9
High-carotenoid vegetables			
Raw tomatoes	20.5	41.1	37.9
Broccoli	14.6	43.2	41.6
Spinach	41.3	32.8	25.2
Greens (i.e. collards)	66.3	17.5	17.2
Carrots	14.6	43.0	41.9
Sweet potatoes	57.5	21.8	21.2
Dairy			
Cheese and cheese spreads[2]		52.1	45.3
Yogurt	29.6	42.3	27.1
Frozen yogurt	65.5	18.9	15.7
Whole milk[1]	75.4		
Low fat milk	27.7	36.2	36.2
Soy milk[3]	98.0		
Rice milk[3]	100.0		
Nuts and beans			
Peanut butter	22.5	43.4	34.0
Peanuts, other nuts and seeds	27.2	40.5	32.3
Baked beans	29.6	45.5	24.9
Chili with beans	53.0	29.7	17.3
Refried beans and bean burritos	44.0	28.9	27.1
Mixed dish with meat			
Vegetable stew	63.7	19.7	16.9
Spaghetti with tomato sauce and meat[2]		59.8	35.7
Vegetable soup	31.0	36.4	32.6
Other soups (i.e. chicken noodles)	30.0	35.7	34.2

Mixed dishes with beef or pork	51.3	24.9	23.9
Pasta salad or other pasta dish[2]		46.8	46.0
Chicken stew or pot pie	19.8		
Eggs and meat			
Eggs or egg biscuits[2]		56.7	35.9
Beef (i.e. roast, steak, sandwiches)	24.9	41.2	34.0
Liver or liverwurst[3]	92.4		
Pork (i.e. chops, roasts, dinner ham)	28.7	48.2	23.5
Ribs or spareribs	66.4	18.8	14.9
Gizzard, neck bones, or chitlins[3]	94.3		
Fried chicken	41.2	30.0	29.1
Fried fish	61.9	24.1	14.9
Chicken not fried	10.5	45.3	44.0
Fish not fried	56.1	26.1	16.6
Tuna (casserole or sandwich)	48.0	26.4	26.0
Shellfish (i.e. shrimp, crab)	32.4	38.0	29.0
Oysters[3]	92.1		
Processed meat			
Hot dogs or dinner sausage	30.8	38.1	31.1
Ham (i.e. bologna, lunch meats)	18.9	49.7	31.6
Bacon	24.3	39.2	36.5
Breakfast sausage	46.5	27.8	26.6
Rice or dishes with rice[2]		50.3	41.0
Refined grains			
White bread	15.1	42.5	42.4
Cornbread or hushpuppies	58.1	23.8	18.7
Cereal (excluding fiber or fortified)	21.6	46.0	32.8
Cooked cereal or grits	36.0	38.8	25.3
Bagels, English muffins or buns[2]		49.3	44.9
Biscuits or muffins	12.1	53.1	34.8
Pancakes or waffles	17.1	47.3	35.6
Tortillas (corn or flour)	32.4	34.5	33.1
Whole grains			
Whole wheat bread (i.e. dark, rye)	29.9	40.0	29.1
High fiber cereals	51.5	24.3	24.3
Highly fortified cereals (i.e. Total)[1]	85.6		
Salty snacks and sweets			
Salty snacks (chips or popcorn)[2]		50.8	42.2
Crackers	14.6	44.4	41.0
Ice cream[2]		51.5	40.5
Pumpkin or Sweet potato pie[1]	81.6		
Pie or cobbler	53.9	32.0	14.0
Chocolate candy or candy bars	13.8	50.2	35.5
Candy (non-chocolate)	32.1	34.5	33.1
Pudding	61.8	20.3	18.0
Doughnuts or pastry	30.0	37.8	32.3
Cookies	11.0	50.7	38.2
Cakes	22.9	41.0	36.2
Jelly, jam or syrup	16.9	41.6	41.5

