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The Influence Of Prenatal And Early Life Factors On BMI Z Scores And The Risk Of Being Obese In Early Childhood

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THE INFLUENCE OF PRENATAL AND EARLY LIFE FACTORS ON BMI Z SCORES AND THE RISK OF BEING OBESE IN EARLY CHILDHOOD

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DEDICATION

This dissertation is dedicated to the **love** of my family and friends.

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ABSTRACT

Childhood obesity is a serious public health challenge. The underlying causes behind the rising levels of childhood obesity might be driven by prenatal and early life factors. Recently, several studies have examined the association between gestational weight gain (GWG) and the risk of obesity in the pediatric population. Findings on the association of both inadequate and excessive GWG with offspring obesity are inconsistent and vary by maternal prepregnancy body mass index (BMI) status. Inconsistent findings also exist for the association of GWG and BMIZ as a continuous outcome. Nevertheless, existing studies mainly focus on the BMIZ upper centiles using logistic regression or the mean using linear regression, which do not capture associations across the entire distribution of BMIZ. Second, child growth in early life as a critical period contributing to lifetime health has been recognized in various populations. It has long been established that the increased growth following intrauterine growth retardation, known as catch-up growth, is associated with increased risks for obesity and insulin resistance. However, catch-up growth only affects a small fraction of all births and it does not accurately summarize the variations in the rates of infant growth in the population. Furthermore, some infants might experience different growth patterns which also predispose them to long-term health risks. In recent years, latent growth modelling approaches have received more attention due to advances in statistical software and analytical packages. This method is particularly useful to identify homogeneous

subpopulations with similar growth patterns. Although BMI Z score is optimal for assessing a child's static weight status in a single occasion, the best scales for measuring weight changes are raw BMI or BMI percentage. To our knowledge, so far few studies have used raw BMI or BMI percentage. Furthermore, infant growth could not happen in isolation and deviant BMI growth patterns during infancy might contribute to future risks of adverse health consequences, known as the hypothesis of the Developmental Originals of Health and Disease.

Therefore, we proposed three main aims in this dissertation and utilized data from a birth cohort of Infant Feeding Practices Survey study (2005-2007) and its Year Six Follow-Up Study to examine those aims. In Aim1, we examined the association between meeting the Institute of Medicine (IOM) GWG guidelines and offspring obesity at age six and the potential moderating role of maternal pre-pregnancy BMI status. We additionally examined association between GWG categories and offspring BMIZ across the deciles of BMIZ at age six and the potential moderating role of maternal pre-pregnancy BMI using quantile regression analysis which provided the estimates of interest beyond the mean. In Aim 2, we identified the underlying infant BMI trajectory using latent class growth analysis and examined its correlates including prenatal factors such as GWG, smoking during pregnancy and early life factors such as breastfeeding practices. Finally, in the third aim, we examined the association between the identified BMI trajectories during the first year of life and the risk of obesity at age six. Results from the first aim suggest that maternal pre-pregnancy BMI played an important moderating role on the association of meeting IOM GWG guidelines and obesity and BMIZ. Excessive GWG had an increased risk of childhood obesity at age six, and this positive association is more pronounced

among mothers who have normal weight before pregnancy. Furthermore, we found that heterogeneous associations exist between GWG and BMIZ indicating that covariates might impact the associations differently across the distribution of BMIZ. In the second aim, we identified three BMI trajectories during infancy labelled as "low-stable" (81.6%), "high-stable" (15.6%), and "rising" (2.8%). Our findings suggest that distinct BMI trajectories are evident among children during the first year of life. Infants born to overweight mothers, minority mothers, and those who smoked during pregnancy had high-stable or rising BMI trajectories in early life and those who were breastfed according to guidelines were protected from being in the rising trajectory. Finally, we found that infants in the high-stable trajectory had an increased risk of obesity at age six.

This finding suggests that a child's BMI trajectory during the first year of life provides additional information regarding his or her risk for obesity at school ages. Obesity prevention program should start as early as infancy and pay special attention to those children with sub-optimal growth trajectories in infancy. The findings from this dissertation suggest that both prenatal factors such as maternal weight before pregnancy and weight gain during pregnancy, and infant growth during their first year of life are critical factors to be considered for future obesity risk. Future studies are needed to warrant our findings and worth of exploring the underlying biological mechanisms.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

The epidemic of childhood obesity has been recognized as one of the most serious public health challenges of the 21st century. Excessive weight and obesity in the pediatric population is commonly assessed by using gender- and age-specific body mass index (BMI) z-scores (BMIZ) (or its equivalent BMI percentile) according to a standard reference.(Must and Anderson 2006) The World Health Organization (WHO) defines overweight and obesity for children aged 0-5 yearsWorld Health Organization. World Health Organization Child Growth Standards. 2006. Accessed Novmber 5, 2015. and 5-19 years separately using different BMIZ cut-off points.(de Onis et al. 2007) Two standard deviation (SD) and three SD cut-offs are utilized to define overweight and obesity for children aged 0-5 years, while one SD and two SD are used to define overweight or obesity for children 5-19 years of age, respectively. Globally, the number of overweight or obese children under age 5 increased from 32 million in 1990 to 42 million in 2013 and is projected to reach 70 million (~11%) by 2025. (World Health Organization,2015). In the United States (U.S.), almost 10% of infants and toddlers are obese,(de Onis et al. 2007, Ogden et al. 2014) and approximately one in every three (31.8%) children ages 2-19 (~12.5 million) are overweight or obese (Obstetricians and Gynecologists 2013, Ogden et al. 2014) Along with the effects on children's health, childhood obesity also imposes substantial economic costs. The direct cost for childhood

obesity alone in the U.S. is estimated to be around $14.1 billion annually.(Heslehurst et al. 2007)

Beyond childhood, obesity in the pediatric population tends to track into adulthood.(Whitaker et al. 1997, Singh et al. 2008) If left untreated, almost half of overweight children will remain overweight or obese as adults, and at risk of obesity-related adverse health outcomes.(World Health Organization, 2015, Rocchini 2011) However, evidence for effective treatment of obesity is lacking; therefore, seeking effective strategies for obesity prevention has been of great interest for researchers, public health practitioners, policy-makers, as well as the general public. Reversal of childhood obesity might minimize negative health consequences associated with adult obesity.(Goldschmidt et al. 2013, Glass and McAtee 2006) Furthermore, childhood is an important life stage to implement effective intervention programs in order to prevent obesity and related complications later in life. Thus, more research on pediatric obesity may shed light on solutions to adult obesity and obesity-related diseases.

The "fetal origin hypothesis" proposed by Dr. David Barker in the late 1980s linking coronary heart disease to low birth weight has stimulated a new perspective on obesity prevention in early life.(Barker 1995a, Oken and Gillman 2003) The underlying causes behind the rising levels of childhood obesity might be driven by prenatal and early life factors.(Tounian 2011, Buchan et al. 2005, Bammann et al. 2014, Dello Russo et al. 2013, Yu et al. 2013, Estevez-Gonzalez et al. 2015)

Prenatal factors

Maternal pre-pregnancy BMI and gestational weight gain (GWG) (i.e., the weight a women gains during pregnancy) are two promising modifiable prenatal determinants of

childhood obesity.(Li et al. 2007a, Mustillo et al. 2003, Ziyab et al. 2014, Carter et al. 2012, van Rossem et al. 2014, Lane, Bluestone, and Burke 2013, Li, Sloboda, and Vickers 2011, Vesco et al. 2009) Maternal obesity, in parallel with obesity in the general population, has increased dramatically in recent decades. In the U.S., about 1 in 5 women entering their pregnancies were obese in 2009.(Hilson, Rasmussen, and Kjolhede 2006) According to the 2011-2012 National Health and Nutritional Examination Survey (NHANES), approximately 30% of childbearing women aged 20-39 were obese.(Ogden et al. 2014) Given the increasing trend in the prevalence of maternal obesity, more studies have focused on the impact of pre-pregnancy BMI on pregnancy and neonatal outcomes and its subsequent disease risk in the offspring over the past decade. These studies found that maternal obesity increases the offspring's risk of being overweight or obese, and the magnitude of the association is heterogeneous across studies and depends on age studied between childhood and young adulthood.(Hinkle et al. 2012a, Hochner et al. 2012, Thompson 2013)

GWG is an intrauterine nutritional marker for pregnancy and has been identified as an important modifiable risk factor for various adverse health outcomes. Studies over the last 40 years have associated GWG with both maternal and offspring short- and long-term health consequences (Luke 1991, Yaktine and Rasmussen 2009) Both the 1990 and 2009 Institute of Medicine (IOM) GWG guidelines proposed GWG as a function of maternal pre-pregnancy BMI. This finding indicates the optimal amount of weight gain during pregnancy varies by pre-pregnancy BMI status.(Luke 1991, Yaktine and Rasmussen 2009) According to the 2009 IOM guidelines for GWG, approximately 43% of women during pregnancy gained excessive weight.(Yaktine and Rasmussen 2009)

Excessive weight gain during pregnancy has been suggested by previous studies as a risk factor for offspring obesity later in life.(2009, Viswanathan et al. 2008)

Moreover, maternal prepregnancy BMI is an established predictor of exceeding GWG recommendations, since overweight or obese women exceed recommendations more than normal weight women. Two out of every three overweight and obese women(Li et al. 2007a, Stotland et al. 2006, Ziyab et al. 2014, Pryor et al. 2011) gained excessive weight during pregnancy. Given the concurrent increasing trends in childhood obesity and maternal obesity before pregnancy, the relationship of pre-pregnancy BMI and GWG with pediatric obesity has become of particular interest.

Both maternal obesity before pregnancy and excessive GWG have been independently and jointly associated with an increased risk of adverse pregnancy outcomes and later health consequences.(Drake and Reynolds 2010, Reynolds, Allan, et al. 2013, Whitaker 2004, Li et al. 2005) Studies have found the relationship between GWG and childhood overweight or obesity was in various shapes: linear (Haga et al. 2012, Oken et al. 2007) and J or U shape. (Whitaker et al. 2004, Li et al. 2005, Reynolds et al. 2013, Winkvist et al. 2015, Schneider et al. 2009, Wilson et al. 1998) These various shapes indicated that the association of GWG with childhood overweight or obesity may vary by pre-pregnancy BMI status. Furthermore, it remains unclear whether the timing and pattern of GWG over the course of pregnancy differs in its relation to childhood obesity. Hence, our current understanding of the complexity of maternal weight prior to pregnancy and weight gain during pregnancy with childhood obesity is still unclear. (Lau et al. 2014) Similarly, the finding of the association of GWG with a continuous outcome of BMIZ is inconsistent. To my knowledge, almost all previous studies used mean linear

regression analysis to examine how the mean of BMIZ changed with GWG, and few studies used quantile regression analysis to investigate this association beyond the mean. Furthermore, the effect modification of this association by maternal pre-pregnancy BMI has not been reported consistently using mean regression analysis.

Early life factors

Infant growth during the first year of life is a critical period, which contributes to lifetime health. This finding is consistent across various populations.(Reynolds, Labad, et al. 2013, Hilson, Rasmussen, and Kjolhede 2006, Winkvist et al. 2015, Fein et al. 2014a, Organization 2015) Although the evidence is not conclusive,(Wrotniak et al. 2008) a number of studies(Schneider and Segre 2009, Wilson et al. 1998, Huh et al. 2011, Rooney, Mathiason, and Schauberger 2011, 2009, Viswanathan et al. 2008) suggest that rapid weight gain (weight-z score 0.67 standard deviation) between two specific time points during the first year of life might increase risk of obesity in childhood as well as young adulthood.(Haga et al. 2012, Lau et al. 2014) However, those prior studies assessed weight at only two points in time ignoring the dynamic patterns of weight over time. Ignoring these weight patterns over time might mislead etiologic research, especially when the growth patterns are non-linear.

However, the trajectory of BMI, a measure of weight adjusted for height, can capture the dynamic physiological process and body growth over time within an individual child. Currently, available information on BMI trajectories in the first year of life is lacking. Little is known about the relative contribution of prenatal and early life factors to the BMI trajectories during the first year of life. Even less is known about the

association between BMI trajectories during infancy and the risk of being overweight or obese in children.

Breastfeeding is considered as another important modifiable factor during children's early life that may alleviate the epidemic of childhood obesity. Breastfed children are at reduced risk of obesity across their life span. (Oken et al. 2007, Yang, Lambert, and Sang 2009) Some studies show that breastfeeding can reduce the risk of obesity by 22% to 24% across childhood and adolescence.(Lau et al. 2014) A meta-analysis reported that the risk of becoming overweight was reduced by 4% for every one month increase in breastfeeding.(Diesel et al. 2015) However, studies on the role of breastfeeding on infant BMI trajectories are unclear and more research is needed.

SCOPE

The scope of this dissertation encompasses data from three separate studies. The first study considers the effect of prenatal health of the mother via pre-pregnancy BMI and GWG on childhood obesity and BMIZ at 6 years old. The second study identifies distinct BMI trajectory in infants during their first year and assesses how prenatal and early life factors such as maternal pre-pregnancy BMI, GWG, and breastfeeding influence these trajectories. The third study further examines how the BMI trajectories in the first year of life influence the risk of childhood obesity at age 6.

AIMS, RESEARCH QUESTIONS AND HYPOTHESES

Each study covered one specific aim and its corresponding research questions and hypotheses. They are as follows:

AIM 1: To examine the associations of maternal pre-pregnancy BMI and GWG with offspring BMIZ and the risk of obesity at age 6.

QUESTIONS AND HYPOTHESES:

Q 1.1 What is the association of maternal pre-pregnancy BMI with the risk of their offspring being obese at age 6?

H 1.1 Children born to mothers who are overweight or obese before pregnancy have a greater risk of being obese at age 6 compared to children born to normal weight mothers. Here, mother's pre-pregnancy BMI is categorized as underweight (<18.5 kg/m^2), normal weight (18.5≤BMI≤24.9kg/m^2), overweight (25.0≤BMI≤29.9kg/m^2) and obese (BMI≥30.0kg/m^2) according to the WHO classification.(Organization 2015) Offspring's obesity at age 6 is defined as ≥ 95th percentile of BMI for age based on sex-specific 2000 CDC growth charts.(Kuczmarski et al. 2002, Ogden and Flegal 2010) Age and-sex specific BMI percentile at age 6 is calculated using a SAS Program provided by CDC. (Centers for Disease Control and Prevention, 2015).

Q 1.2 What is the association of maternal GWG with the risk of their offspring being obese at age 6?

H 1.2.1 Compared to children born to mothers who gain adequate weight during pregnancy, children born to mothers who gain excessive weight during pregnancy have a greater risk of being obese at age 6. Conversely, children born to mothers who gain inadequate weight during pregnancy have a smaller risk of being obese at age 6.

H 1.2.2 The association of maternal GWG with the risk of their offspring being obese at age 6 is modified by maternal pre-pregnancy BMI status.

Here, total GWG is categorized as excessive, adequate, and inadequate if their total GWG is above, within, or below the 2009 IOM GWG guidelines correspondingly.(2009)

Q 1.3 What is the association of maternal GWG with offspring BMIZ across the distribution of offspring BMIZ at age 6?

H 1.3.1 Total GWG is positively associated with offspring BMIZ across the distribution of BMIZ, and the magnitude of this association varies across the distribution of BMIZ.

H 1.3.2 The association of maternal total GWG and offspring BMIZ might be modified by maternal pre-pregnancy BMI status.

H 1.3.3 Compared with children born to mothers who gain adequate weight gain, children born to mothers who gain excessive weight during pregnancy have higher values of BMIZ across the distribution of BMIZ. Conversely, children born to mothers who gain inadequate weight during pregnancy have a lower BMIZ across the distribution of BMIZ.

H 1.3.4 Magnitudes of these associations vary across the distribution of BMIZ, and these associations might be modified by maternal pre-pregnancy BMI status.

Here, both continuous and categorical GWG are used. The categorical GWG is coded as inadequate, adequate and excessive weight gain according to 2009 IOM GWG guidelines. Offspring BMIZ is calculated using a SAS Program provided by CDC. ((Centers for Disease Control and Prevention, 2015).)

AIM 2: To identify BMI trajectories during the first year of life and assess the potential influence of prenatal factors (i.e. pre-pregnancy BMI and GWG) and early-life factors (i.e., breastfeeding) on the identified BMI trajectories.

QUESTIONS AND HYPOTHESES:

Q 2.1 Are there BMI trajectories during the first year of life in children?

H 2.1 The trajectories of BMI during the first year of life in children can be classified using data-driven Latent Class Growth Analysis in a sample of children with between two and five BMI measures during the first year of life.

Q 2.2 Do maternal pre-pregnancy BMI, GWG and breastfeeding influence BMI trajectories in children during their first year of life?

H 2.2.1 Compared with children born to mothers who gain adequate weight, children born to mothers who are overweight or obese before pregnancy have a greater risk of being in the faster growing BMI trajectory in the first year.

H 2.2.2 Compared with children born to mothers who gain adequate weight, the children born to mothers who gain excessive weight during pregnancy have a greater risk of being in the faster growing BMI trajectory. Conversely, children born to mothers who gained inadequate weight during pregnancy have a smaller risk of being in the faster growing BMI trajectory.

H 2.2.3 Compared with children who were breastfed during the first year of life, those who were not breastfed have a greater risk of being in the faster growing BMI trajectory.

AIM 3: To examine the association of the BMI trajectories in the first year (identified in Aim 2) with the risk of obesity among children at age 6.

QUESTIONS AND HYPOTHESES:

Q 3 Do the identified BMI trajectories during the first year of life predict the risk of obesity at age 6?

H 3 Compared with children not being in the faster growing BMI trajectory, those in the faster growing BMI growth trajectory in the first year have a greater risk of obesity at age 6.

CHAPTER 2

LITERATURE REVIEW

This chapter reviewed the extant literature and included three sections corresponding to three aims. First, the literature was summarized regarding the impact of pre-pregnancy body mass index (BMI) on offspring obesity, Institute of Medicine's recommendations for gestational weight gain (GWG) guidelines and measurement, and the independent and joint effects of GWG and pre-pregnancy BMI on childhood obesity. The second section reviewed the literature on the BMI trajectories during early life and their determinants. The final section summarized the literature on the influence of BMI trajectories during early life on childhood obesity.

