

**Measurement Error of Energy Intake During Pregnancy and its Influence on the  
Association Between Carbohydrate Quality and Fetal Growth**

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## **ABSTRACT**

**ERIC NOWICKI: Measurement Error of Energy Intake During Pregnancy and its Influence on the Association Between Carbohydrate Quality and Fetal Growth**  
(Under the direction of Anna Maria Siega-Riz)

Population studies rely on self-reported dietary intake, which is subject to considerable measurement error. A growing body of literature has shown that subjects tend to underreport energy (food) intake, and that underreporting occurs more frequently in certain subgroups, such as women and overweight persons. Further, recent evidence has demonstrated that systematic reporting error in energy intake can seriously distort nutrient risk estimates. Maternal nutrition plays an important role for both the mother and fetus; however results on associations between diet and pregnancy outcomes thus far have been modest or non-existent. One reason may be systematic reporting bias in nutritional data, although very little is known about this error in pregnant populations.

Adequate fetal growth is an important predictor of newborn complications, and also contributes to a wide array of health conditions in adolescence and adulthood. Maternal glucose is the main energy substrate for intrauterine growth. The glycemic index (GI) and glycemic load (GL) of dietary carbohydrate, has been shown to alter postprandial glucose and insulin concentrations among healthy pregnant women, and thus may alter glucose substrate levels available for the fetus. Despite this strong biological plausibility, research on the carbohydrate quality of maternal diet and fetal growth remains limited.

This dissertation includes two analyses of data from participants in the third phase of the Pregnancy, Infection and Nutrition cohort study (PIN3). The first analysis indicates that measurement error in energy intake is prevalent during pregnancy with 32.8% and 12.9% of subjects reporting intakes that were implausibly low and high, respectively. This error also varied by several maternal characteristics including pregravid body size, which is an important predictor of many pregnancy outcomes. Therefore, determining the nature of measurement error in energy intake may help to improve dietary assessment methodology in reproductive studies and account for bias in the calculation of effect estimates. In the second analysis, no association was observed between carbohydrate quality and fetal growth among generally healthy pregnancies; a null finding that remained after exclusion of participants with implausible energy intakes. Strengths and limitations of this study and the current literature, as well as and recommendations for future research are noted.

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## **ABBREVIATIONS**

ANOVA	Analysis of Variance
AUC	Area Under the Curve
BMI	Body Mass Index
BMR	Basal Metabolic Rate
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence Interval
CV	Co-Efficient of Variation
DAG	Directed Acyclic Graph
DLW	Doubly Labeled Water
DRI	Daily Reference Intakes
EER	Estimated Energy Requirement
EI	Energy Intake
FAO	Food and Agriculture Organization
FFQ	Food Frequency Questionnaire
GDM	Gestational Diabetes Mellitus
GI	Glycemic Index
GL	Glycemic Load
HER	High Energy Reporting
IOM	Institute of Medicine
LBW	Low Birth Weight
LCL	Lower Confidence Limit
LER	Low Energy Reporting
LGA	Large for Gestational Age
LMP	Last Menstrual Period

LRT	Likelihood Ratio Test
MET	Metabolic Equivalents of Task
MLE	Maximum Likelihood Estimation
MVPA	Moderate-to-Vigorous Physical Activity
NHANES	National Health and Nutrition Examination Survey
OLS	Ordinary Least Squares
OR	Odds Ratio
PA	Physical Activity
PAL	Physical Activity Level
PIN	Pregnancy, Infection and Nutrition Study
PIN1	Pregnancy, Infection and Nutrition Study (First Phase)
PIN2	Pregnancy, Infection and Nutrition Study (Second Phase)
PIN3	Pregnancy, Infection and Nutrition Study (Third Phase)
RMR	Resting Metabolic Rate
RRS	Revised Restraint Scale
RR	Relative Risk
SAS	Statistical Analysis Software
SES	Socioeconomic Status
SGA	Small for Gestational Age
TEE	Total Energy Expenditure
UCL	Upper Confidence Limit
UK	United Kingdom
US	United States
WHO	World Health Organization
WIC	Women, Infants and Children

## **Chapter One**

### **Background and Significance**

#### **1.1. Assessment of Diet During Pregnancy**

Measuring diet accurately is challenging in human populations. Food is a universal and essential exposure and its consumption is driven by numerous physiological, psychosocial, cultural and environmental circumstances. In the United States and other developed countries, a person's dietary intake can vary substantially from day to day (1), which introduces random error in estimates of usual intake. Day-to-day variation in intake arises from multiple biologic and environmental influences such as appetite, physical activity, illness, season of the year, holidays, and personal economic conditions. The direct observation and accountability of all food consumed is costly and impractical for most research. Therefore, population based studies must rely on self-reported dietary intake, which is subject to considerable measurement error. An emerging literature has begun to identify sources of systematic bias in nutritional data and the influence of this error on diet-disease associations. However, such research in pregnant populations is exceedingly limited.

Dietary assessment in pregnant women presents some distinctive challenges. Gestation is the most intensive period of human growth and development. Conception triggers an array of complex physiological and behavioral changes that affect maternal nutrient absorption and metabolism, energy and nutrient needs, appetite, and meal

patterns (2, 3). Nausea, which is estimated to occur in 50-80 percent of pregnancies, typically persists throughout most of the first trimester. Heartburn and constipation can also occur as a result of pregnancy and may trigger changes in usual food habits. Pica, an eating disorder characterized by the compulsion to eat substances that are not food, may affect up to one half or more of pregnant mothers. In addition, pregnant women may develop food preferences and aversions due to changes in the sense of taste and smell. Dietary intake of the mother may also change once they learn of their pregnancy in response to clinical recommendations or their own perception of an appropriate prenatal diet. In fact, recent evidence has observed moderate intra-individual changes in energy and certain nutrient intakes between trimesters (4, 5). Another issue unique to pregnancy is that both optimal fetal growth and appropriate maternal weight gain are a primary focus in prenatal care. Such increased emphasis on maternal nutrition, food habits and weight consciousness may promote social desirability response bias in self-reported dietary data.

Determining the time period during pregnancy in which to assess dietary intake is an important methodological consideration. The critical window whereby the primary nutrient or food of interest may influence the primary outcome is a key factor. For example, diet in the first trimester may be more important to the development of various organs, while diet later in pregnancy may be more important for endpoints such as fetal growth. Other circumstances such as physiological changes, stages of prenatal care, and study feasibility can also play a role. Certain diet related health conditions that are diagnosed during pregnancy, such as gestational diabetes and preeclampsia, may bias future dietary assessment, as well as, pregnancy outcome. Further, enrollment in

pregnancy cohort studies typically begins after the woman has become pregnant, which complicates ascertainment of diet in the first trimester (6)

The Food Frequency Questionnaire (FFQ) has been shown to be an appropriate method for assessing dietary information in a wide variety of epidemiological settings, including studies among pregnant women. FFQs are designed to ask respondents to report their usual frequency of consumption for specific foods or food groups over a previous period of time (i.e. month, year). Compared with other self-report methods, such as 24-hour dietary recalls and food records, the FFQ generally collects less detail regarding foods consumed, cooking methods, and portion size. As such, the quantification of intake is considered less accurate (7). However, the FFQ can be self-administered and imposes less subject burden compared to other self-report measures. Also, unlike records or recalls, FFQs are designed to capture usual dietary intake, which is desirable for examining the association between health outcomes and relevant dietary exposures (8). Moreover, the FFQ is particularly useful for ranking nutrient exposures, as opposed to estimating absolute intake, which lends itself well to epidemiologic studies. The ability of FFQs to capture habitual intake over a previous specified period of time is particularly useful in pregnancy studies where enrollment may not begin until the second trimester.

FFQ methodology relies on data sources to develop food lists, portion sizes and a nutrient database to convert responses into estimates of daily nutrient intake. The Block and Willett FFQs or modifications of either are among the most widely used dietary research (9). These two FFQs differ on several dimensions, such as the number of food items, specific food items, the way food items are grouped, the frequency categories, and

scoring methods. The Block FFQ also differs from the Harvard FFQ in that it asks an individual to approximate the usual portion size of each food item consumed. The Block FFQ utilizes the most recent available nationally representative dietary data to develop the food lists, portion sizes, and nutrient databases (10). And, the Willett FFQ database is constructed using multiple governmental and commercial sources, including tables from food manufacturers and journal articles (8). FFQs are typically adapted for a given study population depending upon demographic factors such as age, income, education, race/ethnicity, as well as, study objectives including the nutrients or food groups of interest and the period of recall. Other considerations are the inclusion of seasonal foods and supplements, as well as, cognitive issues regarding comprehension, number and order of food items, and format. Both the Willett and Block FFQs have been utilized extensively in studies of pregnant women. Some investigators have also designed their own FFQ specifically for maternal dietary assessment in their study population (11).

### **1.1.2. Validity of FFQs in Pregnant Populations**

A large body of literature in non-pregnant populations indicates that FFQs can provide reasonably good measures of dietary composition when compared with more detailed assessments of diet or biochemical measures of intake (12). Correlation coefficients between FFQs and reference methods in adult populations typically range between 0.40–0.70 for most foods and nutrients, including composite measures of carbohydrate intake such as glycemic index and glycemic load (13, 14, 15). Sources of



measurement error include difficulty with recall, assessment of portion sizes, and social desirability bias. It has been noted that the similarity of correlation coefficients across validation studies suggests a ceiling of validity, which may be attributed to both the inherent complexity of diet that cannot be fully captured by a structured questionnaire, as well as, error in the comparison methods. FFQs also depend on the participants' long-term knowledge of their own dietary patterns, which consists of subjective assumptions about the nature of their habitual diet. As such, they may not qualify for absolute validation procedures. Validation of FFQs among pregnant women has been examined, however, research in this population remains limited (11, 16, 17, 18, 19, 20). Some factors unique to pregnancy that may affect FFQ performance include gestational age (i.e. trimester), nausea, and parity; however, their potential influence has been addressed in only a small number of studies.

A seminal validation study of FFQs in pregnant woman was conducted in 1994 on participants of the Women, Infants, and Children (WIC) program, which targets low-income families. Women were enrolled regardless of gestational age and the study population included approximately equal numbers of black, Hispanic and white subjects from multiple geographic areas of the United States. A total of 186 participants with an average age of 25 years completed a self-administered Willett or Block FFQ (randomly assigned), as well as, three nonconsecutive 24-hour dietary recalls for the criterion; although, 16% of the sample was not included in the final analysis because of unreliable 24-hour recall data . Results suggested that neither the Willett nor the Block FFQ performed particularly well in this sample with only one of the eight nutrients analyzed having a correlation coefficient greater than 0.40. The lowest values were among

Hispanic participants, who had considerably less years of education compared to the African American and white mothers. The authors also noted that the FFQs were not ideal in listing all culturally appropriate foods and deriving nutrient estimates for certain foods commonly selected by Hispanic women. Another study validated a self-administered Willett FFQ in a culturally diverse sample of low-income women in Massachusetts and found slightly higher correlation coefficients with 7 of the 8 nutrients greater than 0.40 (21). However, only women completing a FFQ in English were included in the final analysis. Neither of these earlier studies stratified their results by race/ethnicity or income level likely because of small sample sizes.

More recently, Baer et al reported on a large study of 283 pregnant women enrolled at WIC clinics in North Dakota (16). Nutritional assessment was conducted at 12 weeks and 28 weeks gestation comparing the Willett FFQ with three 24 hr interviews at each period. Correlation coefficients for most nutrients were fairly similar across subgroups when computed separately by ethnicity and poverty level. However, the authors noted that the average correlation coefficient was slightly lower for American Indians than Caucasians (0.46 vs 0.51 at week 12, 0.37 vs. 0.50 at week 28) and slightly higher for women at 100% or less of poverty than 101% or greater (0.51 vs 0.48 at week 12, 0.54 vs 0.40 at week 28). Of note, the sample size for the American Indians group was comparatively smaller than the Caucasians (37% vs. 63%). Interestingly, a study of 56 well educated, white women in Minnesota had correlation coefficients similar to the results of studies in low-income, ethnically diverse WIC populations (22). Using the Willett FFQ and four-day food records, Brown et al. reported an average correlation of 0.45 in 15 nutrients during pregnancy. These women were slightly older than the WIC

populations with a mean age of 32. Nevertheless, these results indicate that socioeconomic status and race/ethnicity may not substantially alter FFQ performance in pregnant populations.

Other validation studies have been conducted in Europe all of which tested their own FFQ design as opposed to a modified Willett or Block questionnaire. A community-based study of 569 women in the United Kingdom reported correlations ranging from 0.27 to 0.55 for 20 energy-adjusted nutrients assessed by a 100-item FFQ and four-day food diaries at 15 weeks of pregnancy (19). Erkkola et al. found somewhat better results in their sample of 113 Finnish women in their third trimester of pregnancy (23). Their 181-item FFQ and two five-day food records had an average correlation coefficient of 0.53 for 45 nutrients and 70% of the foods and 69% of the nutrient estimates fell into the same or adjacent quintiles. Mikkleson et al. utilized both 7-day weighed food diary (FD) and biomarkers to validate their FFQ during 32-38 weeks gestation in 88 pregnant Danish women (24). Intakes estimated from the FFQ and both reference methods were all significantly correlated, ranging from 0.20 for retinol intake to 0.57 for folic acid intake. Bransaeter et al. reported on their FFQ validation in 119 pregnant Norwegian women that the average correlation coefficient between the FFQ and food diaries for daily intake was 0.48 for foods and 0.36 for nutrients; and on average, 68% of the participants were classified into the same or adjacent quintiles by the two methods (11).

Many dietary validation studies in pregnant women cite nausea as a potential source of measurement error (11, 19, 23, 25, 26), but few reports investigated this as a formal hypothesis. In a validation study by Fawzi et al., 70% of women had experienced nausea during the dietary assessment period which was a mean gestational age of 9 weeks(25).

Of these, 57% of African American and 74% Caucasian women reported that they changed their dietary habits as a result of nausea. Conversely, in a longitudinal assessment of energy expenditure using doubly labeled water, 10 out of 12 subjects reported nausea during early pregnancy, yet most women claimed that their appetites were the same as their normal during this time. Brantsaeter et al. found that 76% of subjects reported nausea during the pregnancy, but only 15% reported nausea still at the time of answering the FFQ (12-15 weeks gestation). Robinson presented an analysis by reported nausea severity for correlations of macronutrients for 569 women at 16 weeks of pregnancy(27). With the exception of protein, the greatest correlations between food diary and FFQ were seen in the group of women who reported no nausea. Moreover, the correlations for energy, fat and carbohydrates were significantly attenuated with increasing nausea severity. These results suggest that the presence and severity of nausea may influence reported dietary intake of individual macronutrients; and, as a result, the overall validity of FFQ data may be underestimated in early to mid pregnancy. Conversely, a validation study comparing dietary pattern scores between FFQ and diary data found no trends in agreement across categories of nausea severity (28).

Only one study examined whether the validity of dietary assessment tools was modified by parity or stage of pregnancy. In the study by Baer et al., average deattenuated correlations comparing nutrient intakes estimated from the FFQ and the diet recalls at 12 weeks gestation were 0.47 for those with no previous livebirths, 0.58 for those with one previous livebirth, and 0.41 for those with two or more previous livebirths, and these were similar at 28 weeks gestation. The authors also reported similar validity during the first and second trimesters, as shown by the average

deattenuated correlation coefficients of 0.48 and 0.47 for the week-12 and week-28 FFQs compared to the 24-hour diet recalls (16).

To summarize, the current literature suggests that the agreement between FFQs and more detailed dietary assessment methods is similar, or perhaps, slightly less than in other adult populations. A small reduction in FFQ validity could reflect a less stable diet during pregnancy or the augmentation of other sources of error, such as, social desirability bias. Regardless, validation studies generally conclude that FFQs provide reasonable classification of dietary intake for testing associations between diet and reproductive outcomes. Research does not indicate that FFQ performance during pregnancy is substantially different in lower income or non-white mothers; although special cultural modifications may be necessary for use in Hispanic populations. Further, it does not appear that FFQ validity depends greatly on parity or stage of pregnancy; however, the degree to which nausea may influence dietary assessment and which nutrients are most affected remains unclear.

## **1.2. Underreporting Bias in Dietary Intake**

Although FFQs and other self-report measures are deemed sufficiently valid for supporting causal inference, their threat to internal validity does not end with data collection. A substantial body of literature has demonstrated that all methods of self-reported dietary assessment tend to underreport energy and nutrient intake(29); and understanding the nature and severity of this bias is critical for disclosing true diet-disease associations. Research suggests that underreporting has both conscious and

unconscious dimensions resulting in the omission or the underrepresentation of the frequency and/or portion size of a food item. Reporting fatigue, memory disturbances, and social desirability bias are established sources of misreporting energy and nutrient intake.