Beverages			
Orange juice or grapefruit juice[2]		46.8	44.8
Tomato juice or V-8 juice[1]	81.2		
Real fruit juice (excluding orange and grapefruit)	18.8	41.1	40.2
Coffee	50.6	25.0	24.4
Alcohol[3]	90.5		
Light beer[3]	98.9		
Non-alcoholic beer[3]	93.4		
Drinks with some juice (i.e. Sunny D)[1]	73.7		
Kool-aid, Hi-C drinks	56.5	23.5	21.0
Non-diet soft drinks or Snapple	24.0	40.3	35.6
Tea or iced tea (non-herbal)	32.8	34.9	32.3
Cranberry juice cocktail	55.2	22.6	22.2
Diet soft drinks	69.0	16.4	14.6
Breakfast or diet shakes[3]	90.8		
Water[2]		54.9	42.7
Fast Food			
French fries or fried potatoes[2]		51.7	41.9
Hamburger or cheeseburger	10.2	45.5	44.5
Pizza[2]		55.3	37.2
Cheese dish (i.e. macaroni and cheese)	16.2	43.1	40.6
Chinese dishes	23.3	39.2	37.5
Tacos or burritos	21.1	44.5	34.5
Condiments and other food items			
Butter	36.1	39.3	25.7
Margarine	39.5	33.4	27.1
Gravy	53.3	25.4	21.3
Mayonnaise or sandwich spreads	24.3	48.3	27.4
Salad dressing[2]		56.5	35.4
Salsa, ketchup or taco sauce	15.6	47.5	36.9
Mustard, BBQ sauce, or other sauces	13.7	43.3	43.0
Cream or half and half[1]	80.5		
Non-dairy creamer[3]	93.9		
Sugar or honey in coffee or tea	42.8	28.6	28.5
Breakfast bars or Power bars	47.1	28.0	24.9
Meat substitutes (not just soy)[1]	77.2		

[1] Food items dichotomized as consumed vs. not consumed because there was high prevalence of non-consumption (>70% non-consumption); only percent of non-consumers shown (n=8)

[2] Food items dichotomized as below vs. above the median because there was a high prevalence of consumption (<10% non-consumption); only percent below and above median shown (n=17)

[3] Food items were rarely consumed (<10% consumption) and were not included in analyses as they did not add any useful information (n=10)

APPENDIX V: DIETARY AND ENERGY INTAKE ACCORDING TO LATENT CLASSES, PREGNANCY, NUTRITION, AND INFECTION STUDY (N=430)

	LCA[B]		
Variable	**C1 (n=153)**	**C2 (n=196)**	**C3 (n=88)**
Dietary factors			
Fruits (svg/d)	4.6 (2.8)	4.1 (2.3)	4.2 (3.2)
Vegetable (svg/d)	2.4 (1.5)	2.6 (1.8)	1.3 (1.2)**
Nuts and legumes (svg/d)	0.4 (0.3)	0.3 (0.2)	0.3 (0.3)*
Whole grains (svg /d)	1.0 (0.8)	1.3 (1.5)	0.5 (0.7)**
Low fat dairy (svg /d)	2.4 (2.0)	3.6 (2.3)	1.6 (2.0)**
Red meat (svg /d)	0.5 (0.3)	0.2 (0.2)	0.5 (1.0)**
Sweetened beverages (svg /d)	2.3 (2.1)	1.1 (1.3)	3.3 (3.5)**
Sodium (mg/d)	3294 (1048)	2573 (839)	2546 (1117)**
Energy intake (kcal/d)	2472 (752)	1905 (514)	2047 (1038)**
% energy from carbohydrates	53 (6)	55 (7)	55 (7)*
% energy from protein	14 (2)	15 (3)	13 (3)**
% energy from fat	34 (5)	32 (5)	33 (6)**

**$P<0.01$; *$P<0.05$

[B]Class 1 represents high consumption of some fruits and vegetables, refined grains, pork, beef, pasta, pizza, French fries, processed meats, sweets,
and salty snacks; Class 2 represents high consumption of fruits, vegetables, wheat bread, low fat dairy, breakfast bars, chicken (not fried), and water;
Class 3 represents high consumption of white bread, pork, beef, hamburger, French fries, processed meats, fried chicken, cakes, and soft drinks

APPENDIX VI: MATERNAL LATENT CLASS AND CHILD BMI Z-SCORE AT 36 MONTHS

Association between maternal dietary pattern according to latent classes and child BMI z-score at 36 months of age in Pregnancy, Infection, and Nutrition study (n=276)

	Model 1[A]	Model 2[B]	Model 3[C]
Latent classes[D]			
Class 1	0.28 (-0.02-0.55)	0.23 (-0.04, 0.51)	0.18 (-0.10, 0.45)
Class 2	---	---	---
Class 3	**0.61 (0.30-0.92)**	**0.47 (0.13, 0.82)**	**0.36 (0.01, 0.71)**

[A]Model 1 represents crude association;

[B]Model 2 adjusts for maternal age, race, education, poverty level, smoking status during pregnancy, and marital status

[C]Model 3 adjusts for Model 2 variables and pre-pregnancy BMI

[D]Class 1 represents high consumption of some fruits and vegetables, refined grains, pork, beef, pasta, pizza, French fries, processed meats, sweets, and salty snacks; Class 2 represents high consumption of fruits, vegetables, wheat bread, low fat dairy, breakfast bars, chicken (not fried), and water; Class 3 represents high consumption of white bread, pork, beef, hamburger, French fries, processed meats, fried chicken, cakes, and soft drinks