IMPACT OF MATERNAL PREPREGNANCY BMI ON OFFSPRING OBESITY

The prevalence of maternal obesity has increased rapidly in the past two decades, parallel with the increasing trend of obesity prevalence in the non-pregnant population in both developed and developing countries. Globally, more than 30% of reproductive-aged women are obese.(McDonald et al. 2010, Zambrano and Nathanielsz 2013) In the U.S., approximately 64% of women of child-bearing age are overweight or obese (BMI ≥25 kg/m^2), and 35% (BMI >30 kg/m^2) are obese (8% are extremely obese, i.e., BMI≥40 kg/m^2).(Obstetricians and Gynecologists 2013) In the United Kingdom(Heslehurst et al. 2007), around 33% of pregnant women are overweight or obese. Examples from developing countries include 16% of pregnant women as overweight or obese (BMI ≥25

kg/m^2) in China,(Leung et al. 2008) and 26% of pregnant women are overweight (BMI 25-29.9 kg/m^2) and 8% are obese (BMI ≥30 kg/m^2) in India.(Sahu et al. 2007). Evidence from both animal and human studies suggests that maternal obesity creates an adverse in-utero environment, which affects their offspring's short- and long-term health.(Drake and Reynolds 2010, Reynolds, Labad, et al. 2013, Li, Sloboda, and Vickers 2011) A growing body of literature demonstrates that obesity during pregnancy is positively associated with an increased risk of adverse birth outcomes including stillbirth, neonatal death, large-for-gestational-age neonates, and macrosomia. (Vesco et al. 2009, Aune et al. 2014) In addition to these short-term risks, accumulating evidence shows that maternal obesity has long-term detrimental effects on offspring such as having an increased risk of obesity and higher mean value of BMIZ, as well as morbidity and mortality later in life.(Reynolds et al. 2010, Drake and Reynolds 2010, Reynolds, Allan, et al. 2013) For instance, Hawkins et al (Hawkins et al. 2009) found that the children of mothers who were overweight before pregnancy were 1.37 (95% confidence interval [CI]: 1.18-1.58) times more likely to be overweight at 3 years old than children of normal weight mothers. Reilly et al (Reilly et al. 2005) reported that children of mothers who were obese before pregnancy were 4.25 (95% CI: 2.86-6.32) times more likely to be overweight at 7 years old compared with children of non-obese mothers. A recent systematic review and meta-analysis(Yu et al. 2013) reported that the odds of being overweight or obese for offspring among mothers who were overweight or obese before pregnancy were 1.95 (95% CI: 1.77-2.13) and 3.06 (95% CI: 2.68-3.49) times the odds of being overweight and obese for offspring born to normal weight mothers, respectively.

The association of maternal overweight or obesity with the mean value of their offspring BMI at various ages has also been studied in the literature. Several studies have observed a positive relationship between maternal pre-pregnancy BMI and mean value of BMIZ in children during childhood(Mesman et al. 2009, Lawlor et al. 2007a, Laitinen, Power, and Jarvelin 2001) and in early adulthood. (Tequeanes et al. 2009, Laitinen, Power, and Jarvelin 2001) Mesman and co-workers(Mesman et al. 2009) reported that overall maternal pre-pregnancy BMI was an independent determinant of offspring BMIZ at age 14 months. Specifically, offspring BMIZ increased by 0.03 (95% CI: 0.02-0.056) with a one unit increase of maternal pre-pregnancy BMI. Lawlor and colleagues(Lawlor et al. 2007b) studied the association of maternal pre-pregnancy BMI with offspring BMIZ at 14 years, reporting that for every one-standard-deviation (SD) increase in maternal BMI, the increase in standardized offspring BMI at age 14 was 0.36 SD (95% CI: 0.32-0.40).

In summary, while the majority of previous studies support a positive association between maternal prepregnancy BMI with offspring weight status, the magnitude of this association is heterogeneous. These heterogeneous findings can be explained by various factors such as definitions of offspring overweight or obesity, age range covered, and potential confounders controlled in each study. Furthermore, neither logistic regression nor linear regression can capture associations across the entire distribution of BMIZ. Also covariates might affect BMIZ differently at quantile levels of BMIZ. This dissertation addressed the above using quantile regression analyses.

GESTATIONAL WEIGHT GAIN

Gestational weight gain (GWG), as an intrauterine nutritional marker for pregnancy, has been documented in the literature and identified as an important modifiable risk factor in the function of pre-pregnancy BMI for various short- and long-term adverse maternal and offspring health consequences over the last 40 years.(Wrotniak et al. 2008, Zhu et al. 2015, Hinkle et al. 2012a, Hooper, Coughlan, and Mullen 2008) Maternal prepregnancy BMI is an indicator of exceeding GWG recommendations since overweight or obese women exceed recommendations more than normal weight women. According to the 2009 Institute of Medicine (IOM) guidelines, approximately 43% of women in the general population gain excessive weight during pregnancy. This percentage can be as high as two thirds in certain subgroups such as overweight or obese. (Li et al. 2007a, Stotland et al. 2006, Ziyab et al. 2014, Pryor et al. 2011) Excessive GWG is strongly associated with postpartum weight retention, thus increasing women's risk of becoming overweight or obese postpartum.(Siega-Riz, Evenson, and Dole 2004) Therefore, GWG has recently been a growing concern worldwide due to the increasing prevalence of excessive weight gain on top of maternal obesity, which has been linked to various health consequences mentioned above.(Deputy, Sharma, and Kim 2015) These factors might combine to synergistically increase the likelihood of childhood obesity, as well as obesity in adulthood.(Stuebe, Forman, and Michels 2009, Reynolds et al. 2010, Guo et al. 2015) Establishing the optimal amount of weight gain during pregnancy is of great concern and remains an ongoing debate.(Hutcheon and Bodnar 2014, Bodnar et al. 2011)

INSTITUTE OF MEDICINE'S RECOMMENDATIONS FOR GWG

The first recommendations for weight gain during pregnancy was issued by the Institute of Medicine (IOM) in 1990.(1990) However, since 1990 there have been dramatic shifts in the demographic and epidemiologic profiles of the U.S. population. In particular, the population of reproductive-aged women is more diverse in terms of race composition, older at age of delivery, and heavier at the beginning of pregnancy. (Yaktine and Rasmussen 2009) In response to these changes and in combination with emerging evidence from the literature, IOM released its revision in 2009 (IOM 2009).(Yaktine and Rasmussen 2009) The finding of optimal GWG varying according to pre-pregnancy BMI has been recognized for more than 20 years. (1990)'(Yaktine and Rasmussen 2009) The specific input for the new recommendations for total and rate of weight gain during pregnancy by pre-pregnancy BMI status is illustrated in Table 2.1.

Table 2.1. 2009 IOM recommendations for total and rate of weight gain during pregnancy, by pre-pregnancy BMI[36]

Pre-pregnancy BMI	Total Weight Gain		Rates of Weight Gain* 2nd and 3rd Trimester	
	Range in kg	Range in lbs.	Mean (range) in kg/week	Mean (range) in lbs./week
Underweight (<18.5 kg/m^2)	12.5-18.0	28.0-40.0	0.5 (0.4-0.6)	1.0 (1.0-1.3)
Normal weight (18.5-24.9 kg/m^2)	11.5-16.0	25.0-35.0	0.4 (0.4-0.5)	1.0 (0.8-1.0)
Overweight (25.0-29.9 kg/m^2)	7.0-11.5	15.0-25.0	0.3 (0.2-0.3)	0.6 (0.5-0.7)
Obese (≥30.0 kg/m^2)	5.0-9.0	11.0-20.0	0.2 (0.2-0.3)	0.5 (0.4-0.6)

*Calculations assume a 0.5-2kg (1.1-4.4 lbs.) weight gain in the first trimester.

MEASURES OF GWG

Four measures of GWG are commonly used: 1) total weight gain, 2) net weight gain, 3) adequacy ratio of weight gain, and 4) average weekly rate of GWG (kg/week).

Total GWG is usually defined as the last weight recorded before delivery minus pre-pregnancy weight. This measure is easily acquired, and data are easily available. However, it is problematic due to confounding by less time to gain weight for preterm deliveries, as well as the possibility for other outcomes such as offspring obesity later in life.(von Kries et al. 2013) Net weight gain takes birth weight into account by subtracting birth weight from total weight gain. This measure has a similar disadvantage to total GWG. In contrast to total GWG and net weight gain, the measure of average weekly rate of GWG would perform better by taking duration of gestation into account, if the rate of weight gain was constant throughout gestation. However, this assumption does not hold given the finding of linear growth in the second and third trimester following a pattern of minimal weight gain in the first trimester.(Guo et al. 2015, Diesel et al. 2015, Oken et al. 2007) Adequacy ratio of weight gain is another modified measure of GWG defined by observed weight gain and expected weight gain according to the IOM 2009 GWG guidelines on a trimester-specific weight gain. This measure relies on the assumption of a woman having a healthy pregnancy BMI gain of 0.5-2kg in the first trimester depending upon maternal pre-pregnancy BMI status. (Yaktine and Rasmussen 2009) However, if this assumption does not hold, IOM GWG adequacy ratio would also introduce misclassification bias on GWG category, which can be differential or non-differential.

Given the limitations of existing GWG measures, a weight-gain-for-gestational-age Z score chart has recently been developed in order to limit the bias from traditional methods. This chart was developed in 2013 by a group of researchers and proposed as a standardized method similar to infant growth charts and birthweight-for-gestational age charts to measure and monitor GWG.(Moreira et al. 2007) This new and noteworthy

method overcomes the built-in correlation with gestational age at delivery, which frequently occurs among conventional measures and minimizes the potential for bias.(von Kries et al. 2013) Another emerging tool to minimize potential bias is GWG trajectory/pattern as a function of gestational age. This tool incorporates the dynamic weight change pattern during pregnancy and therefore is less vulnerable to gestational age-related bias.(Lau et al. 2014, Kinnunen et al. 2003) The functional form of GWG regarding gestational age has been facilitated and identified by advanced statistical procedure.(von Kries et al. 2013) The characteristics of each measure including their definitions, advantages and disadvantages, and potential data availability are varied.

In contrast, the approach of standardizing GWG as Z scores or percentiles sheds light on the assessment of GWG without introducing bias from gestational age. The methodology is well established in the assessment of fetal, infant, as well as adolescent growth. To date, the pregnancy weight-gain-for-gestational-age Z score/percentile charts have been created for normal-weight,(Ensenauer et al. 2013) overweight and obese women(Hutcheon et al. 2015) in specific cities of the U.S, as well as a cohort of women in a national representative sample of Malawi.(Xu et al. 2014) However, a large nationally representative sample of women with serial antenatal weight gain measurements as a reference population to develop weight-gain-for-gestational-age charts is currently unavailable for any country. As a result, propagating the use of standardized GWG method is limited. However, a very recent study (Hinkle et al. 2016) compared methods to address bias due to gestational duration between weight-gain-for-gestational-age and a regression-based adjustment for gestational age (GA). The findings from this study found that adjusting for GA achieves unbiased estimates of the association between

total GWG and outcomes such as neonatal mortality. Hence this study provided a promising accessible alternative to the weight-gain-for-gestational-age z-scores when total GWG was used as an independent variable of interest.

As mentioned earlier, the trajectory of GWG is a promising approach to depict the dynamic change in rate of weight gain during pregnancy. The GWG trajectories/patterns are also limited by the lack of serial antenatal weight gain measurements; therefore, its availability in large population-based studies is highly compromised. To the best of our knowledge, only one study has examined GWG pattern/ trajectories across each trimester during pregnancy and linked these measurements to pregnancy-induced hypertension.(Bayol, Simbi, and Stickland 2005)

The existing literature also proposes other ways to minimize the potential for bias. For example, the trimester-specific GWG incorporates the dynamic weight gain during each trimester of pregnancy and roughly represents the picture of average weight gain during early, middle, and late pregnancy trimesters.(de Onis, Blossner, and Borghi 2010, Koenker 2005, Ng et al. 2014) Also restricting the study population to only women with full term births (≥37 weeks of gestation) has the potential to minimize the bias from gestational age.

INDEPENDENT AND JOINT EFFECTS OF MATERNAL PREPREGNANCY BMI AND GWG ON CHILDHOOD OBESITY

Within the past several years, knowledge on the association of prepregnancy BMI and GWG with risk of obesity among pediatric population has proliferated worldwide, but the findings are still inconclusive. The overall findings on the association of prepregnancy BMI and GWG with risk of offspring obesity are mixed with null,(Han, Lawlor, and Kimm 2010, Kramer 1981) and positive [65,](von Kries et al. 2013)·(Bagchi

2010, Robinson et al. 2015, Gillman et al. 2008)' (Jedrychowski et al. 2011, Gillman et al. 2001)' (Yan et al. 2014)' findings. Moreover, some studies (Deierlein et al. 2011, Mayer-Davis et al. 2006) did not find an overall association between excessive GWG and risk of childhood obesity, while there were positive associations among underweight, [96] normal weight [92, 125] or overweight/obese mothers. (Robinson et al. 2015) Another study[134] found positive association between GWG and childhood obesity at 3 to 6 years of age in general, and this association was strengthened among overweight/obese mothers. Another study(Ogden et al. 2014) reported that excessive GWG was positively associated with the risk of children being overweight overall, and this positive association remained among normal weight and overweight mothers. Additionally, several other studies(Ng et al. 2014, Hu 2008a, von Kries et al. 2013) reported heterogeneous associations of GWG with childhood obesity among each trimester of pregnancy with two studies[117,126] emphasizing early pregnancy and the other[124] emphasizing the relevance of the third trimester. For the consideration of the potential bias from gestational age, one study used GWG Z-score standardized for gestational age given prepregnancy BMI.(Diesel et al. 2015) Diesel et al reported that women with a GWG exceeding a Z-score of 0 SD (equivalent to 30kg at 40 weeks) had an increased risk of offspring obesity while those with a Z-score below 0 SD did have an increased risk of having an obese child. Furthermore, some studies restricted the study sample to term children to limit this potential bias.(Deierlein et al. 2012, Deierlein et al. 2011, Harris et al. 2015)

In brief, large variations exist in the current literature due to different definitions and classifications of GWG, specification of a comparison group, different references to generate a child's BMI Z scores or percentile, as well as different cutoff points used to

define childhood obesity. Despite these differences, systematic reviews and even meta-analyses(Ogden et al. 2014, Ebbeling, Pawlak, and Ludwig 2002) concluded that current evidence supports positive associations between excessive GWG and risk of childhood obesity.

The association of maternal GWG with the mean value of their offspring BMI at various ages has also been studied in the literature with inconsistent findings. Hinkle et al (Hinkle et al. 2012b) reported a non-linear relationship between GWG and child BMIZ at 5 years stratified by prepregnancy BMI status, but the association was not significant among underweight mothers. Beyerlein and co-workers(Beyerlein, Nehring, Rzehak, Heinrich, Müller, et al. 2012) analyzed data from Germany and observed a positive association between GWG and offspring BMIZ at 5-6 years of age using quantile regression analysis by prepregnancy BMI status. This study suggested that heterogeneous associations of GWG with the offspring BMIZ across different percentiles of the offspring BMIZ distribution were only observed among normal weight mothers. Branum and colleagues reported a linear relationship between GWG and the offspring BMIZ at age 4 years after adjusting for prepregnancy BMI and other covariates. This same study found that for every 5 kg change in GWG, the offspring BMIZ increased by 0.07 (95% CI: 0.04- 0.11).(Branum et al. 2011) Ehrenthal and co-workers (Ehrenthal et al. 2013) reported that net GWG adjusted for gestational age at birth was positively associated with offspring BMIZ at 4 years. This study observed that with one unit increase of net GWG in kilograms, the offspring BMIZ increased by 0.01 (95% CI: 0.01-0.02). Another study from the Netherlands only reported a significant association between GWG and the

offspring BMIZ at 4 years old among mothers with normal BMI. (Ehrenthal et al. 2013, Deierlein et al. 2011)

In summary, the association of GWG and prepregnancy BMI with childhood obesity is inconsistent, and the results might be explained by several factors. First of all, GWG measures are subjectively defined, and the duration of pregnancy used in calculating total GWG varies. Moreover, other measures of GWG such as net GWG, GWG adequacy ratio, GWG Z score, as well as GWG trajectory across pregnancy, are not widely in use and have intrinsic limitations as mentioned before. Secondly, the criteria used to categorize GWG is not uniform across studies with the majority based on 2009 IOM, while others are based on 1990 IOM or tertile/quartile of GWG. Another important reason for mixed findings is the varied definition of childhood obesity involving different reference populations, such as the study sample itself, 2006 WHO standard, 2000 CDC growth chart, as well as country-specific reference charts. Also some studies used different cut-off points to define childhood obesity such as 90^{th} or 95^{th} percentile. Moreover, the role of prepregnancy BMI status is treated differently in each study with some stratifying and some adjusting for it in the models. Furthermore, it remains unclear whether the timing and pattern of GWG over the course of pregnancy differ in its relation to childhood obesity. The influence of maternal prepregnancy BMI and GWG on the risk of offspring obesity or the mean change of BMIZ has been studied. However, focusing either on the upper percentiles using logistic regression or the mean using linear regression could not capture associations across the entire distribution of BMIZ. Also covariates might affect BMIZ differently at quantile levels of BMIZ.

As pointed out by the most recent research(Hutcheon et al. 2012), the conventional measures of GWG can introduce a non-trivial degree of bias due to its built-in correlation with gestational age. As a result, this bias might also affect the nature of association between GWG and childhood obesity, as well as BMIZ. Therefore, in this study, we addressed a few methodological limitations in measuring GWG in the following ways. First, the dataset that was used in this analyses by design, (n=3,033) consisted of pregnant women with a gestational age equal to or greater than 35 weeks of gestation. Secondly, quantile regression analyses were conducted to examine whether the associations of total GWG with offspring BMIZ measured at age 6 varied across deciles of the BMIZ distribution. Finally, our study also examined the potential interaction between prepregnancy BMI and GWG across different percentiles of the response distribution.

BMI GROWTH TRAJECTORY DURING EARLY LIFE

Infant growth during the first year of life as a critical period contributing to the lifetime health has been confirmed in various populations.(Reynolds, Labad, et al. 2013, von Bonsdorff et al. 2015) A number of studies(Schneider and Segre 2009, Wilson et al. 1998, Huh et al. 2011, Rooney, Mathiason, and Schauberger 2011, 2009, Viswanathan et al. 2008) have recently suggested that rapid weight gain (weight-z score 0.67 standard deviation) between two specific time points during the first year of life might be associated with increased risk of being overweight or obese in childhood as well as young adulthood.(Baird et al. 2005, Lau et al. 2014) However, those prior studies assessed weight at only two points in time ignoring the dynamic patterns of weight over time. This way of assessing infant growth thus might mislead the etiology research on the adverse

health consequences related to early life growth pattern, especially when the growth patterns are non-linear. Therefore, trajectory of BMI might capture the non-linear growth pattern over time within an individual child.

Table 2.2 summarizes literature on BMI trajectories during early childhood and types of trajectory names identified. Studies on BMI trajectories mainly come from developed countries, namely the Netherlands (n=1),(van Rossem et al. 2014) Japan (n=1),(Haga et al. 2012) UK (n=1),(Ziyab et al. 2014) Australia (n=2),(Giles et al. 2015a, Magee, Caputi, and Iverson 2013a) Canada (n=3) (Carter et al. 2012, Pryor et al. 2011, Tu et al. 2015) and U.S.(n=4).(Lane, Bluestone, and Burke 2013, Ventura, Loken, and Birch 2009, Li et al. 2007a, Mustillo et al. 2003) Age ranges covered in these studies varied with three studies examining the BMI trajectory commencing from birth. The majority of studies focused on children during middle childhood. Two analytical methods utilized to model the BMI trajectory were latent class growth analysis and growth mixture models. In addition, BMI as a measure of weight adjusted for height is commonly used as a centile or z-score adjusted for age and sex for growing children using an external reference. Previous studies have modelled BMI(Pryor et al. 2011, Ventura, Loken, and Birch 2009, Magee, Caputi, and Iverson 2013a, van Rossem et al. 2014), BMIZ (Haga et al. 2012, Ziyab et al. 2014, Carter et al. 2012, Giles et al. 2015a), BMI percentage(Lane, Bluestone, and Burke 2013) and a dichotomous indicator for being overweight or obese(Li et al. 2007a, Mustillo et al. 2003). Therefore, change in BMI can be measured in several different ways such as raw BMI, BMIZ, BMI percentage, or a dichotomous indicator. Studies have shown BMIZ is optimal for assessing adiposity on a single occasion (i.e., cross-sectional), but not the best scale for

measuring change in adiposity. (Cole et al. 2005, Hall and Cole 2006) The optimal BMI measures for change are raw BMI and BMI percentage.(Cole et al. 2005, Hall and Cole 2006)

In conclusion, only three (van Rossem et al. 2014)' (Haga et al. 2012, Giles et al. 2015a) of these 12 studies considered the BMI trajectory starting from birth with only one measure of BMI at 12 months of infants 'age. Only one (Giles et al. 2015a)conducted in Australia covered the child's first year of life and extended beyond infancy to 2 and 3½ years. Due to the potential health implication of BMI growth during early childhood, more research is needed. However, it still remains unexamined in the literature whether BMI trajectories exist in the first year of life; if they exist, how many distinct BMI trajectories can be presented; and what are potential influences of prenatal and early life factors on these identified BMI trajectories.