Dietary underreporting includes both random and systematic errors. In general, random misclassification of a risk factor leads to an underestimation of diet-related health effects (8). Studies have demonstrated how this error in the dietary estimates can attenuate measures of association, thereby reducing the power of the study. Of greater concern is the accumulating evidence that nutrient risk estimates also incorporate systematic error, which has a far less predictable bias on the measure of association (30, 31, 32). Several investigators have indicated that the impact of systematic underreporting on the design, analysis and interpretation of nutritional studies may be much greater than previously estimated; and a better understanding of this measurement error is needed (33, 34, 35, 36).

### **1.2.1. Measurement Error in Intake**

Correct estimation of energy intake is vital to many areas of nutrition research. In epidemiologic studies, adjusting for total energy intake is critical to control for confounding, reduce extraneous variation, and predict the effect of dietary interventions. Failure to account for total energy intake can obscure associations between nutrient intakes and disease risk or even reverse the direction of association (37). National survey data show that reported energy intake has decreased in recent decades despite a

rise in the prevalence of obesity. This disparity may be due to a decrease in energy expenditure, a secular increase in under-reporting, or both (38). Further, a growing body of literature has demonstrated that underreporting energy intake is more prevalent in certain population subgroups. However, information on the frequency, magnitude and predictors of energy underreporting during pregnancy is exceedingly limited.

#### **1.2.1.1. Key Concepts for Measurement Error in Intake**

##### **1.2.1.1.1 Total Energy Expenditure (TEE)**

To identify measurement error in energy intake (EI) and factors associated with energy underreporting it is necessary to have an objective estimate of energy requirement, which is based on total energy expenditure (TEE). TEE is the amount of energy spent, on average, in a typical day (kcal/day) to sustain life and is comprised of 3 components: resting energy expenditure, thermic effect of feeding, and energy expenditure of physical activity. According to the fundamental principal of energy metabolism, TEE and EI are equal under conditions of stable body weight (Schoeller, 1990).

Doubly labeled water (DLW) is generally considered the gold standard for assessment of TEE (19). It uses non radioactive isotopes to measure carbon dioxide production, an indirect measure of metabolic rate. Several studies have demonstrated DLW to have a relative accuracy of 1-3% and a within-subject repeatability of 5-8%. While this technique provides confirmation of inaccuracies in reported energy intake, DLW is very costly and its use is precluded in large population studies. In 2002, estimated energy

requirement (EER) prediction equations were published as part of the Dietary Reference Intakes (DRI). EER equations were developed from an extensive normative DLW database, which included TEE measurements on adults, children and pregnant women with a variety of physical activity levels. DRI equations for EER have been utilized in recent studies of energy underreporting (39, 40) and their accuracy has been independently corroborated (41).

#### **1.2.1.1.2. Basal Metabolic Rate (BMR) and Physical Activity Level (PAL)**

Basal Metabolic Rate (BMR) is the minimum caloric requirement needed to sustain life in a resting individual and is the most dominant component of TEE. BMR is measured by gas analysis through either direct or indirect calorimetry, which is much less costly than DLW. In 1985, prior to expansive DLW data, a consultation group for the World Health Organization, published equations to estimate BMR using age, sex, height, and weight; and recommended that TEE be expressed as a multiple of BMR to determine energy requirements. These multiples of BMR are referred to as physical activity levels (PALs) and calculated by dividing TEE by BMR. Thus multiplying the PAL by the BMR estimates actual energy requirements; and the ratio of EI to BMR (EI:BMR) should equal PAL under conditions of stable body weight.

Numerous publications have highlighted the strengths and limitations of this method to estimate caloric requirements. For example, it has been demonstrated that the initial BMR equations developed by Schofield et al. are not representative of certain subgroups and also tend to underestimate BMR among in pregnant populations. In addition, the WHO recommended PALs were derived based on limited DLW data and required



assumptions about the energy costs of physical activity, effect of meals and other thermogenic processes. Despite some concerns about its general application, comparing EI:BMR with PAL has been deemed a convenient and reliable tool for detecting under-reporters in most populations; although it should be modified for use in pregnant women to account for metabolic demands throughout gestation.

#### **1.2.1.1.3. Cutoff Values to Identify Underreporting**

Energy underreporting, also known as low energy reporting (LER), is typically defined as a self-reported EI that falls below some physiologically plausible cutoff. The two validation methods for reported energy intake compare either TEE with EI or EI:BMR with PAL. However, absolute agreement cannot be expected since there is measurement error in all elements of these equations; thus, confidence limits of agreement should be determined. The lower confidence limit represents a value below which it is statistically unlikely that the reported intake represents either 'habitual' long term intake or a low intake obtained by chance. Goldberg et al., produced an equation that accounts for variation in PAL, daily energy intake, number of diet assessment days, and the error in estimated versus measured BMR (26); it was further adapted by Black and Cole to include error in estimated versus measured TEE (42). Overreporting can also be identified using the upper confidence limit of the Goldberg cutoff. However, overreporting food intake occurs less frequently than LER and is typically of less scientific interest. In a meta-analysis of DLW energy expenditure of free-living subjects, Black et al. found that 35% of women underreported their intake while only 2% of

women over-reported. Some researchers use a more simplified EI:BMR cutoff of 1.2, which was also proposed by Goldberg as the minimal requirement to sustain body weight, however, this approach ignores sources of dietary assessment variation and has been shown to be less accurate than a confidence limit approach.

Several studies have shown the Goldberg cutoff to be reliable and conservative, detecting a large proportion of underreporters with a relatively small fraction of false positives. Black et al. found that when individual data on physical activity was available, the Goldberg cutoff sensitivity improved from 0.52 to 0.67 without a loss of specificity (0.98) in a sample of 264 women. A recent paper also demonstrated no difference in sensitivity or specificity when the Goldberg cut-off was applied to either EI:BMR or EER (43). This cut-point methodology also appears robust in identifying subgroups with implausible energy intakes as studies using prediction equations have found similar conclusions as those using DLW.

#### **1.2.1.2. Prevalence of Energy Underreporting**

LER frequency can vary greatly between study populations. DLW studies have provided confirmation on the existence of LER, but this research has been conducted on relatively small samples of highly motivated individuals, which weakens the external validity of their prevalence estimates. On the other hand, a number of large national dietary surveys have estimated the prevalence of underreporting using prediction equations for energy requirements. Although such epidemiologic studies are considered less precise than DLW, this type of research can provide more appropriate population estimates of underreporting, as well as, the opportunity to look at a variety of predictor

variables. LER prevalence can also vary by dietary assessment method however studies comparing the accuracy of these methods are inconsistent in their findings. Among these studies, some have found that the food frequency questionnaire (FFQ) provided less underreporting than diet recalls, diet histories, and food records, while others found the opposite (44).

Regardless of study design and dietary assessment methodology, nearly all researchers have noted that frequency of LER has differed according to certain subject characteristics. In particular, LER is found to be more prevalent among women and overweight persons. A large number of studies have also explored reasons for the disparity of underreporting in these two subgroups. However, despite the abundance of literature regarding gender and obesity specific underreporting, information on the frequency and nature of LER in pregnant women is exceedingly limited.

#### **1.2.1.2.1. Demographic Predictors of Energy Underreporting**

LER is consistently more prevalent in women than men. A review of LER studies using EI:BMR methodology found that in 11 of the 12 studies females were significantly more likely to under-report their dietary intake than males (45). A recent analysis of individual data from 21 DLW studies comprising 429 adults found a prevalence of underreporting of 28% for men and 38% for women (46). Further, LER prevalence from NHANES III data has been reported as 18% for men and 28% for women (47). Several studies have indicated that a higher frequency of weight consciousness and dietary restraint among women contributes to this disparity (48).

Most studies in the United States have found an association between LER and low education or socioeconomic status (SES) (49). This association may be explained, in part, by poor literacy and comprehension of dietary assessment. For example, in a study population of low income women, poor literacy scores were the best predictor of LER (50). However, the effect of education and SES is not always predictable as other studies have shown better educated, higher SES subjects can have a similar tendency toward LER, which may result from greater weight consciousness and social desirability bias (51, 52)

Cultural differences in attitudes toward food and nutrition are well documented. However, the influence of race/ethnicity on dietary reporting behaviors is unclear. LER has been documented in many populations across world and the literature indicates that underreporting is a universal phenomenon in both Western and non-Western cultures. However, research that has directly compared LER prevalence in multiple race/ethnic groups is limited. Those studies do, however, suggest a higher frequency of underreporting among Caucasians compared to African Americans and Hispanic populations (36, 47).

#### **1.2.1.2.2. Overweight and Obesity Related Underreporting**

Early studies of obesity failed to identify excessive energy intake as a causal factor. Moreover, the prevailing attitude of obese persons was that their energy intake was no higher than that of an equivalent lean person. In 1986, Prentice et al. conducted the first study to apply DLW to examine dietary measurement error by comparing TEE and energy intake in lean and obese women. Dietary intake was measured using 7-day

weighed food records and all subjects were matched by obesity status for height, social class, and type of occupation. In the lean group, average recorded energy intake was 2% lower than the measured energy expenditure, while mean intake in obese subjects was 67% of TEE, representing an underestimate of 835 kcal/day. In addition, energy balance was calculated after adjusting for changes in body composition over the measurement period. A mean negative energy balance of 419 kcal/day was found in obese subjects, which suggests that a portion of underreporting bias in obese subjects may be due to dieting or restricted food intake.

Numerous subsequent studies utilizing both DLW and prediction equations have supported the existence of an obesity specific underreporting bias in a variety of populations, particularly among women. In fact, weight status, measured as body mass index (BMI), is the most robust predictor of LER and the magnitude of underreporting generally increases with higher BMI (49). A recent review noted that 22 out of 25 studies found a positive association between LER and higher BMI. Furthermore, in studies that examined a range of variables, BMI explained the largest proportion of variance in LER. However, the association between obesity and low-energy reporting is not absolute. The probability that a subject will underreport increases as BMI increases, but there are obese subjects who do not underreport. Johansson et al. noted that 52% of underreporters had a BMI greater than, 25 kg/m<sup>2</sup>. In some populations, obese subjects have been found to underreport up to half of their total energy intake (53).

There is no plausible biological reason where higher body weight or excess body fat would cause women to underreport energy intake. Thus, measures of body size and adiposity are likely surrogates for psychosocial characteristics that result in

underreporting energy, such as poor awareness of intake or portion sizes, deliberate underreporting, and subconscious biasing toward intake that is perceived to be appropriate (53). In fact, a growing body of literature suggests that psychosocial factors such as restrained eating, concerns about body weight, and social desirability bias may explain LER in both obese and non-obese women. Evidence suggests that such psychosocial characteristics are also prevalent during pregnancy, including a common fear of maternal weight gain (54); but studies on their relationship with weight status and LER in pregnant women have not been published.

#### **1.2.1.3. Energy Underreporting in Pregnancy Populations**

Very few studies have reported on the nature of underreporting dietary intake during pregnancy. Goldberg et al. studied twelve women from Cambridge, UK during 6 to 36 weeks gestation at 6-week intervals and conducted assessments of TEE by DLW method, BMR, energy intake, and body composition at each occasion. Mean reported energy intake from 7-day weighed food records was underestimated compared to TEE by 6 to 15 percent in the first trimester, 12 to 18 percent in the second trimester, and 22 to 24 percent in the third trimester. Using the Goldberg cutoff limits, 3 of the 12 (25%) subjects were consistently identified as LER. All subjects who completed were Caucasian and otherwise healthy, although this study sample was highly selective with a low participation rate and relatively high dropout rate. More than 80 women responded and only 33 agreed to participate in the study. Of these, five conceived before the initial basal metabolic rate (BMR) measurement, three dropped out because they miscarried within the first 16 wk, four dropped out for other reasons, and nine failed to conceive.

Nevertheless, results from this study provide evidence that LER can occur during pregnancy and that the magnitude of underestimation may increase across trimesters.

Winkvist et al. evaluated LER among 490 pregnant Indonesian women in a longitudinal study of dietary intake, using six repeated 24-hour diet recalls at each trimester. BMR was estimated from a prediction equation using body weight and physical activity from occupation. The Goldberg cutoff for EI:BMR was calculated to identify LER and certain risk factors were assessed. For the three trimesters, proportion of LER was 29.7%, 16.2% and 17.6%, respectively. Many women reported nausea during the first trimester and the mean weight gain was only 0.08 kg during that period. Thus, it was concluded that LER frequency in the first trimester likely reflected a true low intake due to nausea, rather than underreporting. LER frequency in the second and third trimester was lower than is typically reported in non-pregnant women from the United States, but was similar to other published data of non-pregnant women in developing countries (55). LER also varied by subject characteristics. At each trimester, LER was more prevalent in women with a BMI greater than 25.0; and was more prevalent in women with less than 7 years of education in the second trimester.

Derbyshire et al. studied LER in a convenience sample of 72 Caucasian, primiparous nonsmokers recruited from three London teaching hospitals. Energy intake was estimated from 4-7 day weighed food records during the first trimester and was also compared with prepregnancy BMI abstracted from medical records. It was reported that prepregnancy BMI was inversely associated with mean EI:BMR; and underreporting occurred in 24% of subjects with LER identified in 5 out of the 6 obese subjects.

In summary, the literature on LER in pregnant women remains sparse and has several limitations. Each study was conducted on a small and relatively homogeneous population. In particular, the two studies in Caucasian populations from the UK consisted of highly selective convenience samples, greatly limiting their external validity. Although the cohort of Indonesian women may be somewhat representative of other pregnant women in the developing world, they are, on average, leaner and more physically active than pregnant women in developed countries. Moreover, all studies estimated BMR using prediction equations that were not designed for use in pregnant women and it is unclear whether the recommended adjustment for changes in pregnancy metabolism was performed (56). Finally, the nature of underreporting is complex and certain risk factors, such as fear of weight gain, are prominent during pregnancy; however, only a few predictors of LER have been assessed in the current literature. A recent study of 35,929 pregnant women found that concern about maternal weight gain was prevalent and that it was also associated with outcomes of fetal growth (57). Greater worry was associated with higher gestational weight gain, higher infant weights, greater likelihood of a large-for-gestational-age infant, and reduced likelihood of a small-for-gestational-age infant.

Despite methodological limitations, these few studies do suggest that underreporting needs to be considered in studies of maternal dietary intake. However, the prevalence, magnitude and predictors of LER in pregnant women are still unclear. Large studies of LER during pregnancy in developed countries have not been reported; and no studies on LER in pregnant women from the United States have been published, to date. Future



population studies should include large samples of diverse pregnant women and explore a variety of predictors of LER.

### **1.2.2. Selective Underreporting of Nutrients**

Some evidence indicates that reporting bias in total EI may also be associated with variable bias in macronutrient intake. More specifically, percent calories from fat and/or carbohydrate tend to be under-reported whereas percent calories from protein are typically accurately reported or even over-reported (45). Research in this area has some inherent limitations, however, since objective criterion methods are only available for estimating protein intake. Therefore, carbohydrate and fat specific underreporting cannot be directly estimated. As a result, studies that explore macronutrient specific under reporting typically compare differences between suspected under-reporters and ‘valid’ reporters using either an EI:BMR ratio or urinary nitrogen techniques.

Several studies have found that carbohydrate intake is under-reported in dietary studies (34, 47, 58, 59, 60, 61). However, these findings are not consistent across all studies. A review of 20 studies found no trend in percent energy from carbohydrates between LER and non-LER subjects (49), although there did appear to be reporting variability between type of carbohydrate. In six of the studies where data on the percentage of energy derived from starches and sugars were available, starch energy tended to be higher in LER, but sugars energy was lower. Further, two recent studies have also noted that high-GI foods may be selectively underreported, particularly among

obese subjects (62, 63). However, formal analyses to support this hypothesis are limited. One of these studies reported an age-adjusted linear decrease of LER across glycemic index tertiles in a large cohort of Spanish women; while no difference in LER by tertile of percent energy from carbohydrate was observed in this population. Most researchers observing selective underreporting of high sugar and high GI foods note social desirability bias as a primary explanation. Additionally, evidence also suggests that snacks and food eaten in between meals are particularly susceptible to underreporting especially in overweight subjects (47, 64, 65). Moreover, snack foods also tend to be higher in sugar and lower in protein and fat compared to meals (66).

Despite a lack of consistency in study findings, it is becoming increasingly acknowledged that selective reporting error does occur in the general population (34). A recent study utilizing DLW and protein biomarkers confirmed overreporting in percentage of energy derived from protein, together with the underreporting of energy intake, which suggests a disproportionate underreporting of fat and/or carbohydrate (36). Some authors have also demonstrated how macronutrient specific underreporting in obese individuals can seriously distort measures of association (67). Therefore, the general underreporting of energy intake among obese subjects may be compounded by food-specific underreporting. To date, however, no publications have addressed macronutrient specific underreporting in pregnant populations.