APPENDIX VII: LINEAR MIXED MODEL RESULTS FOR LATENT CLASS ANALYSIS AND CHILD WEIGHT-FOR-HEIGHT Z-SCORE

Linear mixed model results of the association between maternal dietary patterns according to latent classes and child weight-for-height z-score from birth to 36 months of age, Pregnancy, Infection, and Nutrition study (n=430)

	Model 1[A] β (SE)	Model 2[B] β (SE)	Model 3[C] β (SE)
Intercept	-1.19(0.06)***	-1.29 (0.16)***	-1.36 (0.16)***
Class 1	0.21 (0.08)*	0.16 (0.08)*	0.14 (0.08)
Class 2	---	---	---
Class 3	0.15 (0.10)	0.06 (0.12)	0.01 (0.11)
Time			
Age (years)	1.48 (0.07)***	1.48 (0.07)***	1.48 (0.07)***
Age*Age (years)	-0.34 (0.04)***	-0.34 (0.04)***	-0.34 (0.04)***

*P<0.05, **P<0.01, ***P<0.001

[A]Model 1 adjusts for child age.

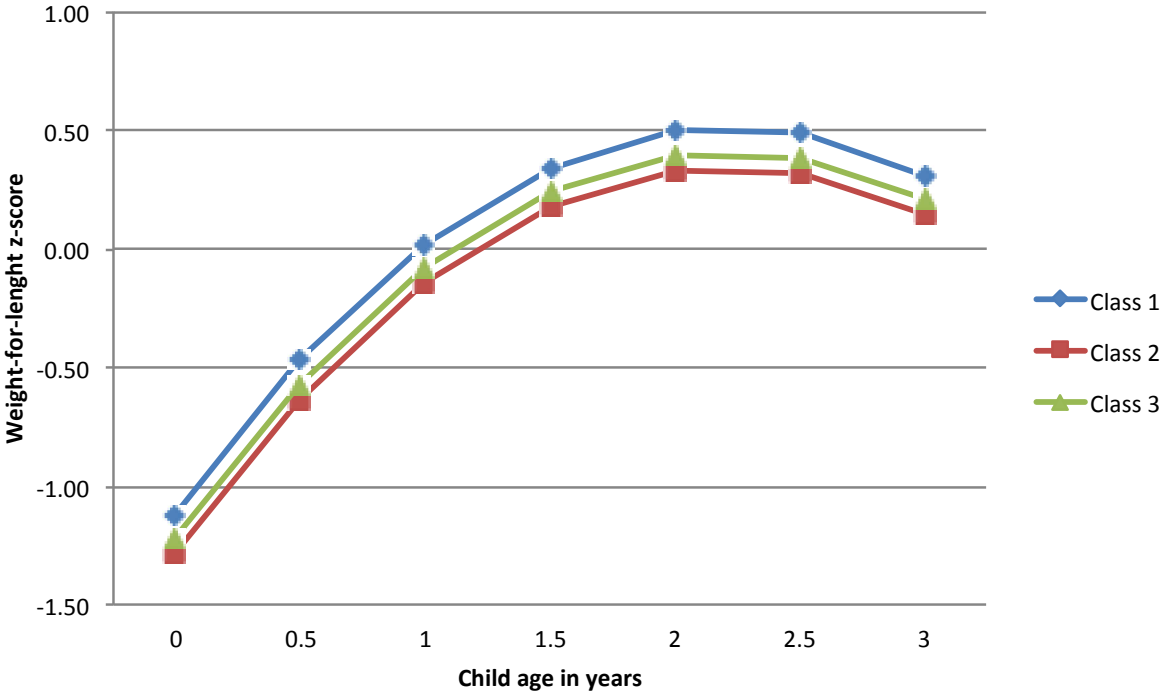
[B]Model 2 adjusts for maternal race, education at recruitment, poverty level, marital status and smoking status during pregnancy

[C]Model 3 adjusts for Model 2 variables and pre-pregnancy BMI

[D]Class 1 represents high consumption of some fruits and vegetables, refined grains, pork, beef, pasta, pizza, French fries, processed meats, sweets, and salty snacks; Class 2 represents high consumption of fruits, vegetables, wheat bread, low fat dairy, breakfast bars, chicken (not fried), and water; Class 3 represents high consumption of white bread, pork, beef, hamburger, French fries, processed meats, fried chicken, cakes, and soft drinks

APPENDIX VIII: PREDICTED CHILD WEIGHT-FOR-HEIGHT Z-SCORE

Predicted child weight-for-height z-score from birth to 36 months of age according to maternal latent classes in the Pregnancy, Infection, and Nutrition study (n=430)*



*Predicted means adjusted for maternal race, education, poverty level, marital status, smoking status during pregnancy, and pre-pregnancy BMI

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