PREDICTORS OF BMI TRAJECTORIES IN YOUNG CHILDREN

Since the infant growth trajectory does not happen in isolation, it is critical to identify risk factors for deviant developmental trajectories. Li and his colleagues(Li et al. 2007a) reported that the risk factors associated with *early onset overweight* trajectory included maternal smoking, maternal prepregnancy BMI larger than 25 kg/m^2, GWG greater than 20.43 kg, male child, and black ethnicity, child's birth weight equal to or greater than 4 kg, and duration of breastfeeding less than 4 months. Haga and co-workers reported that maternal smoking, prepregnancy BMI, skipping breakfast, sleep duration, and paternal smoking were significant predictors for the BMI trajectories among boys, while maternal age and prepregnancy BMI were significant for girls.(Haga et al. 2012) Another study identified highest maternal prepregnancy BMI and shorter duration of

breastfeeding as potential risk factors for the *upward BMI percentile crossing* trajectory.(Ventura, Loken, and Birch 2009) Ziyab et al found that maternal smoking during pregnancy and being overweight during early pregnancy were significant risk factors for being in the *early persistent obesity* trajectory from 1 to 18 years of age.(Ziyab et al. 2014).

Another study(Giles et al. 2015a) from Australia found that a child's male gender and the mother being obese in early pregnancy and parity were significant predictors of *accelerating trajectory* of BMIZ from birth until 3.5 years old. A study from Canada(Carter et al. 2012) reported that living in a rural area, obesity status of the mother when the child was 1.5 years old, maternal smoking during pregnancy, and maternal overeating behavior during pregnancy were significant predictors for children's *high-stable* BMI trajectory

In summary, longitudinal studies have recently emerged worldwide to assess the growth trajectories of BMI during early childhood and have identified important predictors of the trajectories. However, current information on BMI trajectories during infancy, i.e., the first year of life, is largely unclear. Less is known about the relative contribution of pre-pregnancy BMI, GWG and breastfeeding practices to the BMI trajectories during the first year of life. Therefore, our study contributed to the literature by examining if distinct growth trajectories of BMI exist among children during their first year of life. We would also extend current research to further examine the relative influence of modifiable prenatal and early life factors such as prepregnancy BMI, GWG and adherence to breastfeeding guidelines on the identified BMI trajectories after adjusting for other covariates.

Table 2.2: Summary of literature on body mass index trajectories during early childhood

Studies	Study population	Measures	Modelled BMI	Statistical analysis	Labelled Trajectory name (% of study population)
Giles, 2015, Australia[117]	556 (49.3% boy)	Birth, 6, 9 and 12 months, 2 and 3½ years	BMI Z score	latent class growth analysis (LCGA)	*Low* (15% children,), *intermediate* (46% children), *high* (35% children) and *accelerating* (4% children)
Magee, 2013, Australia[118]	4601 (50.6% boy)	4-5 years, 6-7 years, 8-9 years and 10-11 years	Raw BMI	Growth mixture modelling (GMM)	*Healthy weight* (82.4%), *Early onset overweight* (4.0%), *Later onset overweight* (11.6%), and *high risk overweight* (2.3%).
van Rossem, Netherlands[27] 2014	3550 (53.7% boy)	Birth to 11 years	Dichotomized into with and without overweight	LCGA	*Persistent overweight* (3.7%), *Overweight reduction* (8.5%) and *stable* (87.8%)
Carter, 2012, Canada[26]	1556 (48% boy)	4, 6, 7, 8 and 10 years	BMI Z score	LCGA	*Low-increasing* (9.7%), *low-medium, accelerating* (36.2), *Medium-high, increasing* (43.0%), and *high-stable* (11.1%).
Lane, 2013, 10 sites across USA[28]	1238 (51.1% boy) 24% minorities	24, 36, and 54 months and in grades 1, 3, 5 and 6.	BMI percentile	LCGA	*Stable* (38.8%), *Elevated* (24.5%), and *steady increase* (36.7%)
Ventura, 2009 Central Pennsylvania, USA[120]	182 non-Hispanic white girls	7, 9, 11, 13 and 15 years	Raw BMI	GMM	*Upward percentile crossing* (14%), *delayed downward percentile crossing* (20%), *60th percentile tracking* (29%), and *50th percentile tracking.*

Li, 2007, USA[23]	1912 (54.9% boy)	2, 4, 6, 8, 10 and 12 years	Dichotomized into with and without overweight	GMM	*Early onset overweight* (10.9%), *Late onset overweight* (5.2%), and *never overweight* (83.9%).
Mustillo, 2003, USA[24]	991 white children living in rural area	9 to 16 years with annual measures	Dichotomized into with and without obesity	LCGA	*No obesity* (73%), *Chronic obesity* (15%), *Childhood obesity* (5%), and *adolescent obesity* (7%).
Ziyab, 2014, UK[25]	1456 (51.2% boy)	1, 2, 4, 10 and 18 years	BMI Z score	LCGA	*Normal* (71.5%), *Early persistent obesity* (3.9%), *Delayed overweight* (11.5%), and *early transient overweight* (13.1%).
Pryor, 2011, Canada[40]	1957 (41.1% boy)	5 months through 5 years with annual measures and at ages 6, 7, and 8 years	Raw BMI	LCGA	*Low-stable* (54.5% of children), *Moderate* (41.0%), and *high-rising* (4.5%)
Tu, 2015, Canada[119]	7253 (51.9% boy)	1-6 years at baseline and then biennially up to 14-20 years	Raw BMI	LCGA	Boy: *low* (65.7%), *decreasing* (15.0%), *medium* (13.4%), and *high* (5.8%). Girl: *low* (46.5%), *decreasing* (8.0%), *medium* (35.4 %), and *high* (10.2%).
Haga, 2012, Japan[55]	825 boys and 819 girls	Birth to 12 years of age with 11 repeated measures	BMI Z score		Boy: *stable thin* (12.6%), *stable average* (42.2%), *stable higher average* (30.5%), *progressive overweight* (10.5%) and *progressive obesity* (4.2%). Girl: led as the same as boys except one additional one named as *progressive average* (12.1%).

INFLUENCE OF BMI TRAJECTORIES DURING EARLY LIFE AND CHILDHOOD OBESITY

Landmark work known as the fetal origin of disease hypothesis was done by Barker in the late 1980s.(Ventura, Loken, and Birch 2009, Beyerlein, Nehring, Rzehak, Heinrich, Müller, et al. 2012) Understanding the very early determinants of human obesity might help curb the current obesity epidemic and further provide cost-effective selective interventions for those at highest risk of obesity. (Frongillo and Lampl 2011a)

Infants, who are born small for gestational age with catch-up growth, as well as those with adiposity rebound around the age of school entry, are at increased risk of childhood obesity. Rapid growth (usually measured as rapid weight gain) during the first year of life in the pediatric population has recently received particular interest, and most studies observed a positive association between rapid growth and being overweight/obese later in life. (Schneider and Segre 2009, Wilson et al. 1998, Huh et al. 2011, Rooney, Mathiason, and Schauberger 2011, 2009, Viswanathan et al. 2008) (Wilson et al. 1998) Dubois and his colleague(Huh et al. 2011) showed that rapid growth, defined as in the highest quintiles of monthly weight gain between birth and 5 months, is associated with increased risk of childhood obesity at 4.5 years. Rooney and his colleague(Rooney, Mathiason, and Schauberger 2011) defined rapid weight gain as weight gain larger than 2 lbs per month during the first 4 months and reported associations with increased risk of obesity in childhood around age 5, in adolescence around age 14, and in early adulthood. One study used weight-for-age Z scores increase larger than 1 SD between birth and 4 months to define rapid weight gain, and found that rapid weight gain in children in the first 4 months was positively linked to obesity at age 20.(2009) Another study conducted

in Hong Kong defined accelerated infant growth as a change greater than 0.67 in weight Z score standardized using WHO growth standard and found that accelerated infant growth was associated with higher childhood BMIZ at age 6.(2009) Jones and his colleague(Viswanathan et al. 2008) using a sample from Mexico defined accelerated growth as positive change in BMIZ between birth and age 1 year using WHO growth standard and reported positive association with obesity at age 4 to 6 years. Weight-for-length Z score was utilized in one study to define rapid growth as larger than 0.67 SD, as well as larger than 1 SD, and reported that both measures were positively associated with childhood obesity aged 4 to 5 years.(2009) In spite of varied definitions in rapid growth among studies, several systematic reviews and meta-analyses have recently summarized previous studies and unanimously supported positive associations between rapid growth during early life and childhood obesity. (Organization 2015, 2009, Hutcheon and Bodnar 2014, Bodnar et al. 2011, Deierlein et al. 2012)

In addition, a growing number of studies among various populations have repeatedly reported the independent contribution of rapid growth during infancy to the development of obesity among children. Linking distinct infant growth trajectories of BMI and obesity in childhood, as well as obesity later in life, is emerging as a new perspective. To the best of our knowledge, only one study conducted in Australia(Giles et al. 2015a) using LCAG identified 4 trajectories: *low*, *intermediate*, *high*, and *accelerating*. The study reported that in comparison to the *intermediate* trajectory group, those in the high trajectory group had 4.26 (95% CI: 2.50-7.26) times the odds of being overweight/obese at 9 years old, and those in the *accelerating trajectory* group had 15.36 (95% CI: 5.24-45.05) times the odds of being overweight/obese at age 9.

In summary, the influence of early life factors on childhood obesity, as well as obesity later in life, has generated particular interest in recent years. Exposure to a faster growth trajectory might exert long-lasting adverse health consequences. Therefore, the identification of growth trajectories using BMI is of great importance because it would identify the sub-groups of children with sub-optimal growth trajectories and its determinants that future intervention programs should focus on. Linking the BMI trajectories with the development of childhood obesity provides an opportunity to promote and improve obesity prevention strategies.

SUMMARY OF LITERATURE REVIEW

Based on the above literature review, we conclude that the associations of GWG and prepregnancy BMI with childhood obesity are heterogeneous, and the mixed results might be explained by the differences in measures of GWG, definitions of childhood obesity, and conflicting findings on the potential interaction between prepregnancy BMI status and GWG across previous studies. These heterogeneous findings might also be reflective of the complex nature of the association between GWG and childhood obesity across maternal prepregnancy BMI. Hence, current understanding of the complexity of maternal prepregnancy BMI and GWG with childhood obesity is still unclear. In addition, longitudinal studies have recently emerged worldwide to assess the growth trajectories of BMI during childhood and their predictors. However, to our knowledge, it still remains unexamined in the literature whether BMI trajectories exist in the first year of life; if they exist, how many distinct BMI trajectories can be presented; and finally, little is known about the potential influences of prenatal and early life factors on the

identified BMI trajectories. Far less is known about the association between identified BMI trajectories during infancy and the risk of obesity in childhood.

Thus, this dissertation addressed various literature gaps identified above and consisted of three studies. The first study examined the influence of maternal prepregnancy BMI and GWG on offspring BMIZ and risk of offspring being obese at age 6 (Aim 1). The second study identified trajectories of BMI during the first year of life and assessed the potential influence of prenatal and early life factors such as prepregnancy BMI, GWG and adherence to breastfeeding guidelines on the identified BMI trajectories (Aim 2). The third study further examined the associations of the infant trajectories of BMI identified in Aim 2 with the risk of being obese among children at age 6 (Aim 3).

CHAPTER 3

METHODOLOGY

This chapter described the data, study population, and statistical methods used to address each specific aim. Data from the Infant Feeding Practices Study II (IFPS II) and its Year 6 Follow-Up Study (Y6FU) were utilized to answer questions in Aims 1 and 3. The IFPS II without the follow-up data was used to answer questions in Aim 2.

THE INFANT FEEDING PRACTICES STUDY II AND ITS SIX YEAR FOLLOW-UP STUDY

The IFPS II is a longitudinal survey of pregnant women and their offspring using a series of questionnaires administered from the women's seventh month of pregnancy through the infant's first year of life. The original sample consists of 4,902 subjects who were drawn from a nationally distributed consumer opinion panel of 500,000 households. Data collection was conducted by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) between 2005 and 2007. The design of the IFPS II has been described in detail elsewhere.(Fein et al. 2008) The inclusion criteria for the IFPS II study included: mothers were 18 years or older at the time of the prenatal questionnaire, had a singleton newborn with a gestational age equal to or greater than 35 weeks' gestation (i.e., full or nearly full-term baby and a birth weight $\geq$ 2.25 kg, mother and baby were healthy at birth, and the infant did not have an illness or condition likely to affect feeding during the first year of life. A total of 3,452 pregnant women from all states

across the United States (U.S.) qualified for the study. The response rates for each postnatal questionnaire varied from 63% to 83% (see Figure 3.1).

THE YEAR SIX FOLLOW-UP STUDY

The Y6FU study provided the follow-up data on the IFPS II children through a single questionnaire administered in 2012.(Fein et al. 2014a) The main objective of the Y6FU study was to characterize the health, behavioral and developmental outcomes at age six for a geographically diverse cohort of children using in-depth longitudinal information on infant feeding practices collected in the IFPS II.(Fein et al. 2014a) It is the largest longitudinal study in the U.S. to examine long-term consequences of infant feeding. (Fein et al. 2008) The following exclusion criteria were applied for the Y6FU study(Fein et al. 2014a): incomplete information on neonatal (month 1) questionnaire in the IFPS II, being diagnosed with a condition likely affecting feeding, or living in a geographic area to which the post service were not available because of the Gulf Coast hurricanes of 2005. Finally, a total of 2,958 mother-child pairs qualified for the Y6FU; however, only 52.1% of qualified women participated in the follow-up study yielding a sample size of 1,542.

LINKAGE OF IFPS II WITH Y6FU

The Y6FU database was linked to the IFPS II database by matching the participation number that appears in both the IFPS II data and the Y6FU data.Centers for Disease Control and Prevention. http://www.cdc.gov/breastfeeding/data/ifps/index.htm. Accessed, Sep 15, 2015. The flow diagram in Figure 3.1 depicts the selection of participants from IFPS II and its Y6FU study, as well as the sample sizes and response rates for each specific survey questionnaire.

DATASET'S STRENGTHS AND POTENTIAL LIMITATIONS

The main strengths of the IFPS II data include its prospective design; the extensive topics covered in survey questionnaires especially detailed data about infants' feeding patterns, the frequency of data collection, and the large sample size. Linkage of the cross-sectional Y6FU data to the IFPS II collected in a longitudinal perspective further provides a unique opportunity to examine associations of prenatal and early life factors with a large number of health and developmental outcomes at age 6.

The data has several potential limitations. First, the study sample is not nationally representative of the U.S. population since the IFPS II is overrepresented by mothers with higher socio-economic status than that of the general U.S. population. A second limitation is that all data were self-reported by the child's mother. No medical records were examined to verify weight, height, health status, or other medical characteristics of the children. Third, the response rates during the first year of life and in the Y6FU study were not high.(Fein et al. 2014a, Fein et al. 2008). Due to the non-representative sample of this study, researchers have estimated bias relative to a nationally representative sample of new mothers, the IFPS II neonatal sample was compared with women in the National Survey of Family Growth Cycle 6 (1998–2000) who were aged 18–44 at the time of their most recent singleton delivery. Members of the IFPS II sample were older, more highly educated, and less likely to come from low income families than the random sample. In addition, the IFPS II participants were more likely to be employed and white, have fewer other children, were less likely to be from the South, less likely to smoke, took longer maternity leave and received their first prenatal care a little later in pregnancy.(Fein et al. 2008)

GENERAL STRATEGIES HANDLING THE POTENTIAL SELECTION BIASES DUE TO EXCLUSION, MISSING AND NON-RESPONSE.

- Exclusion: both IFPS II and Y6FU study have applied inclusion and exclusion criteria. To the best of our knowledge, if the aim is to estimate the prevalence of an outcome of interest, the application of inclusion/exclusion criteria would be subject to selection bias because the study population might not be representative of the whole population. Hence, this might affect external validity or generalizability of the results. Missing data: By default, observations with missing data on exposures, outcomes, and covariates were deleted from the analyses. To avoid potential bias associated with this, missing values were coded into a special category for covariates and the observations were kept in the analyses. However, this strategy was not appropriate for missing values of exposures and outcomes. To better understand the potential bias due to missing values in exposures and outcomes, the characteristics of the final analytical sample were compared with the original sample prior to the missing deletion.
- Generalizability and non-responses: The researchers from CDC have conducted 3 analyses to describe the potential sample biases. First, they compared the IFPS II data with data from a nationally representative National Survey of Family Growth (NSFG). They found that the IFPS II sample includes children whose mothers were older, more likely to be highly educated, being White, had higher income, and were less likely to smoke than mothers from the nationally representative NSFG. Second, they compared the

differences between respondents and non-respondents to Y6FU. Compared to mothers who did not respond to Y6FU, respondents were more likely to be older, married, and white; did not smoke; and received prenatal care before 13 weeks; and tended to have higher. In addition, respondents were much more likely to have returned 8 of the 10 postnatal questionnaires. However, no difference was found between respondents and nonrespondents by prepregnancy BMI, parity, having returned to work when the infant was 6 weeks old. Compared to children of nonrespondents, children of respondents were more likely to have breastfed longer and not participated in the Special Supplemental Nutrition Program for Women, Infants, and Children. However, children of respondents and of nonrespondents did not differ by infant gender, breastfeeding initiation, birth weight, or gestational age. The fourth analysis compared Y6FU respondents with characteristics of the 6-year-old participants of a nationally representative survey named the 2011-2012 National Survey of Children's Health (NSCH) based on common variables assessed in both data sources. Though similarities were found in some measures of health outcomes, the children in the Y6FU sample were healthier than the NSCH sample. It is also indicated that loss to follow-up further exacerbated these differences. (Fein et al. 2014a)