### **1.3. Methods to Account for Underreporting Bias**

Interpretation of self-reported nutrient data in relation to a disease outcome is critically dependant on the method of data analysis. Underreporting can seriously bias

nutrient and risk estimates, particularly in studies where energy intake and weight status are important exposures. However, it is unclear how to best account for dietary data from LER subjects in the analysis. Ideally, the method of choice is one that best minimizes bias, provides maximum power and is the most strongly related to biological or other objective markers of nutrient intake. And, the goal is to provide insights into diet-disease relationships that would otherwise have been obscured by the measurement error in self-reported intake.

### **1.3.1. Energy Adjustment for Nutrient Intakes**

Intakes of specific nutrients, particularly macronutrients, and their measurement error tend to be highly correlated with intake and variation in total energy consumption, mainly because they are both computed from the same foods. This relationship presents two major problems in the attempt to separate the effect of total EI from the effect of nutrient intake in the analysis of diet and disease associations. First, confounding can result if total energy intake is associated with disease risk, perhaps because of differences in physical activity, body size, metabolic efficiency, or biased reporting. If total energy is associated with disease, virtually all specific nutrients will also tend to be associated with disease risk, in the same direction (37). Therefore, a nutrient that is found to be associated with disease risk could be due merely to an association between physical activity and disease risk, with the association being a result of the relation between total energy intake and physical activity. Also, if an outcome of interest, such as obesity, is related to misreporting total energy intake, a nutrient may be associated with the disease

as a result of reporting bias in overall food intake. Second, failure to control for variation in total energy intake may result in extraneous measurement errors for specific nutrients (37). This has been demonstrated in studies that have examined the correlation between the intake of nutrients and the blood concentrations of these nutrients, which presumably are more directly reflective of biological effects. In general, adjustment for total energy intake increased associations between calculated nutrient intakes and their concentrations in blood or adipose tissue (68, 69).

Several methods for energy adjustment have been proposed and their relative merits have been debated (37, 70, 71). Nevertheless, given the consequences of failing to account for EI, most studies in nutritional epidemiology focus on results using energy-adjusted nutrient intakes. However, many researchers agree that energy adjustment alone cannot eliminate differential reporting bias (34, 72, 73), which includes both systematic underreporting by subject characteristics such as obesity and more universal types of selective underreporting, such as foods of low social desirability. Energy adjustment depends on the assumption that foods, and consequently nutrients are all misreported in similar proportions. Therefore, adjustment for total energy intake may only be meaningful if underreporting occurs at the whole-diet level, and there is accumulating evidence that this is not always so (34). Moreover, given the low precision of self-reported energy intake, energy adjustment methodology may be compromised by failing to control for true energy intake; which could add to residual confounding in estimated associations between disease incidence and energy-adjusted nutrients (7). Furthermore, the ability of current energy adjustment methods to prevent confounding of

risk estimates from differential reporting bias by subject characteristics has not been demonstrated.

### **1.3.2. Exclusion of Low Energy Reporters (LERs)**

Excluding LER subjects from the data set has been adopted in many studies as a solution to minimize dietary reporting bias, particularly when BMI is a variable of interest (39, 59, 63, 73, 74, 75, 76, 77, 78, 79, 80). And, several of these studies have demonstrated that LERs may influence relationships between certain dietary factors and health outcomes. For example, a recent study analyzed a large national survey database using a range of cut-off levels for LER and found that excluding implausible energy intakes modified several associations between diet and BMI (80). Recent studies on the association between glycemic index, glycemic load and BMI have also reported results both with and without LERs, given the authors' suspicion that high-GI foods were underreported (62, 63). Moreover, Bergmann et al. found counterintuitive relationships in their analyses of body mass index (BMI), net weight gain and energy intake during pregnancy; and concluded that underreporting needs to be considered in studies investigating maternal dietary intake (81). More recent studies of diet-disease risk in pregnant populations have also noted the importance of excluding LERs (77, 78).

Although evidence suggests that misleading or spurious diet-disease associations may be reported if LERs are not identified and excluded, the application of this methodology is not universal and has some important caveats. LER is consistently prevalent in nutrition epidemiology and can comprise a substantial proportion of a given study

population. Exclusion of such a large subgroup can introduce selection bias, reduce power, and threaten external validity. In addition, the Goldberg cut-point approach identifies LERs only at the lower end of the energy intake distribution and not those subjects whose diet records are plausible but who nevertheless may be under-reporting at higher energy intakes. Furthermore, the exclusion of LER, as with energy adjustment, cannot eliminate bias due to selective underreporting of foods, nor does it provide corrected estimates of nutrient intake according to systematic underreporting by subject characteristics such as obesity.

### **1.3.3. Calibration and Measurement Error Models for Nutrient Intakes**

Measurement error models are commonly used in nutrition epidemiology to calibrate self-reported dietary data. These models are typically regression-based and use validation sample data to predict a “true” estimate for the entire study population. Statistically, such models assume that either the validation data are measured without error or that any such error is independent of the true dietary exposure. Therefore, correlated biases between self-report instruments dictate the use of objective measures of diet for calibration, such as biomarkers, since their measurement errors are likely to be independent of the errors associated with self-reported estimates (82, 83). Conventional models also assume that measurement error is independent of all other study subject characteristics. However, given the evidence of systematic underreporting bias, some more complex measurement error models have been proposed, including a model that allows all measurement-error parameters to depend on body mass index and incorporates

a random underreporting quantity that applies to each dietary self-report instrument (30, 84, 85).

DLW, the gold standard biomarker for energy consumption, has been used to internally calibrate reported energy intake; and such studies have highlighted the importance of this measurement error (31, 36). Recently, Neuhouwer et al. found that calibrated estimates of energy consumption depended only weakly on FFQ energy and more strongly on other participant characteristics, which suggests that disease associations with calibrated energy may differ greatly from corresponding associations using uncalibrated energy (36). However, given its high cost, performing DLW is not feasible for most epidemiologic studies, even on a small validation sample. Conversely, published energy prediction equations based on DLW data provide an alternative objective measure of TEE that can be applied to entire study populations. However, the application of EER in studies of underreporting bias has been limited to identifying LER and examining the magnitude and predictors in a given population. Therefore, the potential of EER equations to calibrate energy intake and to estimate energy adjusted nutrient intakes has not been adequately explored. Such an application of the EER equations appears valuable for large studies that cannot collect DLW biomarker data and particularly when calibrated estimates depend on participant characteristics.

#### **1.4. Maternal Nutrition and Fetal Growth**

Fetal growth and birth weight are primary indicators of a successful pregnancy outcome. Babies born large for gestational age (LGA) or small for gestational age

(SGA) often have had an unusual rate of development, which can cause perinatal and neonatal complications, including death. SGA, which can result from intrauterine growth restriction (IUGR), is associated with an increased risk of developmental and behavioral problems in childhood. Moreover, epidemiological and experimental evidence has shown that both SGA and LGA may also contribute to a wide array of metabolic disorders and chronic diseases in adulthood (26, 86, 87).

Maternal nutrition plays a critical role in fetal growth and development. Glucose, the main energy substrate for the fetus, is transmitted in a steady stream primarily through metabolism of carbohydrate from the mother's diet. Certain conditions can have a profound impairment on the regulation of this glucose stream, such as diabetes or obesity, where high circulating or postprandial concentrations of glucose can result in excessive nutrient transfer to the fetus and increase the risk of LGA. Other conditions such as famine have the opposite effect, where small, infrequent meals result in lower circulating maternal glucose, which promote slower fetal growth, an increased risk for intrauterine growth restriction, and smaller birth size. While these represent the more extreme conditions, evidence also suggests a similar connection between glucose concentration and fetal growth even in healthy pregnancies (88, 89).

#### **1.4.1. Carbohydrate Quality: Glycemic Index (GI) and Glycemic Load (GL)**

The glycemic index (GI) concept was first published in 1981 after earlier studies had shown that starchy carbohydrate foods had very different effects on postprandial blood glucose responses and subsequent glycemia in both healthy and diabetic subjects (90). Indexing of the glycemic response is based on the average subject's incremental area



under the curve (AUC) of blood glucose after consumption of a given food, expressed as a percentage of incremental AUC for that of the reference food, typically glucose or white bread. In general, foods with carbohydrates that break down rapidly during digestion releasing glucose rapidly into the bloodstream have a high GI; carbohydrates that break down slowly, releasing glucose gradually into the bloodstream, have a low GI.

Some early studies challenged the physiologic relevance of the GI by suggesting that when individual carbohydrate foods are consumed as part of a mixed meal, differences in glycemic responses between foods are minimal or non-existent (91, 92) . Since then, however, numerous studies have supported the importance of the glycemic index in the context of mixed meals (93, 94, 95). In particular, studies have shown that although fat and protein affect the absolute glycemic response, they do not affect the relative differences between carbohydrate-containing foods (96, 97). Moreover, studies using standardized methods have indicated that the correlation between the glycemic index of mixed meals and the average glycemic index values of individual component foods ranges from 0.84 to 0.99 (93, 98). Thus, although other aspects of diet may add to variation in glucose and insulin responses, the effect of these other sources of variation does not appear to seriously affect the validity of calculated glycemic index values for mixed meals under realistic conditions.

GI is now widely recognized as a reliable, physiologically based classification of foods according to their postprandial glycemic effect (99). In 1997 an expert panel created by the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) endorsed the GI concept after reviewing the available research evidence regarding the importance of carbohydrates in human

nutrition and health. *International Tables of Glycemic Index*, which were first published in 1995 and revised in 2002, aim to provide a reliable list of GI values compiled from a variety of sources in the scientific literature and allow GI to be used as a dietary epidemiologic tool, allowing novel comparisons of the effects of different carbohydrates on disease risk (95, 99).

GI, however, does not take into account the amount of carbohydrate consumed, which is also an important determinant of glycemic response. For example, watermelon has a high GI(99) however, it only contains 5 g of carbohydrate per 100 g, and therefore produces a minimal glycemic effect. Glycemic load (GL), which accounts for both the GI of a food and the amount eaten, is a more recent concept and has gained popularity in nutritional research as an estimate of the overall glycemic effect from diet (100, 101). GL is indirectly measured as the product of the GI for a food and the amount of available carbohydrate in the portion of food consumed. It should be noted that this calculation implies GL is directly proportional to the amount of the particular food eaten; whereas research has actually shown that as the amount of a given food increased the rate of increase in AUC declines. For example, eating six times the amount of bread results in an approximately threefold increase in AUC(102). However, recent laboratory data found that GL calculated using GI multiplied by available carbohydrate agreed well with GL measured directly (103). Therefore, GL provides another ranking classification for both the quality and quantity of carbohydrate containing foods; and GL values are also included in the 2002 *International Tables of Glycemic Index*.

### **1.4.2. Influence of Carbohydrate Quality on Fetal Growth**

Given that maternal glucose is the main energy substrate for intrauterine growth, it seems intuitive that the GI concept would be particularly relevant during pregnancy. Thus far, research on maternal dietary glycemic index and gestational diabetes mellitus (GDM) has received the most attention. Studies have demonstrated that high GI diets both prior and during pregnancy may increase the risk of GDM (104). Further, a low GI diet is commonly advised as treatment for women with GDM; and has been shown to reduce obstetric and fetal complications, such as macrosomia (105). It has also been hypothesized that the type of carbohydrate intake in the maternal diet may alter glucose substrates and, in turn, effect fetal growth in non-diabetic women (106, 107, 108); however, research in this area remains limited.

#### **1.4.2.1. Biological Plausibility**

Factors which alter substrate delivery, mainly substrate levels or placental-bed blood flow, regulate the rate of feto-placental growth by initiating a change in synthesis and tonic release of placental growth suppressive peptides into the fetal circulation (109). A fall in placental-bed blood flow and/or maternal substrate level increases the placental release of growth-suppressive peptides, which slow fetal growth rate by decreasing the expression of insulin-like growth factors and increasing their binding proteins in fetal tissues. Conversely, a rise in flow and/or substrate levels decreases the placental release of growth suppressive peptides, which increases fetal growth rate by increasing the expression of insulin-like growth factors and decreasing their binding proteins (109).

In pregnancies complicated by obesity or diabetes, greater plasma volume and the increased placental perfusion along with, greater maternal insulin resistance with decreased glucose disposal is thought to allow more glucose to be transmitted from mother to fetus(110). This may explain the positive association of maternal plasma glucose, especially postprandial glucose level, on infant birth weight (111, 112) among obese and/or diabetic women. However, the literature also suggests a similar connection between glucose concentration and fetal growth in nondiabetic pregnancies (88, 89, 113, 114). On the other hand, severe reductions in maternal energy intake are known to reduce maternal blood sugar levels, fetal growth rate and size at birth (106). And, evidence also suggests that fetal growth restriction even among women of normal body weight and adequate nutrition may be explained by differences in carbohydrate metabolism, such as higher insulin sensitivity, which leads to a reduction in glucose substrates for fetal growth. Caruso et al., found that women who experienced unexplained fetal growth restriction had increased insulin sensitivity during the third trimester, which exhibited a strong negative correlation with relative birth weight compared to controls (115). No differences were seen in fasting plasma glucose, insulin and human placental lactogen samples, age, height, pregravid weight, weight gain, and parity.

The type of carbohydrate eaten can influence insulin resistance and sensitivity, which are the key components of glucose metabolism, and thus glucose substrate levels available for the fetus. Studies have demonstrated that both the quality and quantity of carbohydrate in the diet influence glucose metabolism, affecting insulin demand or sensitivity in healthy individuals (116, 117). Therefore, it is conceivable that part of the

normal variance in birth weight may be related to differences in maternal dietary carbohydrate via altering circulating maternal glucose and insulin levels. Thus, altering the GI and/or GL of maternal dietary carbohydrate may be a valuable in the prevention and management of pregnancies at risk for anomalous feto-placental growth.

#### **1.4.2.2. Dietary Intervention Studies of Glycemic Index and Fetal Growth**

In 1998, Clapp et al. reported on a longitudinal study of 12 healthy women who were recruited before pregnancy and followed through to delivery (118). The women agreed to follow a diet that provided 55–60% carbohydrate with the initial diet being composed of low GI foods. At 8 weeks gestation, they were randomly assigned to continue either the low-GI diet or to follow a high-GI diet for the duration of pregnancy. For women on the high-GI diet, the glucose responses to a standard meal progressively increased during pregnancy, whereas for women who consumed the low-GI diet the glucose responses did not change. Mean infant birth weight was approximately 1000 grams more compared to babies from women who consumed the low-GI diet; and all women who consumed the high-GI diet all had infants that were LGA. Although this study provides intriguing evidence that a high-GI diet may increase the risk of LGA in healthy women, the results are somewhat undermined by the small sample size, and thus compromised internal and external validity.

In 2006, Moses et al. conducted a similar experiment on a larger sample of 62 healthy women enrolled between 12-16 weeks gestation (107). The subjects were alternately assigned to receive dietary counseling that encouraged a low-GI (LGI) carbohydrate foods or a high-fiber, moderate-to-high GI (HGI) foods and were studied 5 times

between 16 wk gestation and delivery; both groups were matched for initial macronutrient intake. Measures of dietary adherence were similar for women in either group; however, neither subjects nor investigators were blinded to the dietary intervention. Compared with the LGI group, women in the HGI group gave birth to infants who were heavier (3408 grams vs. 3644 grams;  $P=0.05$ ), a higher ponderal index (2.62 vs 2.74;  $P=0.03$ ), and a higher prevalence of LGA (3.1% vs. 33.3%;  $P=0.01$ ). Women who consumed the LGI diet did not have an increased number of infants who were either SGA or LGA. These data appear to replicate the earlier finding of Clapp et al. that mixed diets high in GI foods may increase the risk of excessive fetal growth among healthy, free-living pregnant women. Further, neither intervention study observed an increase risk of SGA among subjects on the low-GI diet.

#### **1.4.2.3. Epidemiologic Research on Glycemic Index and Fetal Growth**

To date, Scholl et al.(108) have published the only observational study on carbohydrate quality and fetal growth. They analyzed data from 1,082 delivered gravidas from of an ethnically-diverse, low income cohort who enrolled at prenatal clinics in Camden, NJ between August 1996 and October 2002. Women with serious non-obstetric problems, such as hypertension, diabetes mellitus type 1 or type 2, malignancies, and drug or alcohol abuse, were not eligible. Dietary data were computed from the average of three, nonconsecutive 24-hour recalls obtained at entry to prenatal care and updated at weeks 20 and 28 of gestation. Samples for plasma glucose and for glycosylated hemoglobin were obtained at 24–28 weeks' gestation. Regression models were constructed to test the differences for infant birth weight, plasma glucose and

glycosylated hemoglobin between quintiles of dietary GI and GL. Models were further adjusted for age, parity, ethnicity, cigarettes smoking, body mass index, prior history of LBW, and duration of gestation. Biomarkers of maternal carbohydrate metabolism during the third trimester were positively related to maternal GI, as well as, infant birth weight. Compared to the middle quintile, women in the lowest GI quintile had lower infant birth weights (mean, -105.6 ; 95% CI, -39.0, -172.2), which persisted after adjustment for confounders (mean, -116.2; 95%CI, -50.0, -182.5). However, no significant difference in infant birth weight was observed for women in the highest GI quintile. The risk of SGA was higher for women in the lowest GI quintile with adjusted odds ratio was 1.75 (95% CI, 1.10, 2.77); no increased risk in LGA by strata of GI was observed. Regression models were also performed separately for GL, and indicated that GL and was unrelated to maternal plasma glucose, infant birth weight, or risk of SGA.

In this study, the general relationship between dietary GI, maternal glucose and infant birth appear plausible given the scientific literature. Although, the statistically significant association between low GI and SGA and the null finding of high GI and LGA are not consistent with results from the two dietary intervention studies. Furthermore, the presence of an association between fetal growth and GI, but not GL, seems counterintuitive given that GL is considered a better measure of overall glycemic impact. This study population was primarily comprised of low income, African American and Hispanic women and nearly 50% of the cohort were overweight or obese. Therefore, it is possible that measurement error in dietary intake may have affected these results. For example, the underreporting of high GI foods among obese gravidas, who are already at greater risk for LGA, may have obscured a true positive association

between high-GI and LGA. In addition, GL is calculated using absolute energy intake from carbohydrate, thus a positive association between infant birth weight and GL may have been similarly distorted due to an increased frequency of LER among obese subjects. However, the influence of dietary measurement error was not considered in this study.

### **1.5. Conclusion**

Measurement error is pervasive in nutritional epidemiology and is known to obscure diet-disease associations. The existence of obesity related energy underreporting is well documented in the general population; and emerging evidence has indicated that macronutrient specific underreporting is also prevalent. However, information on the frequency, magnitude and predictors of underreporting bias during pregnancy is exceedingly limited. Moreover, given that both maternal weight status and energy intake are on the causal pathway for many pregnancy outcomes, such as fetal growth, a failure to account for obesity related underreporting may yield erroneous conclusions in such studies.

There is strong biological plausibility for the potential influence of maternal carbohydrate quality on fetal growth and infant birth weight. Preliminary research suggests that low GI diets during pregnancy may reduce maternal glucose levels and restrict fetal growth (108); and high GI diets during pregnancy are associated with higher maternal glucose parameters and larger infant birth weights (106) (107). Results across these studies, however, are not consistent regarding the magnitude and statistical



significance of the observed change in fetal growth. Moreover, etiological studies on this topic remain limited and have yet to explore the potential role of dietary measurement error. A recent review has concluded that further study of glycemic index and glycemic load on parameters of fetal growth is warranted (119). We conclude that such future research include large, diverse study populations of pregnant women, as well as, methods that adjust for systematic underreporting bias in maternal diet.

## **Chapter Two**

### **Statement of the Problem and Specific Aims**

Many adverse health outcomes are associated with an imbalance of nutrients, whether an excess or a deficiency. The ability to detect associations between diet and disease is often complicated by measurement error of dietary intake. Information on the frequency, magnitude and predictors of underreporting bias during pregnancy, however, is exceedingly limited. The course of pregnancy creates some unique physiological, medical, and psychosocial demands, which may alter the patterns of measurement error in energy intake that have been observed in non-pregnant populations. Identifying sources of this bias is necessary to improve dietary assessment methodology in reproductive epidemiologic studies and minimize error for susceptible participants. Further, both maternal weight status and energy intake lie on the causal pathway for many pregnancy outcomes, such as fetal growth; and a failure to account for obesity related underreporting bias may yield erroneous conclusions in such studies. The purpose of this dissertation is: to determine the frequency, magnitude and predictors of underreporting energy intake during pregnancy; to examine the association between the type of maternal carbohydrate consumption, fetal growth and infant birth weight; and finally, to explore the influence of underreporting bias on this association.

**The specific aims include:**

## **Aim 1**

Calculate measurement error in energy intake using the ratio of values from a food frequency questionnaire (FFQ) to total energy expenditure (TEE), as estimated from a validated prediction equation. Upper and lower cutoff values for this ratio will be determined using an accepted methodology from the literature and will identify participants who misreported their energy intake.

This is a descriptive Aim to identify the following groups of measurement error in energy intake:

- A) Low Energy Reporting (LER), also known as Underreporting
- B) Adequate Energy Reporting (AER)
- C) High Energy Reporting (HER)

## **Aim 2**

Compare the distribution of participant characteristics including demographic, psychosocial, and nutritional parameters between LER, AR and HER. In particular, LER status of participants will be modeled on their characteristics to determine independent predictors of energy underreporting.

### *Hypothesis 2a*

LER will be positively associated with body mass index (BMI) and obesity.

### *Hypothesis 2b*

LER will be negatively associated with education status

### *Hypothesis 2c*

LER will be negatively associated with African American race

### *Hypothesis 2d*

LER will be positively associated with dietary restraint

*Hypothesis 2e*

LER will be positively associated with dietary glycemic index (GI)

*Hypothesis 2f*

LER will be positively associated with gestational weight gain

**Aim 3**

Examine the association between maternal dietary GI and dietary glycemic load (GL) during the second trimester, random glucose screen, and fetal growth. Fetal growth will be estimated using infant birth weight adjusted for gestational age. Maternal glucose and fetal growth will be modeled separately against dietary GI and GL and other variables that are shown to be confounders in our study population.

*Hypothesis 3a*

Maternal dietary GI/GL will be positively associated with maternal glucose

*Hypothesis 3b*

Maternal dietary GI/GL will be positively associated with infant birth weight.

*Hypothesis 3c*

Diets high in GI/GL will be associated with a higher incidence of LGA.

*Hypothesis 3d*

Diets low in GI/GL will be associated with a higher incidence of SGA.

**Aim 4**

A sensitivity analysis will be conducted to compare the coefficients and effect estimates from models in Aim 3 after excluding physiologically implausible energy intakes (LER and HER) as determined from Aim 1.

## **Chapter Three**

### **Methods**

#### **3.1. Data Source**

The four aims of this proposal will be accomplished by analyzing data collected in the third phase of the Pregnancy, Infection, and Nutrition Study (PIN3). PIN3 is a prospective cohort study designed to examine whether certain maternal characteristics, such as maternal physical activity or stress, are associated with preterm birth.

##### **3.1.1. Study Population and Subject Recruitment**

PIN3 includes a cohort of pregnant women seeking services from prenatal clinics at University of North Carolina (UNC) Hospitals. Women were recruited for enrollment at <20 weeks gestation. Recruitment began in January 2001 and ended in June 2005. Potential subjects were identified by study staff through a review of all medical charts of new prenatal patients. Women were excluded if they were less than age 16, non-English speaking, not planning to continue care or deliver at the study site, carrying multiple gestations, or did not have a telephone from which they could complete phone interviews. A total of 3,203 women were eligible for the study and 2,006 (63%) were recruited. All participants gave informed consent at the time of recruitment. PIN3 was approved by the UNC School of Medicine Institutional Review Board.

### **3.1.2. Data Collection**

Women enrolled in PIN3 were asked to complete the following: 2 research clinic visits (<20 and 24–29 weeks gestation); 2 telephone interviews (17–22 and 27–30 weeks gestation); 2 self-administered questionnaires distributed at each of the clinic visits; and 1 food frequency questionnaire distributed at the second clinic visit. Delivery logs at study hospitals were examined daily to determine delivery information on all study participants. Following delivery, medical charts were abstracted.

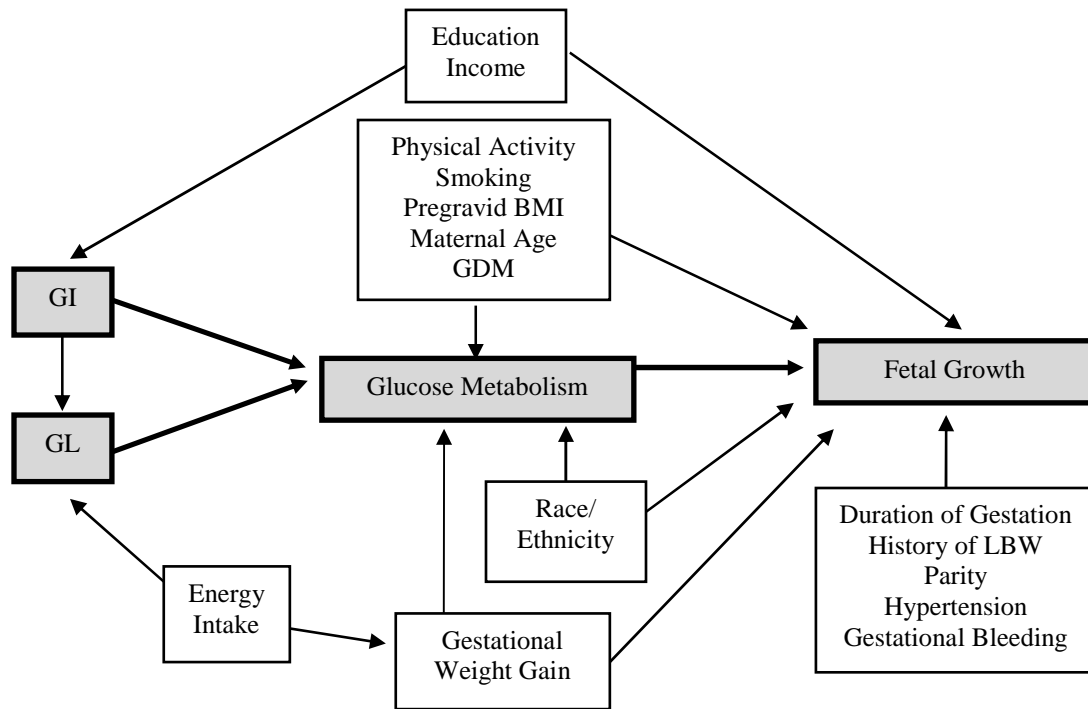
### **3.2.1.5. Statistical Analysis**

Details of the statistical methods will be described for each paper in Chapter 4 and Chapter 5, respectively.

### **3.3.3.1 Causal Diagram for Carbohydrate Quality and Fetal Growth**

Below is a causal directed acyclic graph (DAG), which illustrates a set of potential confounders and effect modifiers for the association between carbohydrate quality and fetal growth. As described previously, variation in glucose metabolism is the proposed biological mechanism for altering fetal growth via carbohydrate quality.

**Figure 3. 1. Causal Diagram of Glycemic Index and Glycemic Load on Fetal Growth**





## **Chapter Four**

### **Predictors of Measurement Error in Energy Intake**

#### **Introduction**

Accurately measuring dietary intake in human populations is challenging. Population based studies typically rely on self-reported dietary assessment, which is subject to considerable measurement error. A growing body of literature has demonstrated that subjects tend to underreport energy and nutrient intake, and this underreporting occurs more frequently in certain subgroups, such as women and overweight subjects (29). Further, there is accumulating evidence that nutrient risk estimates incorporate this systematic error, which can have an unpredictable bias on the measure of association (30, 31, 32).

Pregnancy is a complex period of human growth for both the mother and the fetus. The course of pregnancy creates some unique physiological, medical, and psychosocial demands, and these demands affect maternal energy and nutrient needs, appetite, and meal patterns (2, 3). Maternal nutrition plays an important role during this time; however reported associations between dietary exposures and pregnancy outcomes have been modest or non-existent. One reason for this may be systematic reporting bias in nutritional data, but very little is known about this error in pregnant populations. Therefore, it is possible that the frequency and patterns of measurement error in energy intake may differ between pregnant and non-pregnant populations.

Only a few studies have investigated the misreporting of maternal dietary energy intake (26, 78, 120), and the only population based study of misreporting was conducted in 490 pregnant Indonesian women. Winkvist et al. reported an energy underreporting prevalence of 16.2% during the second trimester and noted that underreporting was more common among women with BMI greater than 25.0. However, this cohort may not be representative of women in developed countries; furthermore, several important predictors were not examined, including certain pregnancy characteristics such as gestational weight gain. Two smaller studies conducted in the UK also found evidence of energy underreporting among pregnant women, but were limited due to small sample size. Therefore, the prevalence, magnitude and predictors of measurement error in energy intake among pregnant women remain unclear. Identifying these components may enhance data collection and analytic methods by reducing systematic bias in reproductive studies.

To identify measurement error in energy intake (EI) it is necessary to have an objective estimate of energy requirement, which is usually based on total energy expenditure (TEE). Doubly labeled water (DLW) is generally considered the gold standard for assessment of TEE (29), however this technique is very costly and is not practical for large population studies. In 2002, estimated energy requirement (EER) prediction equations were published as part of the Institute of Medicine (IOM) Dietary Reference Intakes (DRI). EER equations were developed from an extensive normative DLW database, which included TEE measurements on adults, children and pregnant women with a variety of physical activity levels. DRI equations for EER have been utilized in recent studies of identifying energy underreporting (39, 40) and their accuracy

compared with DLW has been independently corroborated (121). Measurement error in energy intake is typically classified as low energy reporting (LER) and high energy reporting (HER). These categories represent implausible energy intakes and are determined using confidence limits of agreement, which account for the within subject variation expected from the methods used to estimate EI and TEE.

The Food Frequency Questionnaire (FFQ) has been shown to be an appropriate method for assessing habitual dietary intake in a wide variety of epidemiological settings, including studies among pregnant women (11, 16, 17, 18, 19, 20). We examined measurement error in daily energy intake during the second trimester from a FFQ among subjects who participated in the third phase of the Pregnancy, Infection and Nutrition Study (PIN3).

## **Materials and Methods**

### ***Study Population***

PIN3 was a prospective study designed to examine whether certain maternal characteristics, such as maternal physical activity or stress, are associated with preterm birth. Women enrolled in PIN3 were recruited from the prenatal clinics at University of North Carolina Hospitals. Women were recruited for enrollment at <20 weeks gestation from January 2001 through June 2005. Women were excluded if they were less than age 16, non-English speaking, not planning to continue care or deliver at the study site, carrying multiple gestations, or did not have a telephone from which they could complete phone interviews.

A total of 2,006 women were recruited. Of the 1,446 subjects who completed the FFQ: 319 were missing the survey on restrained eating behaviors, which was added to the study protocol after enrollment began; 8 were missing pregravid height and weight; and an additional 119 subjects were missing data for one or more other variables of interest. Some women were recruited into the cohort more than once because of additional pregnancies within the recruitment period. In these instances (n=35), the pregnancy with the most complete information or the first pregnancy (when information was complete for both pregnancies) was included in the analysis. Data from the remaining 988 pregnancies were used in this analysis.

### ***Data Collection***

The PIN Study protocols were reviewed and approved by the Institutional Review Board of the School of Medicine at the University of North Carolina at Chapel Hill. Women enrolled were asked to complete 2 research clinic visits (<20 and 24–29 weeks gestation), 2 telephone interviews (17–22 and 27–30 weeks gestation), 2 self-administered questionnaires, and 1 FFQ distributed at the second clinic visit. Following delivery, medical charts were abstracted. Pregnancies were dated using an algorithm based on first ultrasound performed prior to 22 weeks' gestation (up to 21 weeks, 6 days). If no ultrasound was performed or none was performed prior to the start of week 22, then last menstrual period (LMP) was used to date the pregnancy.

Self-reported pre-pregnancy weight and measured height were recorded at the first prenatal visit. Weight measurements taken at the first prenatal clinic visit were compared with the self-reported pre-pregnancy weights to identify biologically

implausible weight gains. In such cases, an imputed weight was calculated using the measured weight at the first prenatal visit (if taken prior to 16 weeks) minus the recommended amount of weight to be gained in the first and second trimesters as defined by the 1990 IOM recommendations. Pregravid BMI in  $\text{kg/m}^2$  was then calculated by using either reported or imputed pregravid weight and measured height. The rate of gestational weight gain during the second trimester was calculated as the difference between the first clinically measured weight following 12 weeks gestation and the last clinically measured weight recorded prior to week 27, divided by the number of weeks between measurements. Cut points to determine inadequate and excessive weight gains were based on the 1990 IOM BMI-specific recommendations previously used in the literature (122).

Dietary information was collected at 26–29 wk of gestation using a self-administered 110-item Block-98 FFQ. Daily energy and nutrient intake was estimated from all foods and beverages. The Block FFQ has been validated in several populations (10, 123, 124), including the PIN Study. Deattenuated Pearson correlation coefficients between FFQ and multiple 24-h dietary recalls for total energy was 0.32 for PIN1 and 0.33 for PIN2. A more detailed description of the PIN FFQ has been published elsewhere(125) .