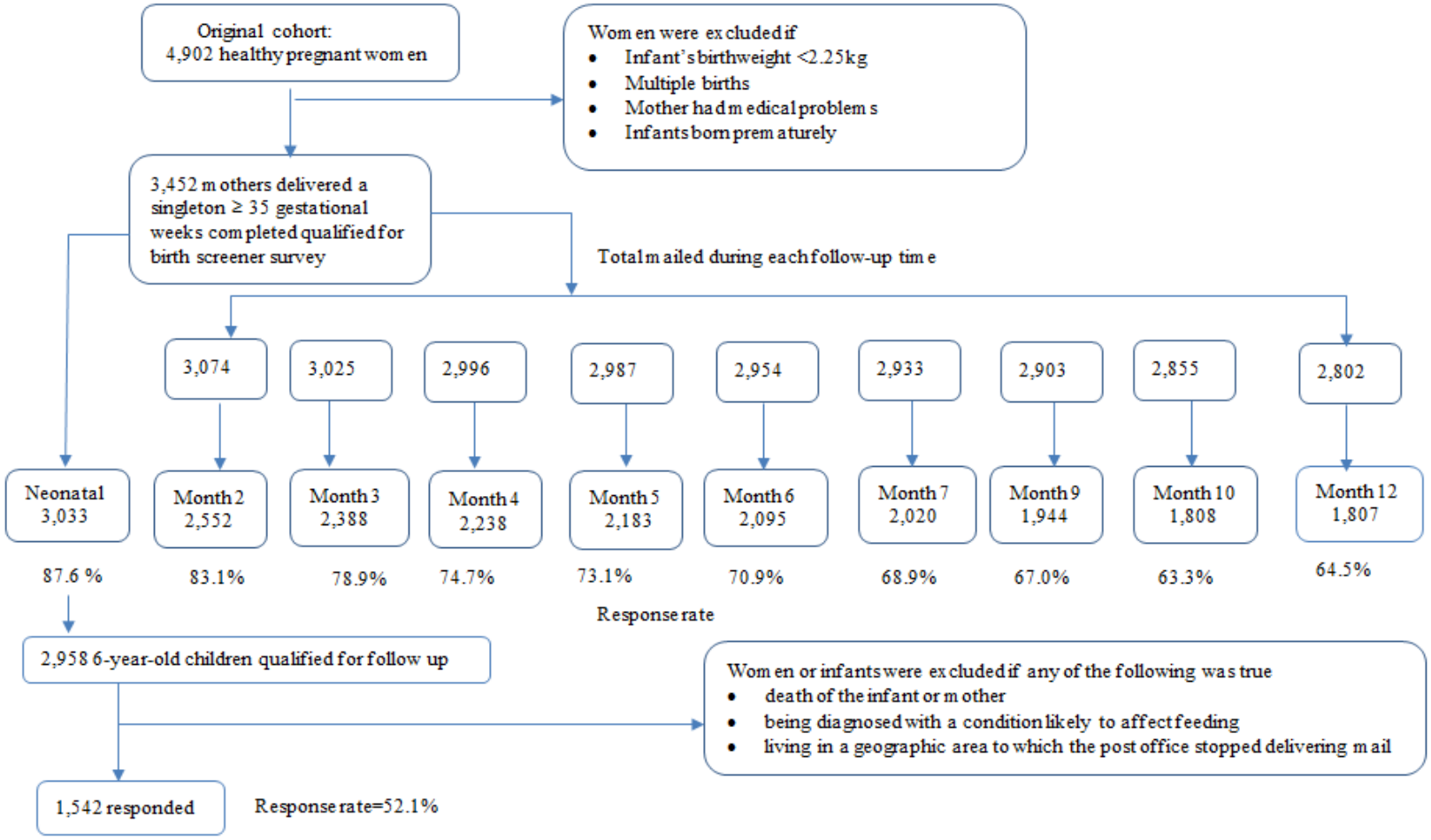

Figure 3.1: Flow chart and sample sizes in the IFPSII and the Y6FU study

DATA AND METHODS FOR STUDY ONE (AIM 1)

STUDY PURPOSE, DESIGN AND RESEARCH QUESTIONS

This study examined the associations of maternal prepregnancy BMI and GWG with offspring BMIZ and the risk of being obese in offspring at age six. This study used the linked dataset of IFPS II with Y6FU, a longitudinal study design.

The following research questions and corresponding hypotheses were examined:

Q 1.1 What is the association of maternal pre-pregnancy BMI with the risk of their offspring being obese at age 6?

H 1.1 Children born to mothers who are overweight or obese before pregnancy have a greater risk of being obese at age 6 compared to children born to normal weight mothers.

Here, mother's pre-pregnancy BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5≤BMI≤24.9kg/m^2), overweight (25.0≤BMI≤ 29.9 kg/m^2) and obesity (BMI≥30.0kg/m^2) according to the WHO classification.(Organization 2015) Offspring's obesity at age 6 was defined as ≥ 95th percentile of BMI for age based on sex-specific 2000 CDC growth charts.(Kuczmarski et al. 2002, Ogden and Flegal 2010) Age- and-sex specific BMI percentile at age 6 was calculated using a SAS Program provided by CDC. Centers for Disease Control and Prevention. http://www.cdc.gov/growthcharts /computer_programs.htm. Accessed November 11, 2015.

Q 1.2 What is the association of maternal GWG with the risk of their offspring being obese at age 6?

H 1.2.1 Compared to children born to mothers who gain adequate weight during pregnancy, children born to mothers who gain excessive weight during pregnancy have a greater risk of being obese at age 6. Conversely, children born to mothers who gain inadequate weight during pregnancy have a smaller risk of being obese at age 6.

H 1.2.2 The association of maternal GWG with the risk of their offspring being obese at age 6 is modified by maternal pre-pregnancy BMI status.

Here, total GWG was categorized as excessive, adequate, and inadequate if their total GWG is above, within, or below the 2009 IOM GWG guidelines correspondingly.(2009)

Q 1.3 What is the association of maternal GWG with offspring BMIZ across the distribution of offspring BMIZ at age 6?

H 1.3.1 Total GWG is positively associated with offspring BMIZ across the distribution of BMIZ and the magnitude of this association varies across the distribution of BMIZ.

H 1.3.2 The association of maternal total GWG and offspring BMIZ might be modified by maternal pre-pregnancy BMI status.

H 1.3.3 Compared with children born to mothers who gain adequate weight gain, the children born to mothers who gain excessive weight during pregnancy have higher values of BMIZ across the distribution of BMIZ. Conversely, children born to mothers who gain inadequate weight during pregnancy have a lower BMIZ across the distribution of BMIZ.

H 1.3.4 Magnitudes of these associations vary across the distribution of BMIZ, and these associations might be modified by maternal pre-pregnancy BMI status.

Here, both continuous and categorical GWG were used. The categorical GWG was coded as inadequate, adequate and excessive weight gain according to 2009 IOM GWG guidelines. [40] Offspring BMIZ was calculated using a SAS Program provided by CDC.

STUDY POPULATION

For Aim 1, the analytical sample was from the Y6FU database linked with IFPS II database. In 2012, 2,958 mothers qualified for the Y6FU after applying the following exclusion criteria: death of the infant or mother, being diagnosed with a condition likely to affect infant feeding, or living in a geographic area to which the post office stopped delivering mail due to the Gulf Coast hurricanes of 2005. However, only 52.1% of qualified mothers completed the questionnaire, resulting in the sample size of 1,542 mother-child pairs. We excluded the children with biologically implausible values of BMIZ (n=25) and height-for-age Z score HAZ (n=21) according to the CDC's recommendation for children at age six which were specified as follows: BMIZ <-4 or >5 and HAZ <-5 or >3,The Centers for Disease Prevention and Control. A SAS program for the 2000 CDC Growth Charts. http://www.cdc.gov/nccdphp/dnpao /growthcharts /resources/sas.htm. Accessed on May 15, 2016. missing values of BMIZ (n=134), missing data on maternal prepregnancy BMI (n=19) and GWG (n=47), resulting in a final analytical sample size of 1,296 mother-children pairs. Figure 3.2 displayed the flowchart of study participants for Aim1.

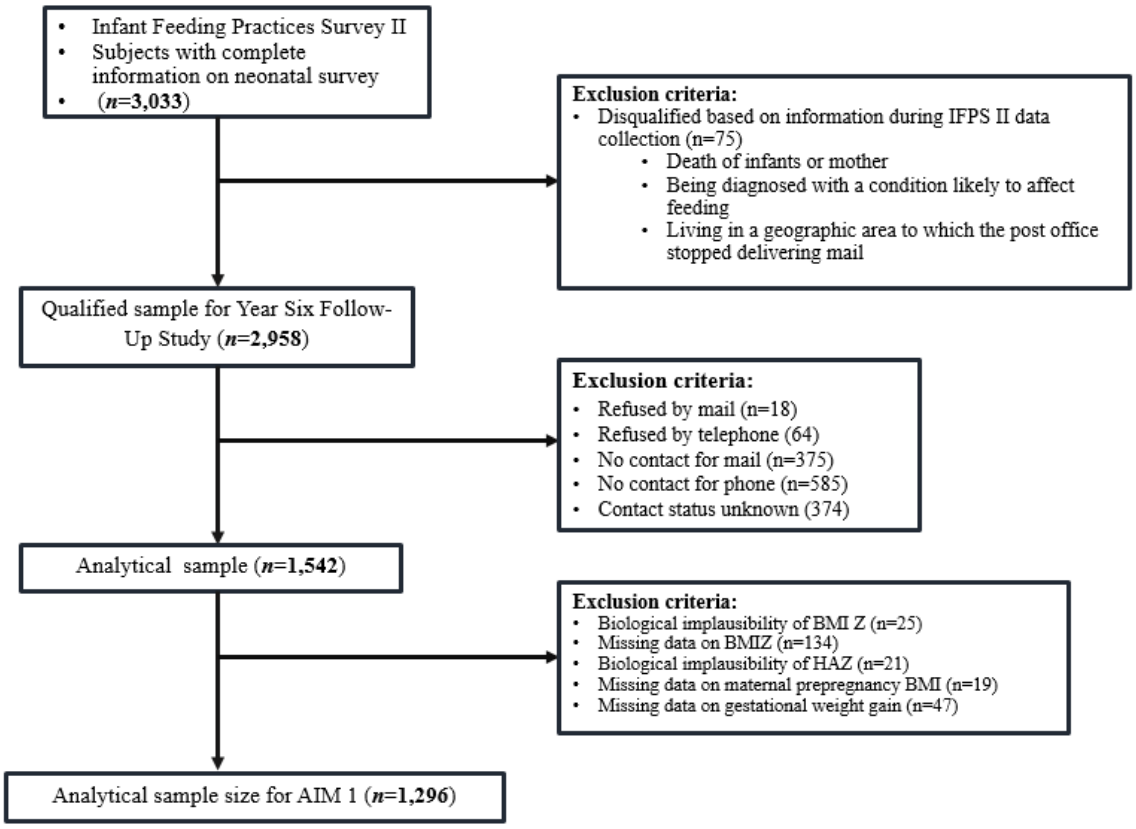

Figure 3.2 The flowchart of study participants for Aim 1

MEASURES

Exposures: The main exposure variables were maternal prepregnancy BMI and GWG. Maternal prepregnancy height and weight were collected via maternal report through prenatal questionnaire. Prepregnancy BMI was coded as a continuous variable as well as a categorical variable as follows: underweight (<18.5 kg/m^2), normal weight (BMI: 18.5-24.9kg/m^2), overweight (BMI: 25.0-29.9 kg/m^2), or obese (BMI 30.0 kg/m^2).[61] Maternal GWG was self-reported in pounds on the basis of neonatal questionnaire administered after three weeks' delivery. The question regarding GWG was defined as "How much weight did you gain during this pregnancy in pounds?" Furthermore, the total GWG was coded according to the 2009 Institute of Medicine (IOM) guidelines as *inadequate*, *adequate*, and *excessive*.(Yaktine and Rasmussen 2009)

Outcomes: Our primary outcome was offspring BMIZ at age 6. Both weight and height for children at 6 years were measured by the mothers using a standard tape according to instructions included in the Y6FU questionnaire.(Fein et al. 2014b) Then, BMI was calculated as weight (kg) divided by height in square meters. BMIZ score is a commonly used measure of relative weight adjusted for child age and sex among pediatric population. In our study, it was calculated using a SAS Program for the 2000 Centers for Disease Control and Prevention (CDC) Growth Charts. The Centers for Disease Prevention and Control. A SAS Program for the 2000 CDC Growth Charts. http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. Accessed on Novermber 11, 2015. The age and sex-specific Z-scores are calculated using the LMS method. The specific formula is Z = [((value / M) **L) – 1] / (S * L), where 'value' is the child's BMI, weight, height, etc. The L(lambda), M(mu) and S(sigma) are three smooth age specific curve parameters. The M and S curves correspond to the median and coefficient of variance of the variable of interest such as BMI, weight or height, whereas the L curve takes the distributional skewness into consideration. The L, M, and S values were in the CDC reference data. The CDC-provided SAS macro which contains child growth reference data for age in months and sex was used to calculate specific Z-scores for height-for-age (HAZ), weight-for-age (WAZ), weight-for-length (WHZ) and BMI-for-age (BMIZ). Our secondary outcome of interest was the occurrence of being obese when children were at age 6. According to the 2000 CDC growth charts, The Centers for Disease Prevention and Control. A SAS Program for the 2000 CDC Growth Charts. http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. Accessed on Novermber 11, 2015. obesity is defined as BMI ≥ 95th percentile.

Covariates: Potential confounding variables were selected based on the findings of previous research on childhood obesity.(Guo et al. 2015, Diesel et al. 2015) A directed acyclic graph (DAG) was used to guide the selection of confounders (Figure 3.3). Maternal characteristics included age at childbirth (18-24, 25-34, 35-43), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian-pacific Islander and non-Hispanic others), maternal education (high school or less, some college, college graduate or higher), household income (i.e., % of federal poverty threshold) (<185%, 185-350%, >350%), parity (primiparous or multiparous), maternal smoking during pregnancy (yes or no), gestational diabetes in this pregnancy (yes or no), gestational duration (<37 weeks or 37 weeks) and adherence to breastfeeding recommendations. Household income was classified using the poverty guidelines published by the U.S. Census Bureau The United States Census Bureau. https://www.census.gov/hhes/www/poverty /index.html. Accessed on November 16, 2015.l in the IFPSII. Adherence to breastfeeding guidelines was created using the breastfeeding initiation, duration and exclusivity data based on the 2005 American Academy of Pediatrics (AAP) breastfeeding guidelines. Breastfeeding status was categorized into four groups: never initiated breastfeeding, initiated breastfeeding but did not exclusively breastfeed for ≥4 months, adhered to exclusivity for ≥4 months but breastfeeding duration <12 months, and adhered to both exclusivity for ≥4 months and breastfeeding ≥12 months.(Sharma, Dee, and Harden 2014, Schwalfenberg, Genuis, and Rodushkin 2013) Children's characteristics at 6 years old include sex, birth weight, days of doing physical activity in a typical week for a total of at least 60 minutes, average hours of watching television per day, and consumption of sugar-sweetened beverages (0, <1 time/week, 1 to <3 times/week, and ≥ 3 times/week).

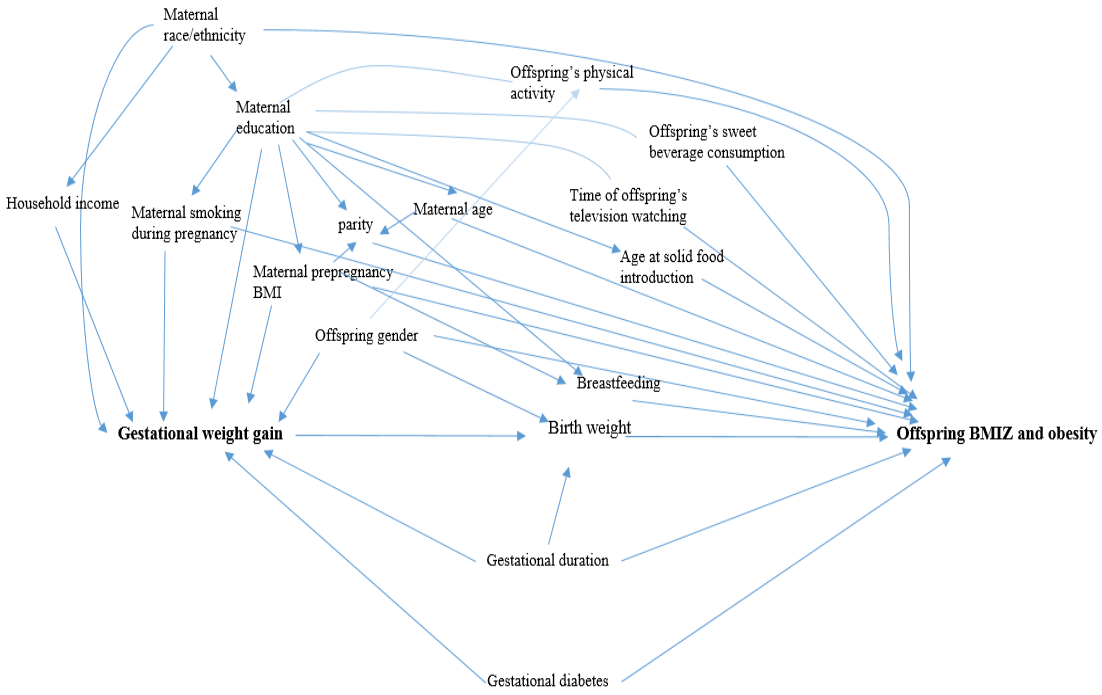

Figure 3.3 Directed acyclic graph used to select potential confounders

STATISTICAL ANALYSES

Logistic regression analysis was utilized to examine the associations of excessive weight gain during pregnancy, maternal obesity, and their potential combinations with the offspring's risk of being overweight or obese at age 6. Quantile regression was used to examine the influence of prepregnancy BMI and GWG on BMIZ across deciles of the BMIZ distribution among children at 6 years of age. As a statistical technique used to model quantiles (i.e., percentiles), quantile regression was introduced by Conker and Bassett in 1978(Koenker and Bassett Jr 1978) and has been of great interest to statistical methodologists.(Koenker 2005) However quantile regression has been underused in epidemiologic and clinical studies so far.(Laitinen, Power, and Jarvelin 2001)

Quantile regression is particularly useful when the outcome distribution is skewed and specifically when the relationship between exposure and outcome is not the same for

all quantiles of the outcome distribution. Therefore, modelling only the mean in linear regression might miss important aspects of the exposure-outcome association. Furthermore, outcome distributions conditional on exposure levels may differ not only by their means, but also (or even only) by their lower or upper percentiles. Quantile regression provides a complete picture of how covariates might influence the conditional distribution of the outcome variable by estimating different coefficients for different quantiles of the conditional distribution. Thus, it may be more informative than ordinary least square regression. In addition, quantile regression is robust to outliers and distributional assumptions. (Koenker 2005, Tequeanes et al. 2009, Laitinen, Power, and Jarvelin 2001)

Sequential modelling strategy is applied to separate out those prenatal and postnatal factors by adjusting for different sets of covariates in three different models. In Model 1, we adjusted for sociodemographic and prenatal factors such as maternal pre-pregnancy BMI, age at childbirth, race/ethnicity, education, household income, parity, smoking during pregnancy, gestational diabetes, and gestational duration. In Model 2, we additionally adjusted for early postnatal child factors such as adherence to breastfeeding recommendations, age at solid food introduction, birthweight (Model 2). And in Model 3, we additionally adjusted for children characteristics at age six including days of daily physical activity, daily screen time and weekly consumption of sugar-sweetened beverages. We considered Model 2 and Model 3 as sensitivity analyses because the additional adjusted variables are potential intermediates for the association of GWG and offspring BMI.

All the data analyses for this study were conducted using SAS software version 9.2 (SAS Institute Inc). Alpha was set up as 0.05 and $P<0.05$ was considered as statistically significant.

DATA AND METHODS FOR STUDY TWO (AIM 2)

STUDY PURPOSE, DESIGN AND RESEARCH QUESTIONS

This study identified trajectories of BMI during the first year of life and assessed the relative influence of prenatal factors (i.e. pre-pregnancy BMI and GWG) and early life factors (i.e., breastfeeding) on the identified BMI trajectories.

The following research questions and corresponding hypotheses were examined:

Q 2.1 Are there BMI trajectories during the first year of life in children?

H 2.1 The trajectories of BMI during the first year of life in children can be classified using data-driven Latent Class Growth Analysis in a sample of children with 2-5 BMI measures during the first year of life.

Q 2.2 Do maternal pre-pregnancy BMI, GWG and breastfeeding influence BMI trajectories in children during their first year of life?

H 2.2.1 Compared with children born to mothers who are normal weight, children born to mothers who are overweight or obese before pregnancy have a greater risk of being in the faster growing BMI trajectory in the first year.

H 2.2.2 Compared with children born to mothers who gain adequate weight, the children born to mothers who gain excessive weight during pregnancy have a greater risk of being in the faster growing BMI trajectory. Conversely, children born to mothers who gained inadequate weight during pregnancy have a smaller risk of being in the faster growing BMI trajectory.

H 2.2.3 Compared with children who were breastfed during the first year of life, those who were not breastfed have a greater risk of being in the faster growing BMI trajectory.

STUDY POPULATION

The current study population was only from IFPS II database. After applying the exclusion criterial set by CDC (mainly mailing issues, see Figure 3.4), the available sample sizes for infants at birth; and the 3rd, 5th, 7th, and 12th months were 3033, 2388, 2183, 2020, and 1807, respectively. Then we further excluded participants with missing values for our outcome variables such as height, weight or biologically implausible values of BMI according to WHO's recommendation for infancy, which were specified as follows: BMIZ) <-5 or >5. The resulting sample sizes were 2981, 1917, 1602, 1327 and 1111 for those time points accordingly. Among these samples, infants with different numbers of BMI measures were also calculated. For this analysis, we included participants with at least two measures of BMI, that is, an analytic sample of 2,322 children. Figure 3.4 displayed the flowchart of study participants for Aim 2.

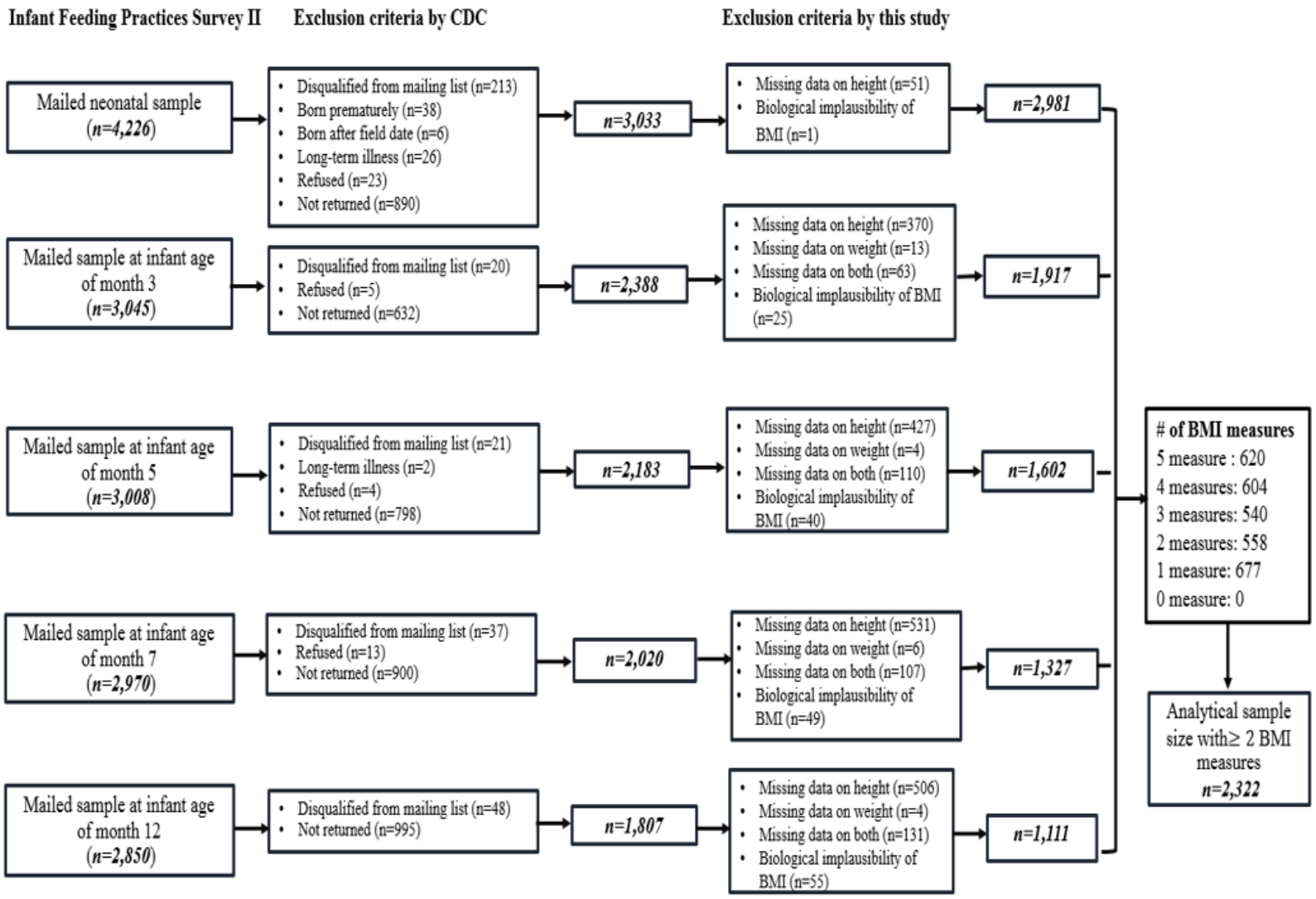

Figure 3.4 The flowchart of study participants for Aim 2

MEASURES

Exposures/Predictors

The primary predictors we considered were as follows: maternal prepregnancy BMI, gestational weight gain (GWG), and adherence to breastfeeding recommendations. Prepregnancy BMI was coded as a categorical variable as follows: normal weight (BMI: 18.5-24.9kg/m^2), overweight (BMI: 25.0-29.9 kg/m^2), or obese (BMI 30.0 kg/m^2). GWG was categorized as inadequate, adequate, and excessive based on the Institute of Medicine (IOM) guidelines for GWG. Adherence to breastfeeding guidelines was created using the breastfeeding initiation, duration and exclusivity data based on the 2005 American Academy of Pediatrics breastfeeding guidelines and categorized into four groups: never initiated breastfeeding, initiated breastfeeding but did not exclusively breastfeed for ≥4 months, adhered to exclusivity for ≥4 months but breastfeeding duration <12 months and adhered to both exclusivity for ≥4 months and breastfeeding ≥12 months.(Sharma, Dee, and Harden 2014, Schwalfenberg, Genuis, and Rodushkin 2013)

Outcome

The trajectories of BMI during the first year of life were our outcome of interest. Through postnatal questionnaires, the mothers were asked to provide their infant's weight and length as measured at their most recent doctor's visit at the time of birth and ages of 3, 5, 7 and 12 months. BMI was calculated by dividing an infant's weight in kilograms by the square of length in meters. Then the multiple measures of BMI was used by latent class growth analysis (LCGA) approach to identify distinct BMI trajectories during the first year of life.

Covariates

Previous literature of studying the infant growth trajectories of BMI and their risk factors are used to help select covariates. Maternal characteristics include age at childbirth (18-24, 25-34, 35-43), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian-pacific Islander and non-Hispanic others), maternal education (high school or less, some college, college graduate or higher), household income (<185%, 185-350%, >350%), maternal smoking (yes or no), gestational diabetes (yes or no) and gestational duration (35 to <37 or 37 weeks). Household income was classified using the poverty guidelines published by the U.S. Census Bureau.The United States Census Bureau. https://www.census.gov/hhes/www/poverty/index.html. Accessed on November 16, 2015.l Children's characteristics include sex and birth weight.

STATISTICAL ANALYSIS

First, LCGA(Jung and Wickrama 2008) was used to identify growth trajectories using serial measurements of BMI at birth, 3, 5, 9 and 12 months. The familial and environmental factors have been known to influence the shapes of growth trajectories underlying each class membership reflecting the biological and environmental characteristics of the individuals assigned to them. LCGA helped to identify distinct groups (latent classes) of infants who shared similar trajectories. This approach is different from conventional latent growth curve modeling which assumes that all individuals are drawn from a single population and that a single growth trajectory can adequately approximate the entire population. Furthermore, conventional latent growth curve models allow individual differences in development over time characterized by random slopes and random intercepts, individuals are assumed to vary around a single mean growth curve. In contrast, the LCGA method used in the current analysis relaxes

the single population assumption to allow for parameter differences across unobserved subpopulations. LCGA assumes a number of discrete classes, each having a specific functional form of the growth shape. Without a prior hypothesis regarding the number of distinct trajectories and their shapes, we modeled each possible combination of numbers of trajectories and trajectory shapes. The Bayesian Information Criterion (BIC) was used to select the number and shape of trajectories that fit the data as parsimoniously as possible.

The second step used multinomial logistic regression to examine the potential influence of prenatal and early life factors such as maternal prepregnancy BMI, GWG and adherence to breastfeeding guidelines on the distinctness of the membership among identified BMI trajectories while controlling for other covariates. Similar to Aim 1, we applied sequential modelling to separate out those prenatal and postnatal factors by adjusting for different set of covariates in three different models.

All the data analyses for this study were conducted using both M-Plus (version 5.4) and SAS software version 9.2 (SAS Institute Inc). Alpha was set up as 0.05 and $P<0.05$ was considered as statistically significant.

DATA AND METHODS FOR STUDY THREE (AIM 3)

STUDY PURPOSE, DESIGN AND RESEARCH QUESTIONS

This study examined the associations of the BMI trajectories in the first year (identified in Aim 2) with the risk of being obese among children at age 6. This study used the linked dataset of IFPS II with Y6FU, a longitudinal study design.

The following research questions and corresponding hypotheses were examined:

Q 3 Do the identified BMI trajectories during the first year of life predict the risk of children being obese at age 6?

H 3 Compared with children not being in the faster growing BMI trajectory, those in the faster growing BMI growth trajectory in the first year have a greater risk of being obese at age 6.

STUDY POPULATION

The current study population was from the Y6FU database linked with IFPS II database. In 2012, 2958 mothers qualified for the Y6FU after applying the following exclusion criteria: death of the infant or mother, being diagnosed with a condition likely to affect infant feeding, or living in a geographic area to which the post office stopped delivering mail due to the Gulf Coast hurricanes of 2005. However, only 52.1% of qualified mothers completed questionnaire and then results the sample size of 1542. The linkage of the IFPS II study with its Y6FU resulted in a sample of 1,530 children. We first excluded children with biologically implausible values of BMIZ during infancy according to WHO's recommendation for infancy during each follow-up. We further excluded children with biologically implausible values of BMIZ at age six (n=24), and HAZ (n=21) according to the CDC's recommendation for children at age six. The Centers for Disease Prevention and Control. A SAS program for the 2000 CDC Growth Charts.http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. Accessed on May 15, 2016. We further excluded children with missing data on BMIZ (n=131). Among 1,354 mother-children pairs, the sample size for children with five measurements of BMI in the first year was 405, with four BMI measurements being 316, followed by 247 (three measurements), 201 (two measurements) and 185 (one measurement). The children at age six with at least two measurements of BMI during their first year of life (n=1,169) was constructed as our analytical sample size. Figure 3.5 displayed the flowchart of study participants for Aim 3.

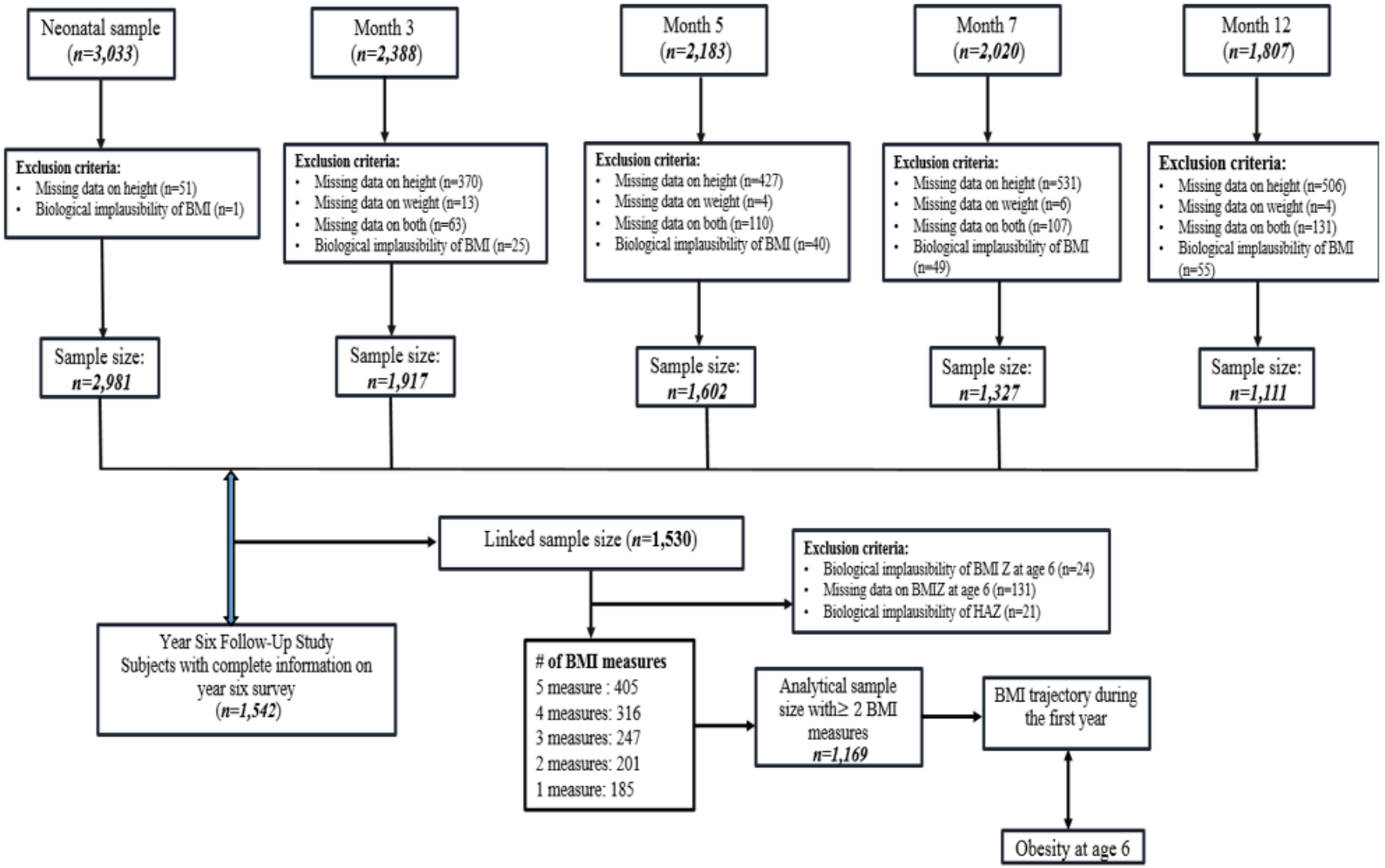

Figure 3.5 The flowchart of study participants for Aim 3

MEASURES

Exposure

Our exposure was the trajectories of BMI during the first year of life identified using LCGA in Aim 2.

Outcome

Our outcome was the occurrence of being obese when children were at age 6. According to the 2000 CDC growth charts, The Centers for Disease Prevention and Control. A SAS Program for the 2000 CDC Growth Charts. http://www.cdc.gov /nccdphp/dnpao/growthcharts/resources/sas.htm. Accessed on Novermber 11, 2015. obesity is defined as BMI ≥ 95th percentile. Both weight and height for children at 6 years were measured by the mothers using a standard tape according to instructions included in the Y6FU questionnaire. Then, BMI was calculated as weight (kg) divided by height in square meters. BMI percentile was calculated using a SAS Program for the 2000 Centers for Disease Control and Prevention (CDC) Growth ChartsThe Centers for Disease Prevention and Control. A SAS Program for the 2000 CDC Growth Charts. http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. Accessed on Novermber 11, 2015. . The age and sex-specific Z-scores/percentile are calculated using the LMS method, where L, M and S indicate three parameters of lambda, mu and sigma. The specific formula is Z = [((value / M) **L) – 1] / (S * L), where 'value' is the child's BMI, weight, height, etc. The L(lambda), M(mu) and S(sigma) are three smooth age specific curves parameters. The M and S curves correspond to the median and coefficient of variance of variable of interest such as BMI, weight or height, whereas the L curve takes the distributional skewness into consideration. The L, M, and S values were in the CDC reference data. The CDC-provided SAS macro which contains child growth

reference data for age in months and sex was used to calculate specific Z-scores for height-for-age (HAZ), weight-for-age (WAZ), weight-for-length (WHZ) and BMI-for-age (BMIZ).

Covariates

Previous literature of studying the infant growth trajectories of BMI and the risk of being overweight or obese are used to help choose potential confounding factors. Maternal characteristics include age at childbirth (18-24, 25-34, 35-43), race/ethnicity (Non-Hispanic White, Non-Hispanic Black Hispanic, Asian-Islanders and Non-Hispanic others), maternal education (high school or less, some college, college graduate or higher), household income (<185%, 185-350%, >350%), maternal smoking (yes or no), gestational diabetes (yes or no) and gestational duration (<37 weeks or 37 weeks). House hold income was classified using the poverty guidelines published by the U.S. Census Bureau. The United States Census Bureau. https://www.census. gov/hhes/www /poverty/ index.html. Accessed on November 16, 2015.l Children's characteristics at 6 years old include sex, birth weight, days of doing physical activity in a typical week for a total of at least 60 minutes, and hours of watching television.

STATISTICAL ANALYSIS

LCGA was used to identify growth trajectories using serial measurements of BMI at birth, 3, 5, 9 and 12 months. Logistic regression was applied to quantify the association between these identified BMI trajectories with the risk of being obese at 6 years-old.

All the data analyses for this study were conducted using SAS software version 9.2 (SAS Institute Inc). Alpha was set up as 0.05 and P<0.05 was considered as statistically significant.

CHAPTER 4

[1]ASSOCIATIONS OF MATERNAL GESTATIONAL WEIGHT GAIN WITH THE RISK OF OFFSPRING OBESITY AND BODY MASS INDEX Z SCORES

[1] JX Liu, NS Boghossian, EA Frongillo, B Cai, LJ Hazlett and JH Liu. To be submitted to *Pediatric Obesity.*

ABSTRACT

Background: Studies on the moderating role of maternal pre-pregnancy body weight on the associations of maternal gestational weight gain (GWG) with offspring obesity and body mass index Z scores (BMIZ) are inconclusive. Existing studies mainly focus on the upper percentiles of BMIZ distribution using logistic regression or on mean BMIZ using linear regression, which do not capture associations across the entire distribution of BMIZ.

Objectives: To examine the associations of meeting the 2009 Institute of Medicine (IOM) GWG guidelines with: 1) offspring obesity at age six years old; and 2) offspring BMIZ across the distribution of BMIZ, in the overall sample and stratifying by maternal pre-pregnancy BMI.

Methods: Data came from the longitudinal birth cohort of Infant Feeding Practices Survey II Study (2005-2007) and its Year Six Follow-Up Study (2012) (n=1,296). Logistic regression models were used to examine the associations of meeting IOM GWG guidelines and the risk of obesity in the offspring. Quantile regression models were used to explore the associations between GWG categories and offspring BMIZ across deciles of BMIZ distribution.