Physical activity data were captured using a 1 week recall questionnaire specifically designed for PIN 3, which was administered by telephone between 17 and 22 weeks' gestation. This instrument assessed the frequency, duration and intensity of a variety of reported physical activities over the last 7 days at either a moderate or vigorous intensity level. Domains incorporated the following settings and/ or roles: at work, for recreation,

for transportation, during care giving and as a part of indoor and outdoor household tasks.

The Revised Restraint Scale (RRS) was administered to assess preconception dieting and restrained eating behaviors. It consists of 10 questions in a multiple choice format: 5 that pertain to diet and weight history; and 5 that pertain to concern with food and eating. Responses to questions regarding dieting behaviors were based on the Likert Scale. Wording of the RRS was changed so that it was clear the questions focused on the period prior to pregnancy and not on weight changes associated with pregnancy. An overall score for Restrained Eating was calculated by summing the scores for all of the questions. Comparisons were made between subjects above and below the median (126).

The Center for Epidemiologic Studies Depression Scale (CES-D) was administered to assess psychological disposition or generalized distress (127). The 20-item scale has Likert-type response categories assessing feelings and activities the respondent experienced during the past week. The range is from 0 to 60 points. A CES-D score of 25 or higher was considered to indicate significant depressive symptoms.

Estimated energy requirement (EER) for each subject was calculated using the 2002 DRI equations, which are sex and age-specific and are based on age, weight and height (128) (Appendix A). For pregnant women, the DRI equations have an additional 340 kcal/d, which was found to be the average energy costs of pregnancy during the second trimester. However, recent evidence has shown that total energy expenditure during pregnancy is dependent on pregravid weight status. Using DLW, Butte et. al. estimated the energy requirements in a group of healthy underweight, normal-weight, and overweight pregnant women(129). Values for energy costs (kcal/d) of pregnancy for the

second trimester were 163 for low BMI ( $\leq 19.8$ ), 356 for normal BMI (19.8–26.0), and 441 for high BMI ( $\geq 26$ ) subjects. We applied these values to our calculation of TEE, which justified our use of the 1990 IOM cutpoints for pregravid BMI.

EER equations also allow for four levels of physical activity; sedentary, low activity, active and very active with a corresponding physical activity coefficient (Appendix A). Each subject was assigned an activity level based on her average daily minutes of moderate and vigorous physical activity, which was calculated from the PIN 7-day physical activity recall questionnaire. Using the American College of Sports Medicine (ACSM) guidelines, weekly moderate physical activity was estimated from minutes spent in reported activities with a MET value of 4.8-7.1; and vigorous physical activity was from minutes spent in activities with a MET value  $\geq 7.2$ . These weekly values were divided by 7 to represent average daily moderate and vigorous physical activity during the second trimester.

### *Statistical Analysis*

To identify physiologically implausible self-reported energy intakes, 95% confidence limits of agreement were calculated for the ratio of reported EI to EER (EI:EER) using the Goldberg method described by Black & Cole (42) and further adapted by Huang et al.(80). The combined within subject coefficient of variation ( $CV_w$ ) was calculated as  $CV_w = \sqrt{(CV^2_{wEI} / d + CV^2_{mTEE} + CV^2_{pER})}$ . Because the FFQ measures habitual intake, the number of days ( $d$ ) is not applicable; thus, combined  $CV_w$  is equal to the variation in measured TEE ( $CV_{mTEE}$ ) and predicted energy requirements ( $CV_{pER}$ ). Using a compilation of data from DLW studies, Black et al. estimated the within subject error in

TEE measured by DLW ( $CV_{mTEE}$ ) to be 9.6% over a period of 13 weeks, which approximates a trimester of pregnancy (42). The error in predicted energy requirements ( $CV_{pER}$ ) was estimated from the published DRI database using the available data on females ages 18-40 (128). We conducted least-squares regression of measured TEE on age, height, weight and physical activity level.  $CV_{pER}$  was then calculated by dividing the SD of the residuals by the mean TEE. This was performed separately for three strata of BMI, which resulted in  $CV_{pER}$  values of 10.9% for low BMI ( $\leq 19.8$ ), 9.9% for normal BMI (19.8–26.0), and 8.1% for high BMI ( $\geq 26$ ) women. Therefore, the lower confidence limit (LCL) for EI:EER was 0.76, 0.73, and 0.72 and the upper confidence limit (LCL) was 1.24, 1.27, and 1.28 for low, normal and high BMI woman, respectively. LER was defined as having a ratio of EI:EER < LCL, adequate energy reporting (AER) was defined as  $LCL \leq EI:EER \leq UCL$ , and HER was defined as  $EI:EER > UCL$ .

A univariate analysis was conducted to compare values of EI, EI:EER, LER, HER across maternal characteristics. Continuous covariates, which included age, education, pregravid BMI and gestational weight gain were additionally coded into discrete ordinal categories. Differences in EI:EER were tested using an independent samples t-test or ANOVA F-test. Independence between proportions of LER and HER was tested using a chi-square test. Multiple logistic regression models were developed separately for LER and HER. First, all maternal baseline characteristics including gestational weight gain were considered one at a time in each model. Any variable with  $P$  value <0.25 was considered for inclusion. Each multivariable model was fit using backward elimination, including all the potential predictor variables and evaluating variables one at a time in



order of the smallest Wald chi-square test. A variable was removed if the change in deviance via likelihood ratio test was not statistically significant ( $P < 0.05$ ). Interactions between predictor variables were also considered, however none were identified. Smooth scatterplots were used to determine linearity on the logit scale for continuous variables.

To examine if nutrient intakes varied by energy reporting status, mean nutrient density (intake expressed as a percentage of total energy) for macronutrients and micronutrients were compared between LER, AER, and HER using ANOVA with Bonferroni adjustment for multiple comparisons. Each nutrient was log-transformed beforehand to improve normality. Threshold for statistical significance was a p-value less than 0.05. All analyses were performed using SAS software (version 9.1.3; SAS Institute Inc, Cary, NC).

## **Results**

This pregnancy cohort consisted of mostly white woman who were married and had at least some college education (Table 1). Average maternal age was 29 SD=5.5 years. Prior to pregnancy, 11.2% of the participants were overweight and 22.0% were obese according to the 1990 IOM cutpoints. Median and IQR for energy intake in kilocalories were  $1483 \pm 451$ ,  $2182 \pm 583$ , and  $3801 \pm 1213$  for LER, AER, and HER, respectively. Median EI:EER was 0.85, indicating that most subjects underreported their energy intake. The prevalence of implausible intakes, LER and HER, was 32.8% and 12.9%, respectively. Univariate analysis also demonstrated that EI:EER, LER and HER varied by several maternal characteristics (Table 1). LER prevalence differed by education, pregravid BMI, gestational weight gain, physical activity, and restrained

eating behavior. Like LER, HER prevalence differed by pregravid BMI, education and restrained eating behavior; but also varied by race, marriage, adequacy of gestational weight gain, and depressive symptoms.

In a multivariable analysis (Table 2), pre-gravid BMI was related to both LER and HER. Compared to normal weight women, LER was higher in overweight (OR=2.06, 95% CI=1.33, 3.19) and obese women (OR=2.93, 95% CI=2.07, 4.13), but lower in underweight women (OR=0.27, 95% CI=0.15, 0.48). Whereas, HER was higher in underweight women (OR=4.58, 95% CI=2.77, 7.60) and lower in obese women (OR=0.44, 95% CI=0.24, 0.82) than in normal weight counterparts.

Other than pregravid BMI, independent predictors of LER and HER were different. LER was more prevalent among married women and those who reported higher levels of physical activity. HER was more prevalent among subjects who were African American, less educated, and had higher depressive symptom scores. Gestational weight gain in the second trimester and restrained eating behavior were not associated with either LER or HER, after adjusting for Pregravid BMI. Both GWG and restrained eating scores were moderately correlated with pregravid BMI, -0.31 and 0.47, respectively.

LER was most common in pregnant women who were classified as obese prior to pregnancy (49.8%). Figure 1 displays the prevalence of LER by pregravid BMI status and adequacy of gestational weight gain according to the IOM guidelines. Among obese women, we observed a similarly high proportion of LER in women whose gestational weight gain over the first two trimesters was classified as inadequate (45.6%) or excessive (52.6%).

Table 3 displays median intakes for macronutrients and micronutrients according to category of energy reporting. Nutrient intakes for LER women were not significantly different compared to those with AER. However, HER women had significantly lower intakes for riboflavin, calcium, and magnesium than AER women.

## **Discussion**

Our results indicate that implausible reported energy intakes, both underreporting and overreporting, are prevalent in this large cohort of pregnant women. Direct comparison of measurement error between dietary studies is somewhat difficult because of variations in dietary assessment, physical activity assessment, estimation of TEE, as well as population characteristics. Black et al. conducted a meta-analysis on studies that utilized both DLW and weighed food records. Among non-pregnant women aged 18-39 years, the authors found that 31% underreported their intake and 3% over-reported (46). Larger population studies on non-pregnant females, which utilized prediction equations for energy requirements and a variety of dietary assessment methods, have reported a frequency of LER ranging from 11%-52% (49). Although LER prevalence has been shown to vary by dietary assessment method, studies comparing these methods have been inconsistent in their findings. Some have found that the FFQ provided less underreporting than dietary recalls or food records (130, 131, 132), while others found the opposite (31, 44, 133, 134)

In our study, pregravid BMI was a positive predictor of LER, which is consistent with most studies in non-pregnant populations. It has been proposed that measures of body size and adiposity are likely surrogates for psychological factors characteristics that

result in underreporting energy, such as poor awareness of intake or portion sizes, subconscious biasing toward intake that is perceived to be appropriate, restrained eating behaviors, and fear of weight gain (47, 48, 53, 135). However, we found no association between dietary restraint score and underreporting in our cohort after adjusting for pregravid BMI. In addition, there was no independent association between LER and gestational weight gain. LER was similarly prevalent among overweight subjects regardless of whether they were categorized as having excessive or inadequate gestational weight gain.

LER was also more common in pregnant women who reported minutes of moderate to vigorous physical activity which met the American College of Obstetrics and Gynecology (ACOG) recommendation for exercise during pregnancy (136). However, this finding was likely attributed to measurement error in reported physical activity. One common bias in these data is the overreporting of minutes spent in a given activity (137). Because physical activity data were utilized in the estimation of TEE, an overreporting bias would result in artificially higher EER, thereby reducing the EI:EER ratio and increasing the tendency to be classified as LER. In fact, a validation study for PIN3 found that minutes of moderate to vigorous physical activities were 85% higher on average when compared with accelerometry, an objective measure of physical activity (138). Further, social desirability bias is a purported reason for both underreporting energy intake (139) and overreporting physical activity (137). Therefore, any association between higher physical activity and LER may also be influenced by correlated error.

Our study is the first to investigate HER, or overreporting, among pregnant women. We determined that 12.9% of subjects overreported their energy intake, which is higher

than typically seen in non-pregnant populations. HER was more common among pregnant women who were underweight, African-American, and had no college education. Additionally, we found that HER was more prevalent among women with higher depressive symptoms scores. Researchers have suggested that depression and anxiety may influence reporting accuracy by impairing cognitive processes such as memory or triggering eating disinhibition (140) and some studies in non-pregnant women have shown a positive association between depression and LER (135), however, to our knowledge the relationship between depression and HER has not been previously reported.

An emerging literature has demonstrated how both energy specific and nutrient specific underreporting can seriously distort measures of association in nutrition epidemiology (30, 34, 67, 141). In our cohort, measurement error in energy intake varied significantly by certain maternal characteristics. However, we did not observe that underreporting bias was associated with variable bias in specific nutrient intakes. This finding suggests that energy underreporting occurred at the whole diet level, which is an important assumption in the analysis of diet and disease since nutrient intakes are typically adjusted for EI to separate the effect of EI from the effect of an individual nutrient on a particular health outcome (34). Nevertheless, many researchers agree that energy adjustment alone cannot eliminate the effects of differential reporting bias (30, 34, 141). Additional methods include stratifying results by LER and AER, as well as a more sophisticated approach of including predictors of LER (i.e. BMI) in a nutrient measurement error model (142).

The main limitation of this study is that TEE was estimated rather than directly measured using DLW. We calculated TEE using DRI prediction equations for EER, which were derived from DLW data. These equations have been deemed a valid alternative to DLW measurements and have also been used in previous studies of LER. Another limitation is that approximately 25% of PIN 3 subjects did not complete the FFQ. On average, women that we excluded from the analysis were more likely to be overweight, younger, less educated, African American and unmarried. Because some of these characteristics were predictive of LER and HER, it is possible that our results may have differed if complete data were available for all subjects. It should also be noted that PIN 3 subjects were not sampled at random and all participants received their prenatal care in the UNC Hospital system. Therefore, generalizability of our results to other pregnant populations may be limited. The primary strength of this project is the prospective study design of PIN 3. Data were collected from the first trimester of pregnancy through delivery. Moreover, dietary information was ascertained during the second trimester, where intake is less likely to be influenced by nausea.

In conclusion, it appears that the level of LER and HER during pregnancy is not grossly different than what has been observed in non-pregnant women. Nevertheless, nearly half of all women in our cohort misreported their energy (food) intake. This measurement error was also associated with maternal characteristics, including pregravid BMI, which is a risk factor for several reproductive, perinatal, and pediatric outcomes (143, 144, 145, 146, 147, 148, 149). Thus, a failure to account for obesity-specific underreporting bias may yield erroneous conclusions in such studies. A few analytical methods to account for this error have been proposed; however more research is needed.

Future studies of maternal diet should consider identifying LER, HER and their predictors to assess the level of potential bias and to help adjust for this error in the calculation of nutrient risk estimates.

**Table 4. 1. Energy Intake, EI:EER and Prevalence of Low Energy Reporting (LER) and High Energy Reporting (HER) by Maternal Characteristics Among Women Enrolled in the Pregnancy, Infection and Nutrition Cohort, North Carolina, 2000-2005.**

		EI		EI:EER		LER		HER	
		N (%)	Median (IQR)	Median (IQR)	p-value*	N (%)	p-value†	N (%)	p-value†
<b>Overall</b>		988 (100.0)	2008 (878)	0.85 (0.87)	-	324 ( 32.8)	-	127 ( 12.9)	-
<b>Age (years)</b>	<25	188 ( 19.0)	2164 (1195)	0.87 (0.48)	0.05	55 ( 29.3)	0.17	42 ( 22.3)	<0.01
	25-<30	288 ( 29.1)	1985 ( 874)	0.84 (0.37)		107 ( 37.2)		25 ( 8.7)	
	30-<35	349 ( 35.3)	1995 ( 868)	0.86 (0.33)		105 ( 30.1)		39 ( 11.2)	
	≥ 35	163 ( 16.5)	1929 ( 800)	0.84 (0.40)		57 ( 35.0)		21 ( 12.9)	
<b>Race</b>	White	750 ( 75.9)	1971 ( 832)	0.85 (0.36)	<0.01	246 ( 32.8)	0.72	81 ( 10.8)	<0.01
	Black	155 ( 15.7)	2344 (1431)	0.89 (0.55)		48 ( 31.0)		37 ( 23.9)	
	Other	83 ( 8.4)	1915 ( 785)	0.80 (0.34)		30 ( 36.1)		9 ( 10.8)	
<b>Married</b>	No	205 ( 20.7)	2258 (1212)	0.91 (0.49)	<0.01	58 ( 28.3)	0.12	45 ( 22.0)	<0.01
	Yes	783 ( 79.3)	1925 ( 844)	0.84 (0.35)		266 ( 34.0)		82 ( 10.5)	
<b>Highest Education</b>	HS	171 ( 17.3)	2249 (1422)	0.88 (0.70)	0.02	57 ( 33.3)	0.03	49 ( 28.7)	<0.01
	Coll. Grad	469 ( 47.5)	1948 ( 969)	0.83 (0.39)		171 ( 36.5)		46 ( 9.8)	
	Grad. School	348 ( 35.2)	1976 ( 716)	0.86 (0.29)		96 ( 27.6)		32 ( 9.2)	
<b>Smoked During Pregnancy</b>	No	890 ( 90.1)	1976 ( 859)	0.85 (0.37)	0.83	293 ( 32.9)	0.80	111 ( 12.5)	0.28
	Yes	98 ( 9.9)	2145 ( 971)	0.88 (0.44)		31 ( 31.6)		16 ( 16.3)	
<b>Nulliparous</b>	No	481 ( 48.7)	2018 ( 915)	0.84 (0.40)	0.75	164 ( 34.1)	0.40	70 ( 14.6)	0.12
	Yes	507 ( 51.3)	1999 ( 828)	0.86 (0.35)		160 ( 31.6)		57 ( 11.2)	
<b>Pregravid BMI</b>	<19.8	134 ( 13.6)	1970 ( 952)	0.97 (0.54)	<0.01	14 ( 10.4)	<0.01	37 ( 27.6)	<0.01



		EI		EI:EER		LER		HER	
		N (%)	Median (IQR)	Median (IQR)	p-value*	N (%)	p-value†	N (%)	p-value†
<b>Gestational Weight Gain (lbs/week)</b>	19.8-26.0	526 ( 53.2)	1997 ( 779)	0.86 (0.35)		155 ( 29.5)		52 ( 9.9)	
	>26.0-29.0	111 ( 11.2)	2053 ( 837)	0.82 (0.37)		47 ( 42.3)		17 ( 15.3)	
	>29.0	217 ( 22.0)	2053 (1098)	0.76 (0.41)		108 ( 49.8)		21 ( 9.7)	
	<0.87	249 ( 25.2)	1929 ( 930)	0.80 (0.38)	0.03	100 ( 40.2)	<0.01	28 ( 11.2)	0.63
	0.87-1.15	241 ( 24.4)	1940 ( 850)	0.85 (0.38)		84 ( 34.9)		36 ( 14.9)	
	>1.15-1.45	234 ( 23.7)	2018 ( 850)	0.88 (0.39)		66 ( 28.2)		28 ( 12.0)	
	>1.45	264 ( 26.7)	2081 ( 858)	0.87 (0.36)		74 ( 28.0)		35 ( 13.3)	
<b>Adequacy of Gestational Weight Gain</b>	Inadequate	207 ( 21.0)	1885 ( 856)	0.82 (0.35)	0.06	75 ( 36.2)	0.12	20 ( 9.7)	<0.01
	Adequate	186 ( 18.8)	1978 ( 895)	0.88 (0.46)		50 ( 26.9)		36 ( 19.4)	
	Excessive	595 ( 60.2)	2034 ( 889)	0.86 (0.36)		199 ( 33.4)		71 ( 11.9)	
<b>Met Physical Activity Guidelines</b>	No	810 ( 82.0)	2042 ( 886)	0.87 (0.38)	<0.01	245 ( 30.2)	<0.01	111 ( 13.7)	0.09
	Yes	178 ( 18.0)	1842 ( 751)	0.76 (0.34)		79 ( 44.4)		16 ( 9.0)	
<b>Restrained Eating Behavior</b>	No	430 ( 43.5)	1976 ( 877)	0.87 (0.40)	<0.01	120 ( 27.9)	<0.01	66 ( 15.3)	0.04
	Yes	558 ( 56.5)	2015 ( 881)	0.83 (0.37)		204 ( 36.6)		61 ( 10.9)	
<b>High Depressive Symptoms</b>	No	743 ( 75.2)	1969 ( 841)	0.85 (0.36)	0.10	243 ( 32.7)	0.92	79 ( 10.6)	<0.01
	Yes	245 ( 24.8)	2125 ( 981)	0.86 (0.43)		81 ( 33.1)		48 ( 19.6)	

\*P-value for difference in EI:EER by maternal characteristic from ANOVA F-test or Independent Samples t-test.

†P-value for independence between LER status (or HER status) and maternal characteristic from Pearson Chi-Squared test.

IQR = Interquartile range.

**Table 4. 2. Predictors of Low Energy Reporting (LER) and High Energy Reporting (HER) Among Women Enrolled in the Pregnancy, Infection and Nutrition Cohort, North Carolina, 2000-2005.**

Low Energy Reporting (LER)			High Energy Reporting (HER)		
		OR (95% CI)*			OR (95% CI)*
<b>Pregravid BMI</b>	<19.8	0.27 (0.15, 0.48)	<b>Pregravid BMI</b>	<19.8	4.58 (2.77, 7.60)
	19.8-26.0	-		19.8-26.0	-
	>26.0-29.0	2.06 (1.33, 3.19)		>26.0-29.0	0.98 (0.51, 1.88)
	>29.0	2.93 (2.07, 4.13)		>29.0	0.44 (0.24, 0.82)
<b>Married</b>	Yes	1.86 (1.29, 2.70)	<b>Race</b>	White	-
	No	-		Black	2.77 (1.62, 4.72)
				Other	0.95 (0.44, 2.03)
<b>Met Physical Activity Guidelines</b>	Yes	2.05 (1.44, 2.91)	<b>Highest Education</b>	High School	3.45 (2.10, 5.67)
	No	-		College Graduate	-
				Grad. School	0.90 (0.54, 1.49)
			<b>High Depressive Symptoms</b>	Yes	1.75 (1.13, 2.73)
				No	-

\*Calculated from logistic regression adjusted for other significant predictors of LER (pregravid BMI, marital status, and physical activity).  
† Calculated from logistic regression adjusted for other significant predictors of HER (pregravid BMI, race, education and depression).

**Table 4. 3. Nutrient density for macronutrients and micronutrients by Energy Reporting Status Among Women Enrolled in the Pregnancy, Infection and Nutrition Cohort, North Carolina, 2000-2005.**

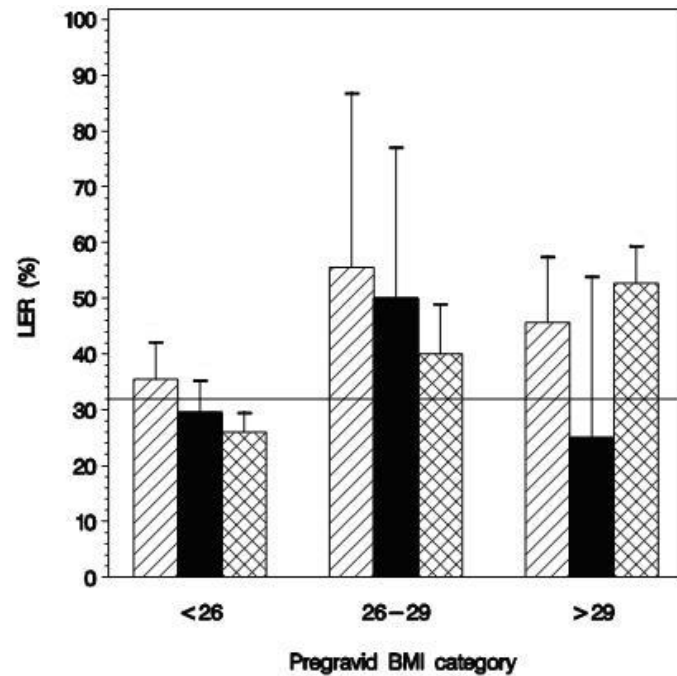
<b>Nutrient</b>	<b>LER</b>	<b>AER</b>	<b>HER</b>
Protein (%kcal)	14.5 ( 3.70)	14.2 ( 3.37)	13.7 ( 3.32)
Carbohydrate (%kcal)	54.8 (11.00)	55.2 ( 8.13)	54.1 ( 8.25)
Fat(%kcal)	33.0 ( 8.75)	33.0 ( 6.74)	33.8 ( 7.52)
Saturated Fat (g/1000 kcal)	11.9 ( 3.52)	12.0 ( 3.10)	12.6 ( 2.67)
Vitamin A (RE/1000 kcal)	636.2 (369.4)	619.6 (375.5)	532.0 (421.9)
Vitamin C (mg/1000 kcal)	95.8 (59.23)	89.0 (45.49)	83.7 (63.16)
Vitamin D (µg/1000 kcal)	96.9 (103.2)	89.0 (80.56)	82.1 (68.42)
Vitamin E (mg/1000 kcal)	4.55 (2.027)	4.62 (1.745)	4.33 (1.540)
Thiamin (mg/1000 kcal)	0.81 (0.227)	0.81 (0.187)	0.77 (0.213)
Riboflavin (mg/1000 kcal)	1.03 (0.412)	1.01 (0.336)	0.91 (0.222)*
Niacin (mg/1000 kcal)	9.45 (2.519)	9.55 (2.631)	9.40 (3.125)
Vitamin B6 (mg/1000 kcal)	0.94 (0.328)	0.93 (0.301)	0.91 (0.300)
Folate (µg/1000 kcal)	192.6 (65.22)	194.7 (57.02)	186.6 (62.76)
Calcium (mg/1000 kcal)	494.2 (251.8)	473.1 (220.6)	425.2 (160.1)*
Iron (mg/1000 kcal)	6.95 (2.553)	7.16 (2.153)	6.90 (2.587)
Zinc (mg/1000 kcal)	5.13 (1.794)	5.08 (1.677)	4.86 (1.755)
Magnesium (mg/1000 kcal)	152.4 (52.03)	150.6 (46.18)	137.7 (47.58)*

LER=Low Energy Reporters; AER=Adequate Energy Reporters; HER=High Energy Reporters.

Data are presented as median and IQR.

\* Significant difference between AER using ANOVA with Bonferonni adjustment for multiple comparisons. Each nutrient was log-transformed prior to statistical testing.

**Figure 4. 1. Percent of Low Energy Reporting (LER) by Pregravid BMI and Adequacy of Gestational Weight Gain (AWG) Among Women Enrolled in the Pregnancy, Infection and Nutrition Cohort Study, North Carolina, 2000-2005.**



Bar patterns represent categories of adequacy of gestational weight gain (AWG). Parallel lines represent inadequate weight gain, solid bars represent adequate weight gain and cross hatched lines represent excessive weight gain.

%LER is calculated separately for each combination of BMI and AWG.

Error bars represent the upper confidence limit for binomial proportions using normal approximation.

Horizontal reference line represents overall LER prevalence for the study population.

## **Chapter Five**

### **Carbohydrate Quality of Maternal Diet and Fetal Growth**

#### **Introduction**

Adequate fetal growth is an important predictor of newborn complications, and also contributes to a wide array of health conditions in adolescence and adulthood. Maternal glucose is the main energy substrate for intrauterine growth. In pregnancies complicated by diabetes, greater maternal insulin resistance and decreased glucose disposal allows more glucose and other nutrients to be transmitted to the fetus, which can result in excessive fetal growth (106, 110). However, accumulating evidence also suggests a similar relationship with maternal glucose concentration and infant birth weight among non-diabetic pregnancies (88, 150). In addition, some studies indicate that fetal growth restriction in healthy pregnancies may also be explained in part by differences in carbohydrate metabolism, such as greater insulin sensitivity, which can lead to a reduction in glucose substrates for fetal growth (88, 115).

The type of carbohydrate eaten has been shown to affect post-prandial glucose and insulin resistance and sensitivity, and thus, may alter glucose substrate levels available for the fetus. The glycemic index (GI) concept was introduced in 1981 based on findings that starchy carbohydrate foods had very different effects on postprandial blood glucose responses and subsequent glycemia in both healthy and diabetic subjects (90). Foods with carbohydrates that break down quickly during digestion and release glucose rapidly into

the bloodstream have a high GI; carbohydrates that break down slowly, and release glucose gradually into the bloodstream, have a low GI. GI is now widely recognized as a physiologically based classification of foods according to their postprandial glycemic effect (99). Glycemic load (GL), which accounts for both the GI of a food and the amount eaten, is a more recent concept and provides another ranking classification for the quality and quantity of carbohydrate containing foods (100, 101).

Despite the strong biological plausibility for an influence of maternal carbohydrate quality on fetal growth in healthy pregnancies, research in this area remains limited. Two dietary intervention studies have found that women randomized to a high GI diet during the second and third trimester of pregnancy had significant increases in the risk for LGA, compared to pregnant women on a low GI diet. The lone epidemiologic investigation found that pregnant women with diets lower in glycemic index had significantly reduced infant birth weight and an approximate twofold greater risk of small for gestational age (SGA) infants. While these results are intriguing, the studies thus far had some key limitations and were not consistent regarding the magnitude and statistical significance of the observed differences in fetal growth endpoints. And recently, two review papers concluded that further study of carbohydrate quality on parameters of fetal growth in the general population is warranted (119, 150).

We examined the association between glycemic index and glycemic load of maternal diet and fetal growth among women who participated in the third phase of the Pregnancy, Infection and Nutrition Study (PIN3). Our study will provide additional evidence to determine if part of the normal variance in birth weight may be related to differences in the quality of maternal carbohydrate intake.

## **Materials and Methods**

PIN3 was a prospective study designed to examine whether certain maternal characteristics, such as maternal physical activity or stress, are associated with preterm birth. Women enrolled in PIN3 were recruited from the prenatal clinics at University of North Carolina Hospitals. Women were recruited for enrollment at <20 weeks gestation from January 2001 through June 2005. Women were excluded if they were less than age 16, non-English speaking, not planning to continue care or deliver at the study site, carrying multiple gestations, or did not have a telephone from which they could complete phone interviews.

A total of 2,006 women were enrolled, of which 1,895 had a live birth without congenital anomaly or respiratory or fetal distress. Subjects with pre-existing diabetes (n=77) were excluded. Of the 1,818 eligible subjects, 448 did not complete the food frequency questionnaire (FFQ), 96 were missing values for post-load glucose screen, and 22 were missing data for one or more other variables of interest. Some women were recruited into the cohort more than once because of additional pregnancies within the recruitment period. In these instances (n=66), the pregnancy with the most complete information or the first pregnancy (when information was complete for both pregnancies) was utilized. Data from the remaining 1,186 pregnancies were used in this analysis.

The PIN3 protocols were reviewed and approved by the Institutional Review Board of the School of Medicine at the University of North Carolina at Chapel Hill. Women enrolled were asked to complete 2 research clinic visits (<20 and 24–29 weeks gestation),

2 telephone interviews (17–22 and 27–30 weeks gestation), 2 self-administered questionnaires, and 1 FFQ distributed at the second clinic visit. Following delivery, medical charts were abstracted. Pregnancies were dated using an algorithm based on first ultrasound performed prior to 22 weeks' gestation (up to 21 weeks, 6 days). If no ultrasound was performed prior to the start of week 22, then date of last menstrual period was used to date the pregnancy.

Self-reported pre-pregnancy weight and measured height were recorded at the first prenatal visit. Weight measurements taken at the first prenatal clinic visit were compared with the self-reported pre-pregnancy weights to identify biologically implausible weight gains. In such cases, an imputed weight was calculated using the measured weight at the first prenatal visit (if taken prior to 16 weeks) minus the recommended amount of weight to be gained in the first and second trimesters as defined by the IOM recommendations (122). Pregravid BMI in  $\text{kg/m}^2$  was then calculated by using either reported or imputed pregravid weight and measured height. The rate of gestational weight gain was calculated as the difference between the first clinically measured weight following 12 weeks gestation and the last clinically measured weight recorded, divided by the number of weeks between measurements. Cut points to determine inadequate and excessive weight gains were based on IOM BMI-specific recommendations (122) previously used in the literature (148, 151).

Dietary information was collected at 26–29 wk of gestation using a self-administered 110-item Block-98 FFQ. Daily energy intake was estimated from all foods and beverages. The Food Frequency Questionnaire (FFQ) has been shown to be an appropriate method for assessing habitual dietary intake in a wide variety of epidemiological settings,



including studies among pregnant women (11, 16, 17, 18, 19, 20). The Block FFQ has been validated in studies of pregnant women and in the two previous PIN study populations. The deattenuated Pearson correlation coefficients between the FFQ and the 24-h dietary recalls for total energy and carbohydrates were 0.32 and 0.44, respectively, for PIN 1 and 0.33 and 0.61, respectively, for PIN 2. A more detailed description of the PIN FFQ has been published elsewhere (125) .

Glycemic index values were applied to the FFQ data by the Department of Nutrition's Clinical Research Unit Epidemiology Core using published values (95). Approximately 25% of the questions on the FFQ contained a single food that had a direct match to published values. For cases of mixed foods, one glycemic index value was derived in those situations through calculations that were proportional to the number of foods embedded in each question. From this, the average glycemic index (the average of the glycemic indexes for all foods and beverages) and glycemic load (summing the products of the glycemic index and the carbohydrate content of the foods contributing to it) were calculated for each subject.

Physical activity data were captured using a 1 week recall questionnaire specifically designed for PIN 3, which was administered by telephone between 17 and 22 weeks' gestation. This instrument assessed the frequency, duration and intensity of a variety of reported physical activities over the last 7 days at either a moderate or vigorous intensity level. Domains incorporated the following settings and/ or roles: at work, for recreation, for transportation, during care giving and as a part of indoor and outdoor household tasks.

A 1 hour 50 gram glucose challenge test was performed as an initial screening for gestational diabetes (GDM) during the second or third trimester. The values for maternal

plasma or serum post-load glucose concentration were abstracted from the medical chart and if necessary, converted to mg/dL. Glucose was also analyzed using a categorical cutoff of >140 mg/dL, which is predictive of impaired glucose tolerance (152).

Delivery logs at the study hospital were examined daily to determine delivery information including birth weight in grams. Fetal growth was further classified using percentile of infant birth weight standardized for gestational length. This calculation utilizes published values on birth-weight-for-gestational-age patterns by race, sex, and parity in the United States population (153). Large-for-gestational-age (LGA) was defined by an infant birth weight for gestation above the 90th percentile of the standard. A small-for-gestational-age (SGA) fetus was defined by birth weight for gestation below the 10th percentile of the same standard.