Results: At age six, 11% of children were obese. Children born to mothers who gained excessive weight during pregnancy had an increased risk of obesity as compared with the children born to mothers who gained adequate weight (adjusted odds ratio (AOR): 1.67, 95% confidence intervals (CI): 1.04, 2.63). The association was strengthened among

normal weight mothers (AOR: 3.50, 95% CI: 1.35, 9.08), while no association was observed among mothers who were overweight or obese before pregnancy.

Similarly, children born to mothers who gained excessive weight had higher BMIZ, which differed in magnitude across the entire distribution of BMIZ. For instance, the magnitude of increase in BMIZ associated with excessive GWG was 0.25 (0.05, 0.45) at the 20th percentile and 0.33 (0.18, 0.49) at the 60th percentile. Most of the associations of excessive weight gain with BMIZ were found among normal weight mothers. Children born to obese mothers who gained inadequate weight gain had lower BMIZ at the 10th, 50th and 60th percentiles of the BMIZ distribution.

Conclusion: Excessive GWG was associated with offspring's higher risk for obesity at age 6, which was more pronounced among mothers who were normal weight before pregnancy. Excessive GWG was also associated with higher offspring BMIZ, which was greatest at higher percentiles of offspring's BMIZ distribution. Furthermore, children born to mothers who gained inadequate weight had lower BMIZ among obese mothers.

Key words: pre-pregnancy body mass index, weight gain during pregnancy, childhood obesity, quantile regression, intergenerational relation

INTRODUCTION

Childhood obesity is a serious public health challenge. Obesity in the pediatric population tends to track into adulthood, and if unmanaged, almost half of overweight children will remain overweight or obese as adults and are at risk for obesity-related adverse health outcomes.(Lobstein et al. 2015, Fein et al. 2014b, McDonald et al. 2010, Zambrano and Nathanielsz 2013, Freedman et al. 2004, Goldschmidt et al. 2013) Reversing the obesity trend in children holds promise to minimize negative health consequences associated with adult obesity.(Goldschmidt et al. 2013, Glass and McAtee 2006)

The rising levels of childhood obesity are driven by prenatal and early life factors.(Tounian 2011, Buchan et al. 2005, Bammann et al. 2014, Dello Russo et al. 2013, Yu et al. 2013, Estevez-Gonzalez et al. 2015) Gestational weight gain (GWG) is a nutritional marker for intrauterine environment. Empirical evidence over the past four decades suggests that GWG is a modifiable risk factor and is associated with both short- and long-term health consequences in mothers and their offspring.(Wrotniak et al. 2008, Zhu et al. 2015, Hinkle et al. 2012a, Hooper, Coughlan, and Mullen 2008) According to the 2009 Institute of Medicine (IOM) guidelines, approximately 43% of U.S. women gained excessive weight during pregnancy, and this percentage can be as high as two thirds in women who are overweight or obese before pregnancy.(Yaktine and Rasmussen 2009) Additionally, excessive GWG is strongly associated with postpartum weight retention, thus increasing women's risk of being overweight or obese post-

delivery.(Siega-Riz, Evenson, and Dole 2004) These factors of maternal prepregnancy BMI and GWG might have jointly impacted the childhood obesity that tracked further adulthood.(Stuebe, Forman, and Michels 2009, Reynolds et al. 2010, Guo et al. 2015)

Recently, several studies have examined the association between GWG and the risk of obesity in the pediatric population. Findings on the association between excessive GWG and offspring obesity are mixed with null(Gillman et al. 2008, Rooney, Mathiason, and Schauberger 2011, Whitaker 2004) or positive(Oken et al. 2008, Wrotniak et al. 2008, Moreira et al. 2007, Robinson et al. 2015, Schack-Nielsen et al. 2010, Olson, Strawderman, and Dennison 2009, Jedrychowski et al. 2011, Diesel et al. 2015) associations reported. A meta-analysis summarized twelve cohort studies and concluded that excessive GWG is positively associated with offspring's obesity in childhood.(Tie et al. 2014) Associations of inadequate maternal GWG with offspring obesity are inconclusive with findings being negative,(Fraser et al. 2010) null(Guo et al. 2015, Olson, Strawderman, and Dennison 2009, Stuebe, Forman, and Michels 2009, Wrotniak et al. 2008, Oken et al. 2008) or positive.(Stuebe, Forman, and Michels 2009) Furthermore, only a few studies have reported the results stratifying by maternal pre-pregnancy BMI status,(Wrotniak et al. 2008, Guo et al. 2015, Olson, Strawderman, and Dennison 2009, Stuebe, Forman, and Michels 2009, Diesel et al. 2015) or the associations were only reported in sub-groups such as underweight,(Wrotniak et al. 2008) normal weight,(Diesel et al. 2015) overweight or obese mothers.(Guo et al. 2015, Olson, Strawderman, and Dennison 2009, Stuebe, Forman, and Michels 2009) Overall, these

studies indicated that the association between GWG and childhood overweight or obesity may vary by the mother's pre-pregnancy BMI status.

Almost all existing studies of BMIZ as a continuous outcome investigated the impact of maternal GWG on the mean value of their offspring BMIZ. The findings are also mixed(Branum et al. 2011, Lawlor et al. 2011, Hinkle et al. 2012a, Schack-Nielsen et al. 2010, Beyerlein, Nehring, Rzehak, Heinrich, Muller, et al. 2012, Guo et al. 2015) with some indicating that the association might vary according to maternal pre-pregnancy BMI.(Hinkle et al. 2012a, Beyerlein, Nehring, Rzehak, Heinrich, Muller, et al. 2012, Guo et al. 2015) Nevertheless, existing studies mainly focus on the BMIZ upper centiles using logistic regression or the mean using linear regression, which do not capture associations across the entire distribution of BMIZ. Additionally, covariates might affect BMIZ differently at different deciles of BMIZ. Thus, the objectives of this study were to examine the association of meeting the IOM GWG guidelines with 1) offspring obesity and 2) offspring BMIZ across the deciles of BMIZ at age six. For each association, we examined the potential moderating roles of maternal pre-pregnancy BMI in the associations.

SUBJECTS AND METHODS

Study population

Data came from the Infant Feeding Practices Survey II (IFPS II) linked with its Year Six Follow-Up (Y6FU) study sponsored by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC). The IFPS II study was a

longitudinal survey of ~5,000 pregnant women recruited in the third trimester and followed up until their offspring reached one year old during the period of 2005-2007. A total of 1,542 mother-child pair had completed Y6FU study visit in 2012 when their children reached six years old. The designs of the IFPS II and Y6FU have been described in details elsewhere.(Ding et al. 2006, Fein et al. 2014a) Briefly, the inclusion criteria for IPFS II included: mothers were at least 18 years old and had a full or nearly full-term (≥35 weeks) singleton birth with birth weight being of at least 2.25 kg. For Y6FU study, the children were excluded if they had incomplete information on neonatal (month 1) questionnaire in the IFPS II, were diagnosed with a condition likely affecting feeding, and were living in a geographic area to which the postal service was not available due to the Gulf Coast hurricanes of 2005.(Fein et al. 2014a) In this study, we excluded participants with missing values on pre-pregnancy BMI (n=19), GWG (n=47), child's weight and height (n=134) at age 6. We also excluded children with biologically implausible values of BMIZ (n=25) at age 6, which were defined as -4 or 8 based on CDC's recommendations.The Centers for Disease Prevention and Control. A SAS Program for the 2000 CDC Growth Charts. http://www.cdc.gov /nccdphp/dnpao/ growthcharts/resources/sas.htm. Accessed on Novermber 11, 2015. This resulted in 1,296 mother-child pairs in our analytical sample. The flowchart of deriving this analytical sample was illustrated in Figure 4.1.

Exposures

The main exposure of interest was maternal weight gain categories according to the 2009 IOM GWG guidelines: inadequate, adequate, or excessive.(Yaktine and Rasmussen 2009) Maternal pre-pregnancy height and weight were collected via maternal report. We categorized pre-pregnancy BMI in kg/m^2 according to the World Health Organization(Organization 2015) cut-off points: underweight (BMI<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), or obese (30.0). Maternal total GWG in pounds was self-reported in neonatal questionnaire administered three weeks after delivery. We defined the GWG adequacy ratio as observed total GWG divided by the 2009 IOM-recommended GWG corresponding to the gestational age at delivery given pre-pregnancy BMI category. The detailed calculation procedures by maternal pre-gravid status are provided elsewhere.(Bodnar et al. 2010, Liu et al. 2014) Furthermore, we categorized the GWG adequacy ratio as inadequate, adequate and excessive.

Outcomes

The main outcome variables were offspring's obesity and BMIZ at age six. In the Y6FU questionnaire, mothers were sent a measuring tape and instructions on how to measure their child's height. They were asked to weigh their child using the scale without shoes and measure their height using the tape. BMI was calculated as weight (kg) divided by height in square meters. The sex-and age-specific BMIZ and percentiles were calculated using SAS programs provided by the CDC.The Centers for Disease Prevention and Control. A SAS Program for the 2000 CDC Growth Charts.

http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. Accessed on Novermber 11, 2015. Obesity was defined as sex- and age-specific BMI ≥ 95th percentile according to the 2000 CDC growth charts.The Centers for Disease Prevention and Control. A SAS Program for the 2000 CDC Growth Charts. http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. Accessed on Novermber 11, 2015.

Covariates

IFPSII's prenatal questionnaire included information on maternal socio-demographic and reproductive factors such as mother's age at childbirth, race/ethnicity, education, household income, parity, smoking during pregnancy, gestational diabetes, and gestational age at delivery. Household income was expressed as percent of federal poverty level using the poverty guidelines published by the U.S. Census Bureau.The United States Census Bureau. https://www.census.gov/hhes/www/poverty/index.html. Accessed on November 16, 2015.l Children's sex and birthweight were reported by their mothers through the neonatal questionnaire. Data on infant feeding practices including breastfeeding and age at solid food introduction were reported by their mothers in 10 postnatal questions at ages 1, 2, 3, 4, 5, 6, 7, 9, 10.5 and 12 months of life. For those who reported still breastfeeding at the last IFPS II questionnaire (12 months), breastfeeding duration data reported in Y6FU were used. Adherence to breastfeeding guidelines was further created using the breastfeeding initiation, duration and exclusivity data based on the 2005 American Academy of Pediatrics (AAP) breastfeeding guidelines. Similar to

previous studies using IFPS II, age at solid food introduction was calculated as the midpoint between the child's age when the mother reported no solid food consumption and when she first reported her child had consumed solid foods in the previous 7 days on the basis of 10 postnatal survey questionnaires.(Barrera et al. 2016, Luccioli et al. 2014) Children's characteristics at age six were reported by their mothers through the Y6FU questionnaire.

Statistical analyses

Descriptive statistics for maternal and offspring characteristics by GWG categories and offspring's BMIZ deciles were summarized as means (standard deviations) for continuous variables and percentages for categorical variables. Chi-square tests were used to compare categorical variables and analysis of variance (ANOVA) was used for continuous variables.

We used logistic regression models to examine the associations of GWG categories with the offspring's obesity at age 6 expressed as odds ratios (ORs) and 95% confidence intervals (CIs). We used quantile regression models to examine the associations of GWG categories with offspring BMIZ across decile intervals of offspring BMIZ at age 6, which were represented by the coefficients and 95% CIs at each decile. The covariates adjusted in the models included maternal pre-pregnancy BMI (<18.5, 18.5-24.9, 25.0-29.9 and 30.0 kg/m^2), age at childbirth (18-24, 25-34, 35), race/ethnicity (non-Hispanic White, non-Hispanic black, Hispanic, Asian/Pacific Islander and other), education (high school or less, some college, college graduate or higher), household

income as percent of federal poverty level (<185%, 185-350%, >350%), parity (primiparous or multiparous), smoking during pregnancy (yes or no), gestational diabetes (yes or no), gestational duration in weeks, adherence to breastfeeding recommendations (never initiated breastfeeding; initiated breastfeeding but did not exclusively breastfeed for ≥4 months; adhered to exclusivity for ≥4 months but breastfeeding duration <12 months; and adhered to both exclusivity for ≥4 months and breastfeeding ≥12 months), birth weight for gestational age(Oken et al. 2003) (small-for-gestational age (SGA), adequate-for-gestational age (AGA) and large-for-gestational age (LGA)), age at solid food introduction (<4, 4 to <6, and ≥6 months). Children's characteristics at age six included: number of days with physical activity ≥ 60 minutes (0, 1-3, and >3 days), duration of daily screen time (0, < 60, and ≥ 60 min) and weekly consumption of sugar-sweetened beverages (0, <1, 1 to <3, and >3 times). A separate category was created to represent the missing data in covariates.

We evaluated potential moderation by conducting stratified analyses according to maternal pre-pregnancy BMI status, and we also tested the moderation using multiplicative interaction terms in multivariable models. Likelihood ratio test was used for logistic models while Wald test was used for quantile regression models. Given the small proportion of women who were underweight (2.9%), these women were not included in the stratified analysis. Model 1 was a crude model that did not adjust for any covariates. In Model 2, we adjusted for potential confounders including maternal pre-pregnancy BMI, age at childbirth, race/ethnicity, education, household income, parity,

smoking during pregnancy, gestational diabetes, and gestational duration. In Model 3, we additionally adjusted for potential mediating factors from birth and early feeding practices including birth weight for gestational age, adherence to breastfeeding recommendations, and age at solid food introduction. In Model 4, on the top of Model 3, we further adjusted for potential mediators from child's characteristics at age six years-old including days of daily physical activity, daily screen time, and weekly consumption of sugar-sweetened beverages. We considered results in Model 3 and Model 4 as mediation analysis because the additional adjusted variables were potential intermediates for the association of GWG and offspring BMI. A directed acyclic graph (DAG) was used to guide the selection of confounders and mediators (Figure 4.5).

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary NC) and R software version 3.2.4. SAS procedure PROC QUANTREG was used for quantile regression analysis. $P<0.05$ was considered as statistically significant.

RESULTS

Sample characteristics

Fifty-six percent of women gained excessive weight during pregnancy and 54% were overweight or obese before pregnancy (Table 4.1). Moreover, 86% of the women were non-Hispanic White, 48% had college or higher education, 7% were smokers during pregnancy, and 8% had gestational diabetes. Nearly 9 out of every 10 children had been breastfed for some duration; however only 1 in 5were exclusively breastfed for 4 months. Eighty-one percent of children had a birth weight appropriate for the gestational age at

delivery, while 7% and 12% were small- or large-for-gestational age, respectively. The majority of children had more than 3 days of daily physical activity for more than 60 minutes at age six (86%), averaged more than 60 minutes of daily screen time (77%), and consumed sugar-sweetened beverages once per week (68%). The variables which were significantly associated with GWG categories were parity, maternal pre-pregnancy BMI, gestational diabetes, gestational age, and children's birth weight. Across the deciles of offspring BMIZ distribution, we observed significant differences for maternal race/ethnicity, marital status, education, household income, pre-pregnancy BMI, infant sex, birthweight for gestational age, daily screen time, and weekly consumption of sugar-sweetened beverages (Table 4.4).

Associations of GWG categories with offspring obesity at age six

At age six, 11% of these children were obese. The percentages of obese children born to mothers who gained inadequate, adequate or excessive weight during pregnancy were 12.9%, 7.1% and 12.5%, respectively (Table 4.1). The children born to normal weight mothers who gained adequate weight during pregnancy had the lowest percentage of obesity at age six in our study sample (2.03%) while the children born to obese mothers who gained inadequate weight had the highest percentage of obesity at age six (20%) (Figure 4.2).

In the crude regression model, compared with mothers who gained adequate weight during pregnancy, those who gained inadequate or excessive weight had increased odds of their offspring being obese [OR=1.93 (95% CI: 1.10, 3.39) and OR=1.84 (1.17,

2.90), respectively] (Table 4.2). After adjusting for maternal socio-demographic and reproductive factors in model 2, the association of maternal inadequate weight gain during pregnancy with obesity at age six became insignificant (adjusted OR (AOR): 1.35, 95% CI: 0.75, 2.44)), while the positive association of excessive weight gain with obesity was maintained (AOR: 1.67, 95% CI: 1.04, 2.63). Compared with ORs in Model 2, the ORs in Model 3 were significantly attenuated and no significant associations were observed. In Model 4, further adjusting for children's characteristics at age six, the ORs were slightly changed from Model 3 (Table 4.2).

We further performed a stratified analysis according to the women's pre-pregnancy BMI status, despite the insignificant likelihood ratio test statistic for interaction term (p=0.25). Among normal weight mothers, women who gained excessive weight during pregnancy had increased odds of their offspring being obese at age six. ORs (95% CIs) in Models 2, 3 and 4 were 3.50 (1.35, 9.08), 3.59 (1.34, 9.63), and 3.06 (1.19, 7.84), respectively, compared with women who gained adequate weight during pregnancy (Figure 4.3). The association was not significant among women who were overweight or obese before pregnancy.

Association of GWG with offspring BMIZ across the distribution of BMIZ

Overall, the associations between GWG categories and their offspring BMIZ were generally not constant across deciles (Table 4.3). Compared with children born to mothers who gained adequate weight during pregnancy, those born to mothers who gained excessive weight had higher BMIZ at age six (Model 2). The magnitudes of the

associations were different across deciles of the BMIZ distribution (10^{th} to 90^{th} deciles). For instance, in the 20^{th} quantile, the beta coefficient for excessive GWG was 0.25 (0.05, 0.45) whereas in the 80^{th} quantile, the coefficient was 0.30 (0.12, 0.48). After adjusting for potential mediators, the magnitudes of the associations of excessive weight gain and BMIZ across the distribution of BMIZ were diluted but not substantively (Models 3 and 4). Conversely, no differences were found between the BMIZ among children born to mothers who gained inadequate weight during pregnancy and those born to mothers who gained adequate weight across the distribution of BMIZ.

The Wald test statistic suggested that the association of GWG categories with offspring BMIZ might be different by maternal pre-pregnancy BMI at various deciles (for instance, P<0.001 for the 10^{th} quantile, P=0.008 for the 50^{th}, P=0.004 for the 60^{th}, P=0.007 for the 70^{th} and P=0.080 for the 80^{th}). We therefore performed stratified analyses by maternal pre-pregnancy BMI. The results from stratified analysis are shown in Figure 4.4 based on Model 2. In general, the associations of maternal inadequate and excessive weight gain in comparison to adequate weight gain with the offspring BMIZ distributions were not homogeneous across deciles. Overall, we observed similar pattern of heterogeneity in normal weight mothers, that is, excessive GWG was associated with higher offspring BMI Z scores and the magnitude was bigger at higher BMI Z percentile. Inadequate GWG was also associated with higher BMI Z score but they mostly were not statistically significant. Excessive GWG and inadequate GWG were not significantly associated with offspring's BMI Z in overweight or obese women, which might be due to

our small sample sizes. Exceptional cases were that inadequate GWG in obese women were associated with reduced BMI Z in the 10th (-0.81, 95% CI: -1.18,-0.44), 50th (-0.44, 95% CI: -0.85,-0.04)), and 60th (-0.42, 95% CI: -0.80,-0.03)) centiles.

DISCUSSION AND CONCLUSIONS

In this study, we investigated the associations between IOM GWG recommendations and offspring obesity at age six years overall and by maternal pregravid BMI. We found that maternal excessive GWG was positively associated with offspring obesity at age six in the overall sample and among mothers who were normal weight before pregnancy. Conversely, maternal inadequate weight gain was not associated with offspring obesity among either the overall sample or by maternal pregravid BMI status.