### ***Statistical Analyses***

Energy adjustment was performed on values of glycemic index and glycemic load by using the nutrient residual method of Willett et al. (37). To enhance the interpretation, the predicted glycemic index and glycemic load value at the mean total energy intake was added as a constant to the nutrient residual. Both glycemic index and glycemic load were categorized into quartiles for all analyses. A univariate analysis was conducted to compare values of maternal characteristics across quartiles of glycemic index. For continuous covariates, linear test for trend was conducted using least-squares regression. Trend for categorical variables was tested using a Mantel-Haenzel chi-square test. A multivariable linear regression model was developed for infant birth weight. Gestational age, race, and parity were included as default independent variables. Next, all maternal

characteristics except for dietary variables were considered for inclusion. The model was fit using a backward regression procedure, first including all potential predictor variables in the model and then with the variables removed one at a time, until the likelihood ratio test statistic exceeded an alpha cutoff of 0.10. After determination of a preliminary final model for infant birth weight, glycemic index and glycemic load were included separately along with total energy intake. Interactions between all independent variables were also considered with a particular focus on pregravid BMI and maternal glucose. As part of a sensitivity analysis on the model of infant birth weight, we excluded subjects with implausibly low and high energy intakes based on the 2002 DRI equations for estimated energy requirement (EER), which are sex and age-specific and are based on age, weight and height; and also include energy costs during pregnancy. To identify physiologically implausible self-reported energy intakes, 95% confidence limits of agreement were calculated for the ratio of reported energy intake to EER using the Goldberg method described by Black & Cole (42) and further adapted by Huang et al.(80). Another sensitivity analysis included the calibration of FFQ energy intake using a method proposed by Prentice et al. (30, 142) (Appendix B), which modifies the classic measurement error model by incorporating subject characteristics such as BMI, a robust predictor of measurement error in energy intake in our data. Values for both glycemic index and glycemic load were then energy adjusted based on calibrated energy intake. Threshold for statistical significance was a p-value less than 0.05. All analyses were performed using SAS software (version 9.1.3; SAS Institute Inc, Cary, NC).

## Results

The PIN3 cohort was comprised of primarily white women (74.5%) and the majority of participants had at least some college level education (82.0%). The average maternal age was  $29.3 \pm 5.5$  years. Most of the women were married (78.8%) and more than half were nulliparous (51.4%). In addition, 33.2% of women were overweight (BMI >26.0 to 29.0) and 21.9% were obese (BMI >29.0) prior to pregnancy.

Several univariate trends in dietary glycemic index by maternal characteristics were observed (Table 1). Women with diets higher in glycemic index tended to be younger, African American, less educated, unmarried, overweight prior to pregnancy, smokers during pregnancy, less physically active during pregnancy, and with higher frequency of a previous low birth weight (LBW) pregnancy. Mean gestational weight gain and adequacy of gestational weight gain did not differ across levels of maternal glycemic index.

Fiber and certain energy adjusted nutrient intakes also varied across quartiles of glycemic index (Table 2). For macronutrients, carbohydrate and protein intake decreased ( $p < 0.01$  for both carbohydrate and protein), whereas fat intake increased ( $p < 0.01$ ) with increasing quartiles of glycemic index. Calcium, Vitamin C, and folate decreased ( $p < 0.01$  for each nutrient) across glycemic index of maternal diet. There was no significant trend in energy intake by level of glycemic index ( $p = 0.63$ ).

Table 3 shows results from a univariate analysis for glycemic index and glycemic load by endpoints for post-load glucose and fetal growth. Mean post-load glucose intake and the proportion of subjects with elevated post-load glucose did not vary by glycemic index, but significant trends were observed for glycemic load. Comparing the lowest to highest quartile of glycemic load, mean glucose was 108.4 mg/dL versus 104.5 mg/dL and the

prevalence of elevated glucose was 13.2% compared to 8.1%. However, this association with glycemic load and post-load glucose was not statistically significant after adjusting for other confounders in our data, including pregravid BMI, maternal age, smoking during pregnancy, parity, race and physical activity during pregnancy. The odds of an elevated random glucose screen ( $>140$  mg/dL) for the lowest GL quartile were 1.71 (95% CI = 0.98, 2.96) compared to the highest quartile. We found no trends in the frequency of SGA or LGA across levels of glycemic index or glycemic load. Not surprisingly, these null associations remained after adjustment for potential confounders (results not shown).

In a multivariable analysis, several maternal characteristics were predictors of infant birth weight (Table 4). After adjusting for a gestational age and all other covariates, we observed a higher mean birth weight for subjects with higher pregravid BMI, higher gestational weight gain, maternal age and maternal height. Infant birth weight was lower among women who were nulliparous, had a previous LBW pregnancy, smokers during pregnancy, and African American (compared to Caucasian mothers). Factors for glycemic index and glycemic load as quartiles were added separately to this full model for infant birth weight; and neither of these classifications for maternal carbohydrate quality were statistically significant. Several maternal characteristics were examined as possible effect modifiers such as pregravid weight status, race, elevated post-load glucose, protein intake; however there was no strong evidence of effect modification by any of these factors.

We also conducted various sensitivity analyses for the primary model of infant birth weight, as well as SGA, LGA and maternal glucose. These included modeling both glycemic index and glycemic load with and without kilocalories, after exclusion of prior

LBW, and after exclusion of subjects with GDM. Additionally, we used two methods to account for systematic measurement error in energy intake, which were: the exclusion of energy underreporters and overreporters; and the calibration of energy intake and glycemic load. However, none of the above approaches altered the results for carbohydrate quality and infant birth weight (results not shown).

## **Discussion**

It is conceivable that birth weight may be related to differences in the type of maternal dietary carbohydrate via circulating glucose levels, even among generally healthy pregnancies. However, we found no evidence that glycemic index or glycemic load of maternal diet during the second trimester was associated with post-load glucose or fetal growth parameters in a large cohort of pregnant women living in central North Carolina. These null findings are in contrast to the few published studies that have addressed this research question.

Clapp et al. conducted a dietary and exercise intervention study in 20 healthy women recruited prior to pregnancy. All women agreed to follow a diet of low glycemic index foods and at 8 weeks gestation were randomly assigned to either continue with the low glycemic index diet or to follow a high glycemic index diet for the duration of pregnancy. Women randomized to the high glycemic index diet compared to the low glycemic index diet had significantly higher levels of post-prandial glucose and insulin levels during mid to late pregnancy; and delivered symmetrically larger infants (approximately 840 grams) all of which were considered LGA. However, maternal weight gain was also remarkably greater in the high glycemic index group compared to the low glycemic index group (18.6

kg vs. 10.4 kg,  $p<0.01$ ), which confounds the inference that glycemic index per se was responsible for the observed differences in carbohydrate metabolism and infant birth weights between the two groups.

Moses et al. conducted a similar experiment on a larger sample of 62 healthy women enrolled between 12-16 weeks gestation (107). The subjects were alternately assigned to receive dietary counseling that encouraged a low-GI (LGI) carbohydrate foods or a high-fiber, moderate-to-high GI (HGI) foods; both groups were matched for initial macronutrient intake. Compared with the LGI group, women in the HGI group gave birth to infants who were heavier (3408 vs. 3644 grams;  $P=0.05$ ), a higher ponderal index (2.62 vs 2.74;  $P=0.03$ ), and a higher prevalence of LGA (3.1% vs. 33.3%;  $P=0.01$ ). However, we noticed that BMI at baseline was significantly higher in the HGI group (26.6 vs 24.4  $\text{kg/m}^2$ ,  $P=0.04$ ), which may have explained part or all of the observed difference in infant birth size and LGA.

Scholl et al.(108) analyzed data from 1,082 non-diabetic gravidas who enrolled at prenatal clinics in Camden, NJ. Dietary data were averaged from three, nonconsecutive 24-hour recalls obtained at entry to prenatal care and weeks 20 and 28 of gestation. No significant difference in infant birth weight or LGA incidence was observed for women in the highest GI quintile; and glycemic load was unrelated to maternal post-load glucose or infant birth weight. However, women in the lowest GI quintile, compared to all other subjects, had lower infant birth weights after adjustment for confounders (mean, -116.2; 95%CI, -50.0, -182.5). Further, the risk of SGA was greater for women in the lowest GI quintile compared to the middle quintile with an adjusted odds ratio of 1.75 (95% CI, 1.10, 2.77). Of note, this study population was ethnically diverse with a large proportion of

African-American women, who have demonstrated higher insulin levels and lower glucose concentrations compared to Caucasian women. Therefore, the suggested influence of a lower glycemic index diet and reduced fetal growth in this study may be due to ethnic differences in carbohydrate metabolism.

The lack of finding for higher glycemic index diets and excessive birth weight in our study and the Camden Study disagree with results from the two dietary intervention trials. Of course there is a tradeoff between dietary intervention and epidemiologic study designs regarding factors such as selection bias, confounding bias, statistical power and dietary measurement error. Of note, however, neither epidemiologic study monitored dietary intake throughout the third trimester, which may be the most important critical window of exposure. Even among healthy subjects, maternal glucose tolerance decreases and insulin resistance increases throughout pregnancy, which is seen as a normal physiological adaptation that restricts maternal glucose uptake and guarantees sufficient glucose availability for the growing fetus (154). This deterioration in maternal glucose tolerance typically begins during the second trimester, but worsens progressively until delivery. In fact, results from Clapp et. al. suggest that a high glycemic index diet may be most influential on maternal glucose and insulin during 32-36 weeks gestation. Pregnancy is characterized by complex physiological and behavioral changes that affect maternal nutrient absorption and metabolism, energy and nutrient needs, appetite, and meal patterns (2, 3). Thus, it is conceivable that intakes of glycemic index and glycemic load may vary significantly from the second to third trimester of pregnancy.

One particular event that may induce changes in the type of carbohydrate consumption during pregnancy is the diagnosis of gestational diabetes mellitus. For example, a low GI



diet is commonly advised as treatment for women with GDM; and has been shown to reduce obstetric and fetal complications, such as macrosomia (105). In our cohort, dietary intake was assessed prior to screening for GDM; therefore women who were subsequently diagnosed with GDM may have altered the amount and type of carbohydrate intake during the third trimester in response to clinical recommendations. However, we observed a low incidence of GDM in our cohort (3.5%) and there was still no association between either glycemic index or glycemic load and infant birth weight even after excluding these subjects.

In pregnancies complicated by diabetes, higher circulating concentrations of maternal glucose can lead to increased transport of glucose and other nutrients to the fetus. In response, fetal insulin secretion is stimulated which acts as a growth factor and increases the storage of glucose, amino acids and other nutrients, thereby increasing the intrauterine growth rate and resulting in higher infant birth weights. However, despite the contention from some authors that maternal glucose in non-diabetic pregnancies is positively associated with higher infant birth weight and excessive fetal growth (88, 106, 150), other studies including ours have not observed such a connection (107, 155). It is plausible that pregnancies with normal glucose concentrations result in little or no extra maternal glucose for excessive fetal growth (108). Or, perhaps other markers of maternal glucose homeostasis are needed to elucidate this relationship. Interestingly, Moses et al. found significantly higher LGA infants among HGI compared to LGI, but no differences in maternal postprandial glucose, insulin resistance, beta cell function, or insulin sensitivity between the two groups. These results indicate that excessive fetal growth can occur among healthy women independent of changes in maternal carbohydrate metabolism. On

the other hand, this study also suggests that carbohydrate quality may affect fetal growth regardless of any change in maternal carbohydrate metabolism. Therefore, additional work is needed to determine the influence of dietary glycemic index on both glucose homeostasis and fetal growth in healthy pregnant women.

The primary limitation of our study was that measurement of glycemic index and glycemic load were ascertained using an FFQ, which cannot accurately assess combinations and portions of foods, both in recipes and during meals, and thereby introduces error in the overall glycemic index and quantity of carbohydrate intake. Measurement of glycemic load via FFQs has been validated in previous studies, which have demonstrated reasonable correlations with more detailed dietary assessment methods and suggest that FFQs provide a valid representation of usual intake for ranking subjects. Studies of glycemic index and glycemic load on other outcomes such as diabetes have found positive associations using a variety of dietary methods, including FFQs. Furthermore, the PIN FFQ was validated in previous PIN cohorts against 24 hour dietary recall and performed reasonably well for most nutrients including carbohydrate intake. Also, in our data we observed a significant inverse relationship between glycemic index and fiber intake, which is the hallmark characteristic of dietary glycemia.

To date, there is no compelling evidence that carbohydrate quality of maternal diet is associated with fetal growth among generally healthy pregnant women. In a large cohort of non-diabetic gravidas, we found no relationship between glycemic index or glycemic load of maternal diet and infant birth weight. Our results partially conflict with another cohort study, which found that women with diets lower in glycemic index were associated with a decrease in birth weight and an increase in SGA. Conversely, two dietary

intervention studies suggest that a high GI diet during pregnancy may significantly increase the risk of LGA compared to a low GI diet. However, these trials were limited by small sample size and a lack of adjustment for important confounders such as pregravid BMI and gestational weight gain. Nevertheless, there is accumulating evidence that maternal glucose levels within normal limits are adversely related to fetal growth (106), as well as other obstetric outcomes (156, 157, 158). Further, the glycemic index of foods has also been shown to alter postprandial glucose and insulin concentrations among healthy pregnant women. Therefore, additional study of the carbohydrate quality in maternal diet remains important. Future research should focus on larger scale intervention trials and epidemiologic studies that adequately account for measurement error in dietary assessment and capture food intake throughout the third trimester.

**Table 5. 1. Maternal characteristics by quartile of dietary glycemic index**

	Glycemic Index				
Characteristic	Quartile 1 (43 to <50)	Quartile 2 (50 to <53)	Quartile 3 (53 to <56)	Quartile 4 (56 to 68)	p-value
<b>Age (%)</b>					
<25 years	15.9	19.9	17.9	23.9	0.0092
25-<30 years	31.1	25.3	29.7	31.0	
30-<35 years	35.5	34.3	39.5	31.0	
35+ years	17.6	20.5	12.8	14.1	
<b>Race (%)</b>					
White	77.0	78.5	76.4	66.3	0.0109
Black	15.2	15.5	15.5	20.5	
Other	7.8	6.1	8.1	13.1	
<b>Education (%)</b>					
<=High School	17.6	16.2	14.9	23.6	0.0019
>High School to Undergraduate	40.9	47.5	51.4	47.5	
Graduate School	41.6	36.4	33.8	29.0	
<b>Married (%)</b>	81.4	79.8	79.7	74.1	0.0374
<b>Nulliparous (%)</b>	63.2	53.5	50.0	39.1	<0.0001
<b>Prior LBW (%)</b>	7.4	5.1	9.5	11.4	0.0219
<b>BMI (%)</b>					
<19.8 kg/m <sup>2</sup>	12.2	16.5	13.2	13.8	0.0560
19.8-26 kg/m <sup>2</sup>	56.8	53.9	55.4	45.5	
26-29 kg/m <sup>2</sup>	11.8	9.4	7.8	16.2	
>29 kg/m <sup>2</sup>	19.3	20.2	23.6	24.6	
<b>Smoked Cigarettes During Pregnancy (%)</b>	6.1	5.4	10.8	14.5	<0.0001
<b>Met Recommendations for Physical Activity During Pregnancy (%)</b>	20.9	19.9	15.5	14.8	0.0222
<b>Gestational Weight Gain in kg/week (mean, SD)</b>	1.03 (0.39)	1.06 (0.39)	1.05 (0.44)	1.00 (0.45)	0.3921
<b>Adequacy of GWG (%)</b>					
Inadequate	18.9	17.5	19.6	23.6	0.2550
Adequate	20.3	19.9	18.6	17.5	
Excessive	60.8	62.6	61.8	58.9	

**Table 5. 2. Median intake of energy, energy-adjusted macronutrients, selected micronutrients and fiber by quartile of dietary glycemic index**

	<b>Glycemic Index</b>				
	<b>Quartile 1 (43 to &lt;50)</b>	<b>Quartile 2 (50 to &lt;53)</b>	<b>Quartile 3 (53 to &lt;56)</b>	<b>Quartile 4 (56 to 68)</b>	<b>p-value</b>
Kilocalories	2046 (849.1)	1989 (885.4)	2010 (867.7)	2048 (926.7)	0.8592
Protein (g)	81.6 (19.15)	77.0 (15.58)	75.9 (13.58)	73.5 (16.49)	<0.0001
Carbohydrate (g)	305.8 (47.42)	309.5 (47.10)	298.6 (39.06)	297.0 (49.16)	<0.0001
Fat (g)	77.2 (16.34)	78.7 (16.39)	81.6 (13.73)	82.8 (16.62)	<0.0001
Vitamin C (mg)	232.5 (119.5)	229.4 (106.0)	198.8 (101.1)	165.0 (98.20)	<0.0001
Folate (ug)	451.5 (128.1)	422.5 (119.1)	414.8 (98.64)	391.5 (106.2)	<0.0001
Calcium (mg)	1250 (472.2)	1043 (428.8)	990.0 (343.8)	816.8 (304.2)	<0.0001
Iron (mg)	15.9 ( 4.78)	15.4 ( 4.18)	15.5 ( 4.44)	15.1 ( 5.34)	0.6310
Fiber (g)	21.1 ( 9.02)	19.5 ( 7.11)	17.9 ( 6.87)	15.8 ( 5.34)	<0.0001