Our findings relating maternal excessive GWG with childhood obesity are largely in agreement with previous studies using the overall sample whereas the findings from our subgroup analysis are inconsistent with previous studies. (Oken et al. 2008, Wrotniak et al. 2008, Moreira et al. 2007, Robinson et al. 2015, Schack-Nielsen et al. 2010, Olson, Strawderman, and Dennison 2009, Jedrychowski et al. 2011, Diesel et al. 2015) Moreover, there were contradictory findings regarding the association of inadequate weight gain with childhood obesity in both the overall sample and subgroups. Wrotniak and colleagues(Wrotniak et al. 2008) in a cohort of individuals born in the 1960s reported similar findings as in our study, which is positive associations of excessive GWG with

obesity overall and null association of inadequate GWG with obesity in either overall or subgroups. However, in subgroup analysis, this study found that the positive association reported in the overall sample was stronger among mothers who were underweight before pregnancy (BMI<19.8). Another study(Beyerlein, Nehring, Rzehak, Heinrich, Muller, et al. 2012) conducted in Germany reported a positive association of excessive weight gain with offspring obesity at age 5-6 years only among underweight and normal weight mothers. In contrast, three prior studies reported that inadequate GWG was positively associated with their offspring obesity.(Crozier et al. 2010, Lawlor et al. 2011, Branum et al. 2011) The study conducted within-family analysis among siblings suggested that only inadequate weight gain rather than excessive weight gain might be associated with increased offspring BMI.(Branum et al. 2011) A more recent study conducted by Diesel and colleagues(Diesel et al. 2015) classified GWG using a novel method of maternal weight gain Z-score, and reported that excessive GWG increased the risk of offspring obesity in the overall sample. Furthermore, the positive associations were only maintained among lean mothers (pregravid BMI<25 kg/m^2). Additionally, Diesel et al suggested a nonlinear relationship between GWG and offspring obesity risk by maternal BMI. This nonlinear relation was evidently supported by another study(Stuebe, Forman, and Michels 2009) conducted among the 18-year-old daughters of women enrolled in the Nurses' Health Study II. Specifically, a U-shaped association between GWG and offspring obesity was reported, and these associations were stronger among mothers who were overweight before pregnancy. However, the small proportion of women who were

underweight (2.9%) in our study did not allow us to conduct a stratified analysis in this subgroup. Furthermore, the individual findings were summarized by a recent systematic review(Lau et al. 2014) and meta-analysis reporting that the combined OR and 95% CI for excessive weight gain was 1.43 (95% CI: 1.24-1.65) for childhood obesity among children aged 2 to 20 years, whereas no association was observed for inadequate weight gain. Yet, no findings from subgroup analysis by maternal prepregnancy BMI were provided in these systematic review and meta-analysis studies.

We additionally investigated the heterogeneous associations of these GWG categories with offspring BMIZ across the entire distribution of BMIZ overall and by maternal pregravid BMI. The overall findings were that excessive weight gain was differentially and positively associated with offspring's BMIZ across the distribution of BMIZ in overall and among normal weight mothers whereas maternal inadequate weight gain was inversely associated with certain percentiles of offspring BMIZ in total and among obese mothers.

For the continuous outcome of offspring BMIZ, most of previous research focused on the mean of BMIZ using linear regression. Ehrenthal et al. reported a positive association of inadequate GWG with BMIZ at age four, while no such association was found for excessive GWG.(Ehrenthal et al. 2013) In contrast, Hinkle and colleagues observed that excessive GWG was associated with an increase in child mean value of BMIZ at age five among normal and overweight mothers only(Hinkle et al. 2012a) while

no association was observed among underweight or obese mothers. Utilization of mean regression may miss important distributional heterogeneous associations between maternal GWG and their offspring BMIZ across the distribution of BMIZ. To the best of our knowledge, our study is one of the few focusing the distributional association of GWG and offspring BMIZ across the entire distribution of BMIZ using quantile regression analysis.(Beyerlein, Nehring, Rzehak, Heinrich, Muller, et al. 2012) Our findings are broadly consistent with findings from a German study using quantile regression(Beyerlein, Nehring, Rzehak, Heinrich, Muller, et al. 2012), which showed positive heterogeneous associations between GWG and offspring BMIZ at 5-6 years of age among mothers who were normal weight before pregnancy. However, no significant patterns were found in children of underweight, overweight and obese mothers in this Germany study. Moreover, the German study did not provide the results from quantile regression for GWG categories according to IOM GWG guidelines. Furthermore, this study only adjusted for birth weight, maternal age and maternal smoking status without taking other important confounders such as socio-economic factors into consideration. However, our study extended previous findings by demonstrating heterogeneous associations of GWG categories according to the current IOM GWG guidelines with offspring BMIZ across the BMIZ distribution. These findings of null associations of excessive GWG with BMIZ among overweight and obese mothers are to some degree in contrary to the general findings that overweight or obese mothers with excessive weight gain during pregnancy were more likely to have their children with greater mean value of

BMIZ.(Guo et al. 2015, Hinkle et al. 2012a) However, we need to be cautious to interpret these null findings, which might be due to small sample sizes and under power to be detected. Nevertheless, our findings, as indicated by another study(Schack-Nielsen et al. 2010) in terms of offspring BMI, suggested that gaining above the IOM recommended amount may not be more harmful in obese mothers than in the normal weight group. Future studies with large sample sizes are needed to verify the distributional patterns of maternal inadequate and excessive weight gain with offspring BMIZ in different populations, especially among women with high preconception BMI.

The mechanisms which explain the relationships between maternal meeting IOM GWG recommendations and offspring BMI remain unknown. The detrimental effects of maternal gaining outside range of IOM GWG recommendations on offspring obesity later in life are biologically plausible in the following aspects. First, we know body size tracks from birth across the life course, which very likely has occurred in our study but not in others,(Hochner et al. 2012, Stuebe, Forman, and Michels 2009) because the association in our study is substantively changed after the adjustment for birth weight. Second, offspring might inherit their mother's genetic predisposition to gain weight. However, as previous studies,(Oken et al. 2007, Wrotniak et al. 2008, Guo et al. 2015) we are not able to assess this possibility in our study. The third potential pathway is through shared environmental and lifestyle factors between mothers and their offspring.(Cameron et al. 2011, Santaliestra-Pasias et al. 2015) We were able to test this mechanism since our study

had comprehensive data on maternal pre- and peri-natal characteristics, as well as offspring characteristics. Significant positive correlations between maternal characteristics and offspring characteristics such as sweet beverages consumption and time of television watching were found in our study. Furthermore, after adjusting for maternal pre-and peri-natal factors, the positive association of inadequate weight gain with offspring obesity disappeared. Conversely, the magnitude of association between excessive weigh gain and obesity was diluted by 9%. Fourth, intrauterine metabolic programming and epigenetic modifications might result in persistent and adverse influences on the fetus arising from the greater delivery of glucose, amino acids and free fatty acids to the developing fetus in utero.(Taylor and Poston 2007, Fall 2011) These adverse influences might lead to permanent changes in appetite control, neuroendocrine functioning and energy metabolism in offspring.(Stoger 2008) These proposed mechanisms might be acting differently among women with different pre-pregnancy BMI status. The heterogeneous findings by maternal pre-pregnancy BMI in our study suggest that different biological mechanisms might be involved in the association of maternal GWG with offspring BMI. In other words, maternal weight gain outside of IOM recommended range might not only shift but change the BMIZ distribution across the population.

The major strength of our study is the longitudinal assessment of maternal pre- and post-natal characteristics and offspring characteristics at birth and six years. Rich

data in IFPS II and its follow-up study made it possible to control for a number of potential confounders. This study has several limitations. First, although the study population is well distributed throughout the U.S., it is not nationally representative of the U.S. population. Hence, the generalization of these findings might be compromised. Another limitation is that all data were self-reported by the child's mother. No medical records were examined to verify weight, height, and health status of children. Third, lost to follow-up at children's 6 years old might introduce bias. Compared with non-respondents, mothers who responded to Y6FU were more likely to be older, married, and white; had higher education and income; and were less likely to smoke. Children of respondents were more likely to be breastfed for a longer duration.(Fein et al. 2014a)

In conclusion, we found that excessive GWG was independently and positively associated with offspring obesity, and this association was stronger among normal weight mothers. Our study provides evidence that excessive GWG increased BMIZ differently across deciles of BMIZ distribution, which was more pronounced among normal weight mothers. Inadequate GWG may not be associated with offspring obesity. Inadequate GWG was inversely associated with BMIZ only among obese mothers. Future studies with large sample size are warranted to further investigate the GWG-obesity relationship, especially among subgroups by maternal prepregnancy BMI. Moreover, a potential nonlinear relationship between GWG and offspring obesity risk varying by maternal BMI

is worthy of further investigation. Also future studies should utilize quantile regression to examine the associational patterns of GWG –BMIZ relationship.

Table 4.1 Basic characteristics of maternal and their offspring characteristics according to 2009 Institute of Medicine gestational weight gain guidelines in a sample of Infant feeding Practice Survey II linked with its Year Six Follow-Up Study, 2004-2005 and 2012.

Variables	Total sample	Gestational weight gain			p values
	n=1296	Inadequate n=210	Adequate n=366	Excessive n=720	
Maternal Characteristics					
Age (y),%					0.548
18-24	14.2	15.2	13.7	14.2	
25-34	66.1	63.3	64.5	67.7	
≥35	19.7	21.4	21.9	18.1	
Race/ethnicity,%					0.119
Non-Hispanic White	86.3	84.8	84.2	87.8	
Non-Hispanic Black	3.1	3.3	1.9	3.6	
Hispanic	4.8	5.7	5.7	4.0	
Others	5.9	6.2	8.2	4.6	
Married,%					0.472
Yes	81.3	80.5	84.4	79.9	
Education,%					0.387
High school or less	15.3	16.9	13	15.9	
Some college	36.8	37.3	34.9	37.7	
College graduate or higher	47.9	45.8	52.1	46.4	
Household income as percent of poverty level,%					0.365
<185%	34.6	39.5	31.4	34.7	
185-350%	37.9	36.7	39.3	37.5	
>350%	27.6	23.8	29.2	27.9	
Parity, %					0.009
Primiparous	28.1	23.8	23.8	31.6	
Multiparous	71.9	76.2	76.2	68.4	
Smoking during pregnancy,%					0.623
Yes	7.1	7.7	6.0	7.5	
Prepregnancy BMI status,%					<0.001
Underweight (<18.5)	2.9	3.8	4.1	2.1	
Normal weight (18.5-24.9)	42.8	46.2	53.8	36.1	

Overweight (25.0-29.9)	27.6	14.3	21.9	34.3	
Obese (≥30)	26.8	35.7	20.2	27.5	
Gestational diabetes,%					0.002
Yes	7.6	13.4	7.7	5.9	
Gestational age (weeks)	39.3(1.2)	39.4(1.3)	39.4(1.2)	39.3(1.2)	0.039
Offspring Characteristics					
Child's sex,%					0.222
Boy	49.9	44.8	49.5	51.5	
Girl	50.1	55.2	50.5	48.5	
Birth weight for gestational age ,%					<0.001
Small for gestational age	7.3	8.6	10.1	5.4	
Appropriate for gestational age	81.2	83.7	83.1	79.6	
Large for gestational age	11.5	7.7	6.8	15	
Age at solid food introduction,%					0.602
<4 months	42.3	41.9	39.9	43.6	
4 to <6 months	48.6	48.3	49.4	48.4	
≥6 months	9.0	9.9	10.7	8.0	
*Adherence to breastfeeding recommendations,%					0.322
1	13.4	12.4	14.2	13.3	
2	65.9	70.5	61.5	66.8	
3	4.2	2.9	4.4	4.4	
4	16.5	14.3	20.0	15.4	
Days of daily physical activity≥60 min,%					0.413
<3 days	13.8	15.7	14.8	12.7	
≥3 days	86.2	84.3	85.2	87.3	
Daily screen time,%					0.494
<60 min	22.8	24.4	24.4	21.6	
≥ 60 min	77.2	75.6	75.6	78.4	
Weekly consumption of sugar-sweetened beverages,%					0.154
0	18.9	19.5	21.6	17.3	
1 time	67.8	65.7	68.2	68.2	
≥ 2 times	13.4	14.8	10.1	14.6	
Obesity at age six					0.018
Yes	11.0	12.9	7.1	12.5	

* 1: Never initiated breastfeeding; 2: Initiated breastfeeding, did not exclusively breastfeed for ≥ 4 months, duration <12 months; 3: Adherence to exclusivity for ≥ 4 months, duration <12 months; 4: Adherence to both exclusivity for ≥4 months and duration for ≥ 12 months. Categorical variables were expressed as percentages while continuous variables were expressed as mean and standard deviation.

Table 4.2. Maternal weight gain during pregnancy (according to 2009 IOM guidelines) and subsequent offspring risk of obesity at age six.

GWG categories according to GWG guidelines	Odds Ratios and 95% Confidence Intervals			
	Model 1	Model 2	Model 3	Model 4
Inadequate weight gain	1.93(1.10, 3.39)*	1.35(0.75, 2.44)	1.36(0.76, 2.45)	1.30(0.72, 2.34)
Adequate weight gain	1.00	1.00	1.00	1.00
Excessive weight gain	1.84(1.17, 2.90) *	1.67(1.04, 2.63) *	1.54(0.97, 2.44)	1.49(0.94, 2.35)

*indicates $p<0.05$

Model 1: Unadjusted model;
Model 2: Adjusted for maternal socio-demographic and reproductive factors including age at childbirth, race/ethnicity, education, household income as percent of poverty level, maternal prepregnancy BMI, parity, smoking during pregnancy, and gestational diabetes.
Model 3: Model 2+additionally adjusted for infant early life factors including birth weight for gestational age , adherence to breastfeeding recommendations, and age at solid food introduction.
Model 4: Model 3+additionally adjusted for children characteristics at age six including days of daily physical activity ≥ 60 minutes, daily screen time and weekly consumption of sugar-sweetened beverages.

Table 4.3. Quantile coefficients and 95% confidence intervals for the association of maternal GWG categories with offspring BMIZ across the distribution of BMIZ

Quantiles of BMIZ	Inadequate weight gain				Excessive weight gain			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
10th	-0.17(-0.60,0.26)	-0.32(-0.69,0.05)	-0.27(-0.59,0.06)	-0.02(-0.36, 0.32)	0.18(-0.14,0.50)	0.14(-0.13, 0.41)	-0.01(-0.25,0.23)	0.07(-0.18, 0.32)
20th	0.21(-0.12,0.54)	0.11(-0.16,0.38)	0.00(-0.25,0.25)	0.08(-0.17, 0.32)	**0.29(0.05,0.54)**	**0.25(0.05,0.45)**	0.17(-0.02,0.35)	**0.24(0.06, 0.42)**
30th	0.16(-0.09,0.40)	0.12(-0.11,0.36)	0.11(-0.09,0.32)	0.10(-0.11, 0.32)	**0.27(0.08,0.45)**	**0.30(0.11,0.47)**	**0.25(0.10,0.40)**	**0.20(0.05,0.36)**
40th	**0.33(0.09,0.56)**	0.12(-0.10,0.34)	0.16(-0.05,0.36)	0.17(-0.03, 0.36)	**0.37(0.19,0.54)**	**0.28(0.12,0.44)**	**0.21(0.06,0.36)**	**0.24(0.09, 0.38)**
50th	**0.29(0.05,0.53)**	0.16(-0.06,0.39)	**0.20(0.01,0.39)**	**0.24(0.05, 0.44)**	**0.36(0.19,0.54)**	**0.31(0.15,0.48)**	**0.24(0.10,0.39)**	**0.25(0.10, 0.39)**
60th	**0.28(0.05,0.51)**	0.10(-0.11,0.31)	0.10(-0.10,0.31)	0.12(-0.08, 0.33)	**0.39(0.22,0.57)**	**0.33(0.18,0.49)**	**0.25(0.10,0.41)**	**0.21(0.06, 0.37)**
70th	**0.27(0.02,0.51)**	0.06(-0.15,0.28)	0.02(-0.18,0.23)	0.00(-0.22, 0.22)	**0.40(0.22,0.58)**	**0.24(0.09,0.40)**	**0.17(0.02,0.33)**	**0.16(0.01, 0.33)**
80th	0.16(-0.12,0.45)	0.08(-0.17,0.32)	0.00(-0.20,0.20)	-0.05(-0.23, 0.13)	**0.48(0.26,0.69)**	**0.30(0.12,0.48)**	**0.21(0.06,0.36)**	**0.18(0.04, 0.31)**
90th	**0.41(0.10,0.73)**	-0.21(-0.48,0.06)	-0.14(-0.35,0.06)	0.00(-0.20, 0.21)	**0.36(0.13,0.59)**	0.17(-0.03,0.36)	**0.18(0.03,0.34)**	**0.31(0.15, 0.45)**

Model 1, 2, 3 and 4 adjusted the same covariates as in the logistic regression analysis

Table 4.4. Basic characteristics of maternal and their offspring characteristics across deciles of BMIZ in a sample of Infant feeding Practice Survey II linked with its Year Six Follow-Up Study, 2004-2005 and 2012.