**Table 5. 3. Fetal growth and glucose parameters by quartiles of glycemic index and glycemic load.**

	<b>Glycemic Index</b>				
	<b>Quartile 1 (43 to &lt;50)</b>	<b>Quartile 2 (50 to &lt;53)</b>	<b>Quartile 3 (53 to &lt;56)</b>	<b>Quartile 4 (56 to 68)</b>	<b>p-value</b>
<b>SGA (%)</b>	8.1	7.4	6.1	7.4	0.6116
<b>LGA (%)</b>	6.8	13.1	7.8	9.8	0.6299
<b>Post-load Glucose in mg/dL (mean, SD)</b>	106.8 (26.87)	106.0 (27.00)	108.2 (31.25)	106.2 (25.12)	0.9601
<b>Elevated Post-load Glucose (%)</b>	11.5	10.8	10.1	9.8	0.4669
	<b>Glycemic Load</b>				
	<b>Quartile 1 (58 to &lt;139)</b>	<b>Quartile 2 (50 to &lt;152)</b>	<b>Quartile 3 (53 to &lt;164)</b>	<b>Quartile 4 (164 to 276)</b>	<b>p-value</b>
<b>SGA (%)</b>	7.1	9.4	6.1	6.4	0.4190
<b>LGA (%)</b>	7.8	10.4	11.1	8.1	0.8302
<b>Post-load Glucose in mg/dL (mean, SD)</b>	108.4 (31.14)	108.5 (29.38)	105.8 (25.36)	104.5 (23.93)	0.0457
<b>Elevated Post-load Glucose (%)</b>	13.2	12.8	8.1	8.1	0.0123

**Table 5. 4. Least squares regression model of infant birth weight on glycemic index and glycemic load of maternal diet**

	Glycemic Index			Glycemic Load		
	Beta	SE	P-value	Beta	SE	P-value
<b>Quartile 1 vs. 4</b>	1.388092	41.9090690	0.9736	3.189178	41.5620638	0.9388
<b>Quartile 2 vs. 4</b>	50.555746	41.5487248	0.2239	54.011534	41.4832380	0.1932
<b>Quartile 3 vs. 4</b>	-6.038944	41.2201411	0.8835	68.041571	41.1951398	0.0989
<b>Kilocalories (per 100)</b>	-2.180351	1.6238457	0.1796	-1.562058	1.6546963	0.3454
<b>Prior LBW</b>	-236.632568	56.2921062	<.0001	-243.941969	56.2012273	<.0001
<b>Gestational Age (weeks)</b>	193.174012	8.0039414	<.0001	192.270240	7.9962281	<.0001
<b>BMI (kg/m<sup>2</sup>)</b>	21.110396	2.4837569	<.0001	21.077698	2.4846101	<.0001
<b>GWG (kg/week)</b>	266.040114	37.0431579	<.0001	263.110877	37.0597498	<.0001
<b>Maternal Age</b>	6.095776	2.9215143	0.0371	6.179476	2.9399740	0.0358
<b>Nulliparous</b>	-221.241200	31.7633497	<.0001	-220.861079	31.3245466	<.0001
<b>Smoked During Pregnancy</b>	-172.471905	52.0303471	0.0009	-174.936846	51.7281635	0.0007
<b>Maternal Height (inches)</b>	25.025754	5.4712238	<.0001	25.155210	5.4543646	<.0001
<b>Black vs. White</b>	-167.299359	43.8773634	0.0001	-168.606301	44.0125216	0.0001
<b>Other vs White</b>	-63.079589	52.1607308	0.2268	-67.031515	51.9727266	0.1974

## **Chapter Six**

### **Conclusions**

The findings from this research support many of the initial hypotheses from the specific aims. These results highlight potential issues regarding nutritional assessment during pregnancy and provide additional evidence whether the modification of the carbohydrate quality in maternal diet can affect fetal growth among generally health pregnancies.

### **Specific Aim 1**

The first aim of this dissertation was to identify pregnant women who reported energy intakes that were physiologically implausible. Statistical methodology to determine LER and HER had been previously established, however, its application for dietary assessment during pregnancy required some important modifications. The 1 to 1 ratio of EI:EER is based on the assumption of energy balance, which may be violated in the case of pregnancy where additional caloric needs are required to support adequate gestational weight gain and increases in BMR. To account for this, the 2002 DRI equations for EER in pregnant women provide an overall estimate of additional kilocalories per day to account for energy deposition during the second and third trimesters. However, this ignores the recent finding that additional energy requirements during pregnancy are also a function of pregravid BMI. Therefore, we applied three separate values for daily change in TEE based on underweight, normal weight, or overweight prior to pregnancy. In addition, because of variability in TEE



estimation by weight status, we calculated a separate within subject CV for the EER prediction equation based on the same categories of pregravid weight status. These updates to the EI:EER cutpoint methodology may prove useful for future studies of measurement error in energy intake during pregnancy.

Results from Aim 1 indicate that measurement error of maternal energy intake should be considered in studies of maternal diet. Nearly half of the women reported implausible intakes with LER and HER being 32.8% and 12.9%, respectively. This overall LER prevalence is similar to what has been found in non-pregnant women; whereas HER for this study was somewhat higher, which may be unique to pregnancy, a time period characterized by increased energy intake. However, comparing the frequency of measurement error across studies is complicated due to variations in the assessment of diet and physical activity, as well as subject characteristics. Therefore, additional studies on pregnant women would be needed to determine whether the overall prevalence of measurement error in reported energy intake is grossly different between pregnant and non-pregnant populations. Nevertheless, estimates of LER and HER from Aim1 are the first published values from a large cohort of pregnant women in a developed country.

## **Specific Aim 2**

Aim 2 was an extension of Aim 1 to determine if the prevalence of LER and HER varied by maternal characteristics. LER was most common in pregnant women who were classified as obese prior to pregnancy (49.8%). Measures of body size and adiposity are likely surrogates for psychosocial characteristics that result in misreport energy (food) intake. Previous studies have suggested that restrained eating behaviors may explain much of the

variation in LER, although we found no independent association between dietary restraint score and underreporting in our cohort. However, we did find women with higher depressive symptoms were more likely to overreport energy intake, a finding that has not been previously noted in the literature. Gestational weight gain was not related to LER or HER after adjustment for pregravid weight status, which, as was hypothesized, a robust predictor of measurement error.

We did not observe that reporting bias in energy intake was associated with variable bias for most nutrient intakes, as well as glycemic index and glycemic load. This suggests that food intake was misreported on the whole diet level, which is an important assumption when relying on energy adjusted nutrient intakes to represent diet composition. However, many researchers agree that energy adjustment alone cannot eliminate the effects of differential reporting bias. Pregravid BMI is an important predictor of many reproductive outcomes, and obesity specific bias in energy intake during pregnancy may distort nutrient risk estimates between diet and reproductive outcomes, particularly if total energy intake is also related to the outcome.

### **Specific Aim 3**

The goal of Aim 3 was to determine if the carbohydrate quality of maternal diet was associated with fetal growth within a generally healthy pregnant population. However, we found no evidence that either glycemic index or glycemic load during the second trimester was related to either post-load glucose or fetal growth parameters. These null findings are in contrast to the few published studies in this research area; one suggested that a low glycemic diet increases the risk of SGA and two concluded that a high glycemic diet may increase the

risk of LGA. However, each of these studies including ours had differences with respect to study population and study design, which could explain the inconsistency in results.

It is conceivable that birth weight may be related to differences in the type of dietary carbohydrate via circulating maternal glucose levels, even among generally healthy pregnancies. However, not all studies including ours have found a positive association between maternal glucose and fetal growth. Perhaps, pregnancies with normal glucose concentrations result in little or no extra maternal glucose for excessive fetal growth. Or, perhaps other markers of maternal glucose homeostasis are needed to elucidate this relationship. Regardless, additional work is needed to determine the influence of maternal carbohydrate metabolism and fetal growth among healthy pregnant women. Moreover, the validity of the GI concept during pregnancy has been assessed for only a small number of foods in limited subjects. Certain physiological changes during pregnancy, such as decreased gastric emptying, may reduce the impact of dietary glycemic index and glycemic load on postprandial glucose. Thus, although biological plausibility exists, more research is needed to determine the capacity for carbohydrate quality to influence maternal glucose substrates in pregnant women without diabetes.

It is also possible that there is no true association between glycemic index and fetal growth among non-diabetic pregnancies, as the current analysis on the PIN3 data would suggest. However, this study is not without limitation. The main concern with the PIN3 data is that measurement of glycemic index and glycemic load were ascertained using an FFQ, which cannot accurately assess combinations and portions of foods, and consequently less valid than other diet assessment tools. Moreover, there were no validation data to compare GI and GL values from the PIN3 FFQ with those from a more detailed assessment method,

although a previous validation study suggested moderate agreement between total carbohydrate intake from the PIN FFQ and multiple 24 hour dietary recalls. Nevertheless, the PIN3 FFQ was not specifically designed to assess habitual intake of foods with respect to glycemic index. Therefore, while the PIN3 design has several strengths, it is not an entirely optimal data source to address the specific research hypotheses of Aim 3.

#### **Specific Aim 4**

The purpose of Aim 4 was to conduct a sensitivity analysis on the results from Aim 3 to explore the potential influence of misreporting energy intake. Results from Aim 4 suggest that misreporting energy intake per se did not affect the observed null association between glycemic index or glycemic load and infant birth weight. Perhaps no true relationship exists; however, the method of excluding implausible energy intakes has some caveats with regard to removing measurement error from diet disease estimates. Mainly, LER and HER subjects comprise a large proportion of the study population and their removal may exclude important subjects particularly with respect to pregravid BMI. Thus, exclusion of physiologically implausible energy intakes cannot correct estimates of nutrient intake according to systematic error, such as obesity specific bias. One such method to calibrate systematic bias has been proposed in the literature, however, its application to studies where BMI is both a predictor of measurement error and the disease outcome remains questionable.

#### **Overall Conclusions**

This work suggests that measurement error in energy intake is common during pregnancy and that obesity-specific bias exists. Person-specific bias has been shown to distort nutrient risk estimates in studies of diet and disease and its influence may be underemphasized in

nutrition epidemiology. Identifying predictors of systematic underreporting is an important step in reducing the impact of measurement error on the results. However, additional research is needed to generate methods of improving the data of susceptible subgroups during the dietary assessment and analytic phase of nutritional studies.

As a whole, this dissertation indicates that carbohydrate quality of maternal diet is not related to fetal growth among generally healthy pregnant women and that measurement error in energy intake does not account for this null finding. The primary limitation of this work was the use of FFQ to ascertain energy intake as well as glycemic index and glycemic load. Yet, the FFQ remains an important and commonly used tool in nutrition research, including pregnancy cohorts.

Maternal diet is a critical component for reproductive outcomes and modifying the quality of carbohydrate eaten during pregnancy may provide an opportunity to reduce the risk of inadequate or excessive fetal growth. Prior research in this area has some considerable limitations; however, the findings are intriguing and additional study of the carbohydrate quality in maternal diet remains important. Results from this work including the insights on the current literature will add to the etiological evidence and may improve future studies of maternal diet and fetal growth.

### **Public Health Significance**

Diet has enormous exposure potential in the prevention and treatment of disease. Yet, the importance of nutrition in public health is somewhat undermined by measurement error in self-reported dietary data. In some cases, nutritional biomarkers can provide an objective measure that is independent of memory, capacity to estimate average intake over a period of time, and social desirability bias. Errors associated with biologic variables are also

independent of those associated with self-report data, which are important for statistical analyses involving measurement-error correction (159). However, there are also several limitations with their use including biological variability, cost, subject burden, and temporal relationship with dietary intake. Thus, while incorporating biomarkers can enhance the study design, biomarkers are complementary to, rather than a replacement for, self-report tools, particularly in large epidemiologic studies (12). Accordingly, it is critical to improve existing self-report instruments and develop new methods of querying subjects on nutritional intake in order to establish valid relationships between diet and disease.

Measurement error of diet during pregnancy has some additional considerations; however, research in this population remains limited. This work provides some new insights on implausible dietary intakes and the sources of systematic bias in maternal diet. Additional work is needed to implement similar methodology in other pregnancy cohorts and to improve validity in the diet assessment of vulnerable subgroups. Further, adjusting for implausible energy intakes in analysis may help discern the importance of nutrition during pregnancy and should be considered future studies of diet and reproductive outcomes.

Modification of the quality and quantity of carbohydrate in woman with diabetes during pregnancy can have important benefits with respect to fetal growth. If this association also existed in the general population of pregnant women, it could have a considerable public health impact. However, results from the PIN3 data and a critique of the literature suggest there is no overwhelming evidence of a relationship between either glycemic index or glycemic load of maternal diet on fetal growth in generally healthy pregnancies. It is possible that less detailed assessment methods used in epidemiologic studies cannot adequately quantify the habitual intake of glycemic index foods. In which case, intervention

studies comparing the effects of a high and low glycemic index diet on both glucose and fetal growth parameters may help address this issue. However, the tradeoff with intervention studies is typically a more selective study population, which may not be representative with respect to dietary intake and other factors related to fetal growth among the general population. Therefore, both large cohort studies and diet intervention studies of pregnant women may be needed to determine if glycemic index and glycemic load can prevent anomalous fetal growth.

## Appendix A

### Daily Reference Intakes (DRI) Equations for Estimated Energy Requirement (EER), Institute of Medicine, 2002.

Girls 9-18 years	$EER = 135.3 - (30.8 \times \text{age [y]}) + PA \times \{ (10.0 \times \text{weight [kg]}) + (934 \times \text{height [m]}) \} + 25$
Women 19 years and older	$354 - (6.91 \times \text{age [y]}) + PA \times \{ (9.36 \times \text{weight [kg]}) + (726 \times \text{height [m]}) \}$
Pregnancy in 2 <sup>nd</sup> trimester	Non-pregnant EER + 340
PA=Physical Activity Coefficient	

### Physical Activity Coefficients (PA) Values for DRI ERR Equations, Institute of Medicine, 2002.

	<b>Sedentary</b>	<b>Low Active</b>	<b>Active</b>	<b>Very Active</b>
	Typical daily living activities (e.g., household tasks, walking to the bus)	Typical daily living activities PLUS 30 - 60 minutes of daily moderate activity (ex. walking at 5-7 km/h)	Typical daily living activities PLUS At least 60 minutes of daily moderate activity	Typical daily living activities PLUS At least 60 minutes of daily moderate activity PLUS An additional 60 minutes of vigorous activity or 120 minutes of moderate activity
Girls 3-18 years	1.00	1.16	1.31	1.56
Women 19 years and older	1.00	1.12	1.27	1.45



## Appendix B

### Regression Calibration Estimator

A classic measurement error model would be

$$W = Z + \mu,$$

where  $Z$  represents typical daily average energy consumption,  $W$  represents an objective measure of energy intake, and  $\mu$  is a mean zero error variable that is independent of  $Z$  and independent of other study subject characteristics. However, because the measurement error associated with FFQ intake depends on subject characteristics, this calibration model was modified to incorporate key predictors of systematic reporting bias in dietary intake (30, 142). This approach is a relaxed dietary measurement error model that allows all measurement error parameters to depend on a vector of subject characteristics (i.e. BMI, age, social desirability bias). The resulting model is

$$W = Z^* + \varepsilon,$$

Where  $\varepsilon$  is a random error term independent of  $Z^*$  and certain subject characteristics and  $Z^*$  is the actual ‘target’ of the FFQ assessment that could plausibly be expressed as

$$Z^* = \gamma_0 + \gamma_1 Z + \gamma_2^T V + \gamma_3^T VZ + \eta,$$

Where  $\eta$  is a person-specific random effect and ‘ $T$ ’ denotes vector transpose. Note that the term  $\gamma_3^T VZ$  makes a provision for systematic bias in that, if a component of  $\gamma_3$  is non-zero, then there is systematic bias in the self-report assessment of  $Z$  that is associated with the corresponding element of  $V$ . Also, the mean zero random effect,  $\eta$ , accommodates a further person-specific bias. Its variance is allowed to depend on  $V$ , but when rescaled to have unit variance the random effect is assumed to be independent of  $(V, Z)$ . The random effect allows the measurement errors in repeat self-report assessments of  $Z$  to be correlated.

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