Variables	Deciles of BMI Z distribution									
	D1 (n=129)	D2 (n=131)	D3 (n=129)	D4 (n=130)	D5 (n=129)	D6 (n=130)	D7 (n=130)	D8 (n=128)	D9 (n=130)	D10 (n=130)
Maternal Characteristics										
Age (year),%										
18-24	20(15.5)	20(15.3)	13(10.1)	19(14.6)	20(15.6)	12(9.2)	19(14.6)	17(13.3)	19(14.6)	25(19.2)
25-34	79(61.2)	82(62.6)	88(68.2)	86(66.2)	84(65.6)	89(68.5)	84(64.6)	93(72.7)	90(69.2)	81(62.3)
35	30(23.3)	29(22.1)	28(21.7)	25(19.2)	24(18.8)	29(22.3)	27(20.8)	18(14.1)	21(16.2)	24(18.5)
Race/ethnicity, %										
Non-Hispanic White	111(86.1)	109(83.2)	119(92.3)	118(90.8)	115(89.2)	104(80.0)	110(84.6)	116(90.6)	109(83.9)	107(82.3)
Non-Hispanic Black	3(2.3)	7(5.3)	1(0.8)	0	2(1.6) 7(5.4)	1(0.8)	4(3.1)	3(2.3)	8(6.2)	11(8.5)
Hispanic	6(4.7)	4(3.1)	3(2.3)	5(3.9)	5(3.9)	11(8.5)	6(4.6)	5(3.9)	7(5.4)	8(6.2)
Others	9(7.0)	11(8.4)	6(4.7)	7(5.4)		14(10.8)	10(7.7)	4(3.1)	6(4.6)	4(3.1)
Married,%	101(78.3)	104(79.4)	115(89.2)	108(83.1)	113(87.6)	111(85.4)	109(83.9)	104(81.3)	99(76.2)	89(68.5)
Education, %										
High school or less	22(17.9)	20(16.5)	13(10.1)	19(15.2)	14(11.1) 40(31.7)	12(9.4)	11(9.0)	19(15.3)	26(20.5)	34(27.9)
Some college	51(41.5)	36(29.8)	47(36.4)	41(32.8)	72(57.1)	49(38.6)	44(36.1)	52(41.9)	47(37.0)	52(42.6)
College graduate or Higher	50(40.7)	65(53.7)	69(53.5)	65(52.0)		66(52.0)	67(54.9)	53(42.7)	54(42.5)	36(29.5)
Household Income,%										
<185%	53(41.1)	40(30.5)	42(32.6)	36(27.7)	43(33.3)	45(34.6)	35(26.9)	49(38.3)	40(30.8)	65(50.0)
185-350%	41(31.8)	48(36.6)	46(35.7)	53(40.8)	45(34.9)	57(43.9)	61(46.9)	48(37.5)	55(42.3)	37(28.5)
>350%	35(27.1)	43(32.8)	41(31.8)	41(31.5)	41(31.8)	28(21.5)	34(26.2)	31(24.2)	35(26.9)	28(21.5)
Parity,%										
Primiparous	34(26.4)	40(31.2)	29(22.8)	38(29.2)	48(37.8)	39(30.5)	33(26.2)	31(25.0)	33(26.2)	33(25.6)

Multiparous	95(73.6)	88(68.8)	98(77.2)	92(70.8)	79(62.2)	89(69.5)	93(73.8)	93(75.0)	93(73.8)	96(74.4)
Smoking during pregnancy,%	11(8.5)	9(6.9)	5(3.9)	9(6.9)	7(5.5)	8(6.2)	8(6.3)	8(6.3)	12(9.2)	15(11.5)
Prepregnancy BMI status, %										
Underweight	14(10.9)	4(3.1)	4(3.1)	1(0.8)	3(2.3)	3(2.3)	4(3.1)	2(1.6)	2(1.5)	1(0.8)
Normal weight	58(45.0)	66(50.4)	70(54.3)	72(55.4)	70(54.3)	56(43.1)	50(38.5)	44(34.4)	37(28.5)	31(23.9)
Overweight	31(24.0)	40(30.5)	28(21.7)	29(22.3)	22(17.1) 34(26.4)	41(31.5)	41(31.5)	38(29.7)	45(34.6)	42(32.3)
Obese	26(20.2)	21(16.0)	27(20.9)	28(21.5)		30(23.1)	35(26.9)	44(34.4)	46(35.4)	56(43.1)
Gestational diabetes, %	4(3.1)	7(5.3)	7(5.4)	14(10.8)	14(10.9)	9(6.9)	11(8.5)	7(5.5)	9(6.9)	16(12.3)
Gestational duration (weeks)	39.2(1.2)	39.4(1.2)	39.4(1.1)	39.4(1.4)	39.1(1.3)	39.3(1.2)	39.3(1.1)	39.4(1.2)	39.4(1.3)	39.5(1.2)
Adherence to breastfeeding recommendations,%										
Never initiated	20(15.5)	21(16.0)	20(15.5)	16(12.3)	10(7.8)	20(15.4)	18(13.9)	9(7.0)	18(13.9)	22(16.2)
Initiated, did not exclusively breastfeed for ≥4 months	82(63.5)	80(61.1)	72(55.8)	87(66.9)	90(69.8)	84(64.6)	85(65.4)	94(73.4)	88(67.7)	92(70.8)
Adherence to exclusivity for ≥4 months, duration<12 months	5(3.9)	6(4.6)	5(3.9)	5(3.9)	3(2.3)	8(6.2)	11(8.5)	3(2.3)	5(3.9)	3(2.3)
Adherence to both exclusivity for ≥4 months and duration for ≥12 months	22(17.1)	24(18.3)	32(24.8)	22(16.9)	26(20.2)	18(13.9)	16(12.3)	22(17.2)	19(14.6)	13(10.0)
Offspring Characteristics										

Infant gender, %										
Boy	76(58.9)	59(45.0)	62(48.1)	76(58.5)	59(45.7)	54(41.5)	65(50.0)	70(54.7)	57(43.9)	68(52.3)
Girl	53(41.1)	72(55.0)	67(51.9)	54(41.5)	70(54.3)	76(58.5)	65(50.0)	58(45.3)	73(56.2)	62(47.7)
Birth weight for gestational age, %										
SGA	16(12.4)	14(10.7)	8(6.2)	10(7.7)	8(6.2)	4(3.1)	10(7.7)	8(6.3)	9(6.9)	7(5.4)
AGA	103(79.8)	112(85.5)	106(82.2)	105(80.8)	116(89.9)	111(85.4)	101(77.7)	103(81.1)	97(74.6)	98(75.4)
LGA	10(7.8)	5(3.8)	15(11.6)	15(11.5)	5(3.9)	15(11.5)	19(14.6)	16(12.6)	24(18.5)	25(19.2)
Age at solid food Introduction,%										
<4 months	59(49.2)	51(41.5)	31(26.3)	54(42.9)	42(34.7)	50(40.3)	49(40.5)	55(46.2)	59(46.8)	65(54.6)
4 to <6 months	53(44.2)	59(48.0)	77(65.3)	59(46.8)	66(54.5)	61(49.2)	63(52.1)	55(46.2)	56(44.4)	43(36.1)
≥6 months	8(6.6)	13(10.6)	10(8.5)	13(10.3)	13(10.7)	13(10.5)	9(7.4)	9(7.6)	11(8.7)	11(9.2)
Daily physical activity ≥ 60 min,%										
3 days	23(17.8)	16(12.3)	21(16.3)	20(15.4)	22(17.2)	12(9.2)	18(13.9)	10(7.8)	14(10.9)	22(16.9)
≥ 3 days	106(82.2)	114(87.7)	108(83.7)	110(84.6)	106(82.8)	118(90.8)	112(86.2)	118(92.2)	115(89.1)	108(83.1)
Daily screen time ,%										
< 60 min	29(23.0)	37(28.9)	40(31.0)	32(25.0)	31(24.2)	29(22.5)	32(24.8)	21(16.7)	18(14.0)	23(18.1)
≥ 60 min	97(77.0)	91(71.1)	89(69.0)	96(75.0)	97(75.8)	100(77.5)	97(75.2)	105(83.3)	111(86.0)	104(81.9)
Weekly consumption of sugar-sweetened beverages,%										
0	27(20.9)	25(19.1)	37(28.7)	24(18.5)	20(15.6)	28(21.5)	32(24.6)	16(12.6)	17(13.1)	18(13.9)
1 time	79(61.2)	94(71.8)	85(65.9)	90(69.2)	91(71.1)	87(66.9)	79(60.8)	93(73.2)	92(70.8)	87(66.9)
≥ 2 times	23(17.8)	12(9.2)	7(5.4)	16(12.3)	17(13.3)	15(11.5)	19(14.6)	18(14.2)	21(16.2)	25(19.2)

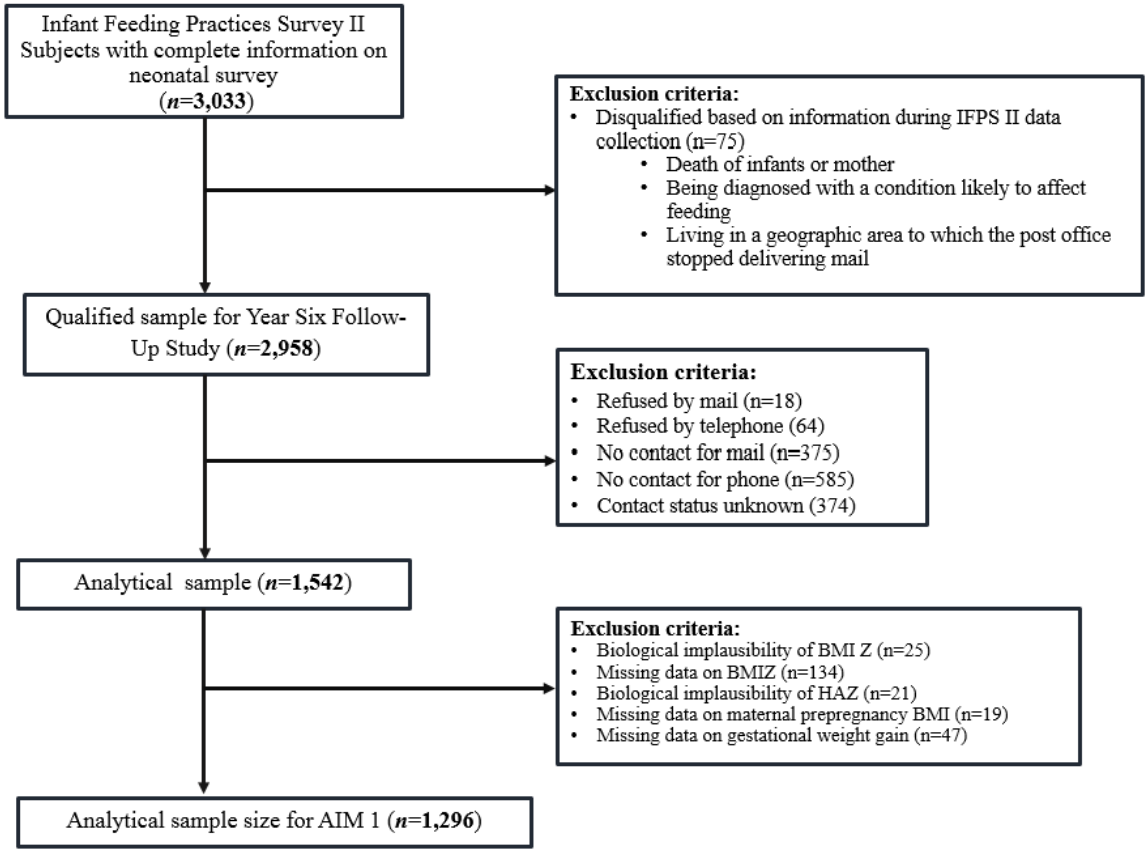

Figure 4.1. The flowchart of study participants

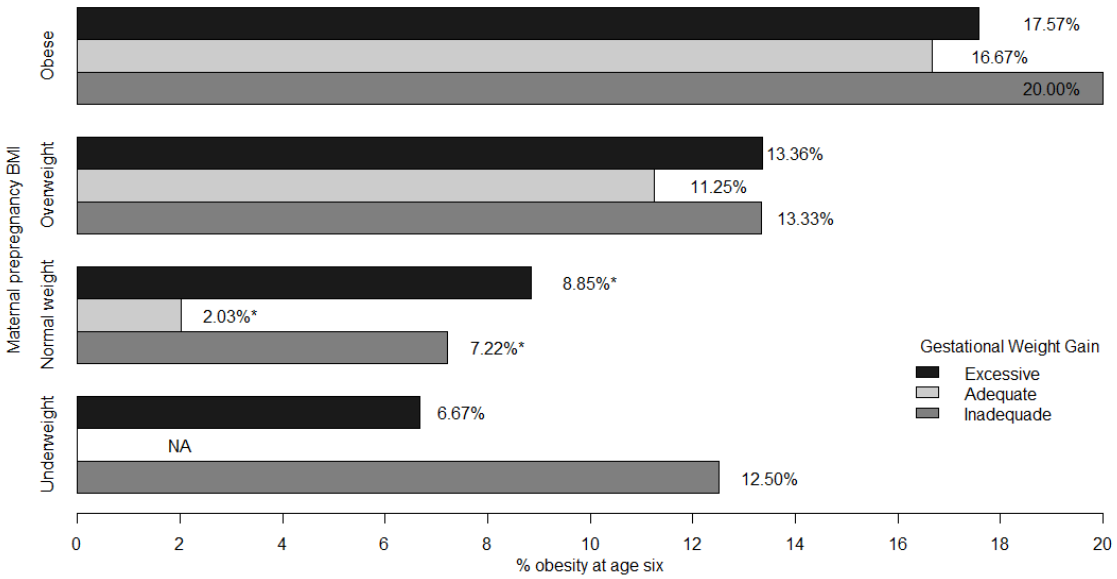

Figure 4.2. Percentage of children who were obese at age six according to 2009 IOM gestational weight gain guideline and maternal prepregnancy BMI. * indicated significant differences in offspring obesity at age six among normal weight mothers (p-value =0.0093).

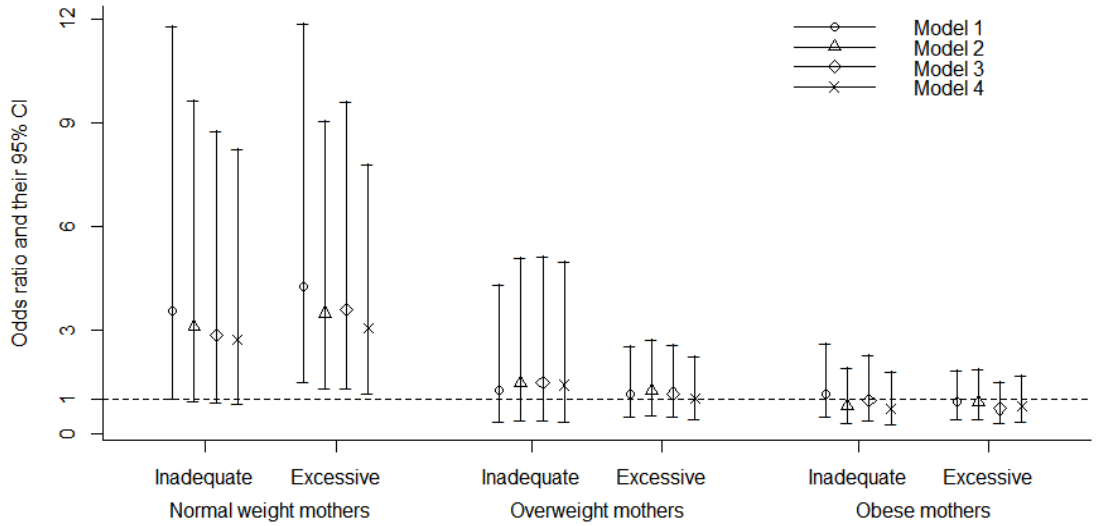

Figure 4.3. The estimated odds ratios and their 95% CIs for inadequate and excessive weight gain during pregnancy compared with adequate weight gain in four models by maternal pre-pregnancy BMI.

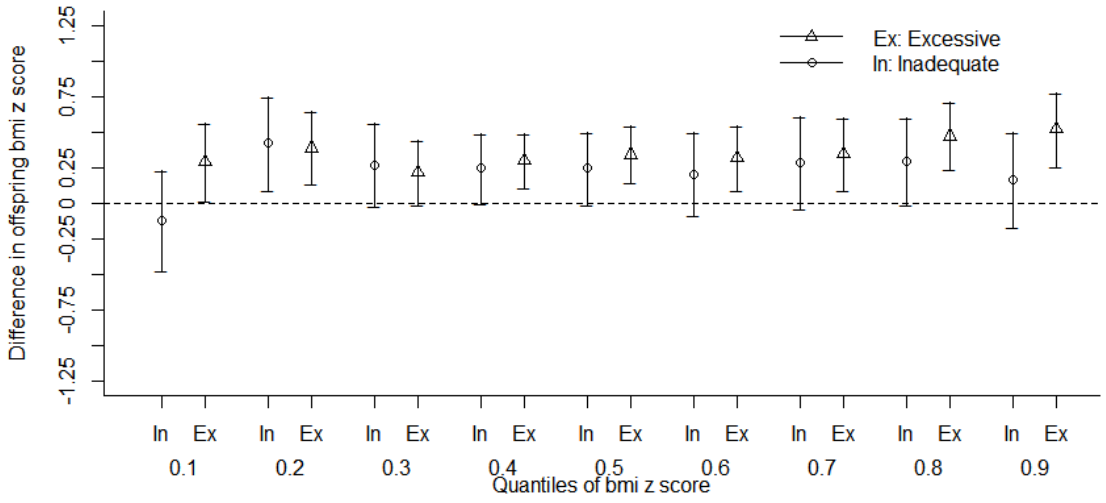

Figure 4.4 A: Association of gestational weight gain with offspring BMIZ across the distribution of BMIZ among normal weight mothers

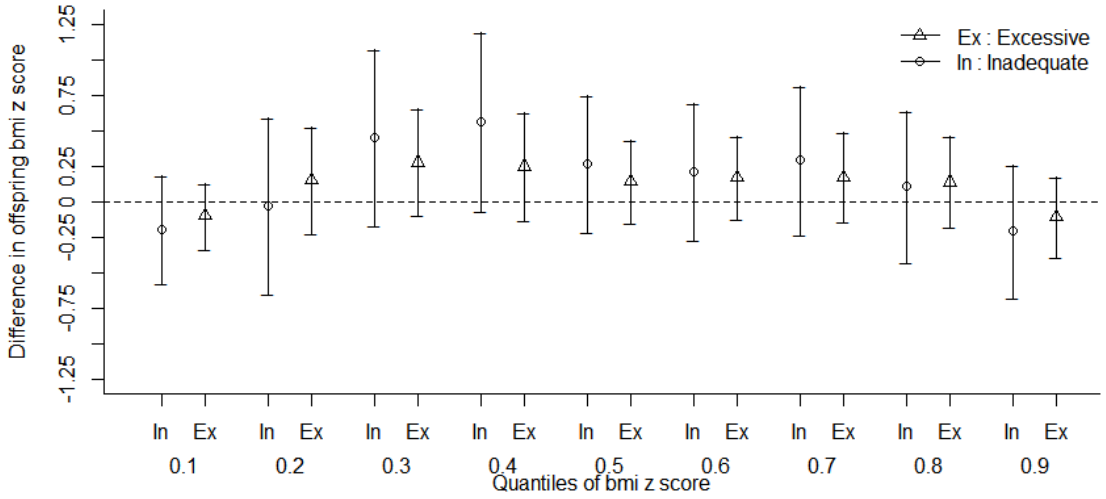

Figure 4.4 B: Association of gestational weight gain with offspring BMIZ across the distribution of BMIZ among overweight mothers

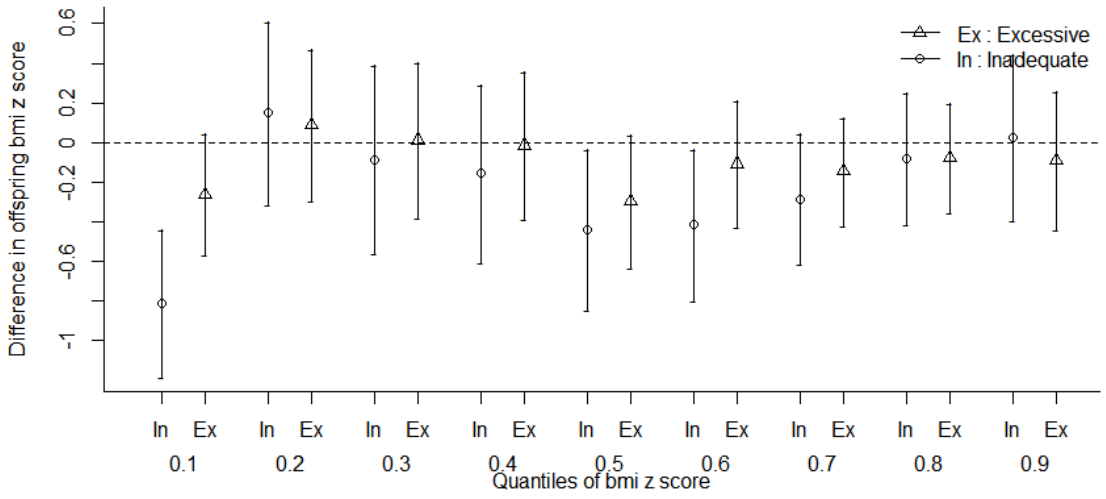

Figure 4.4 C: Association of gestational weight gain with offspring BMIZ across the distribution of BMIZ among obese mothers

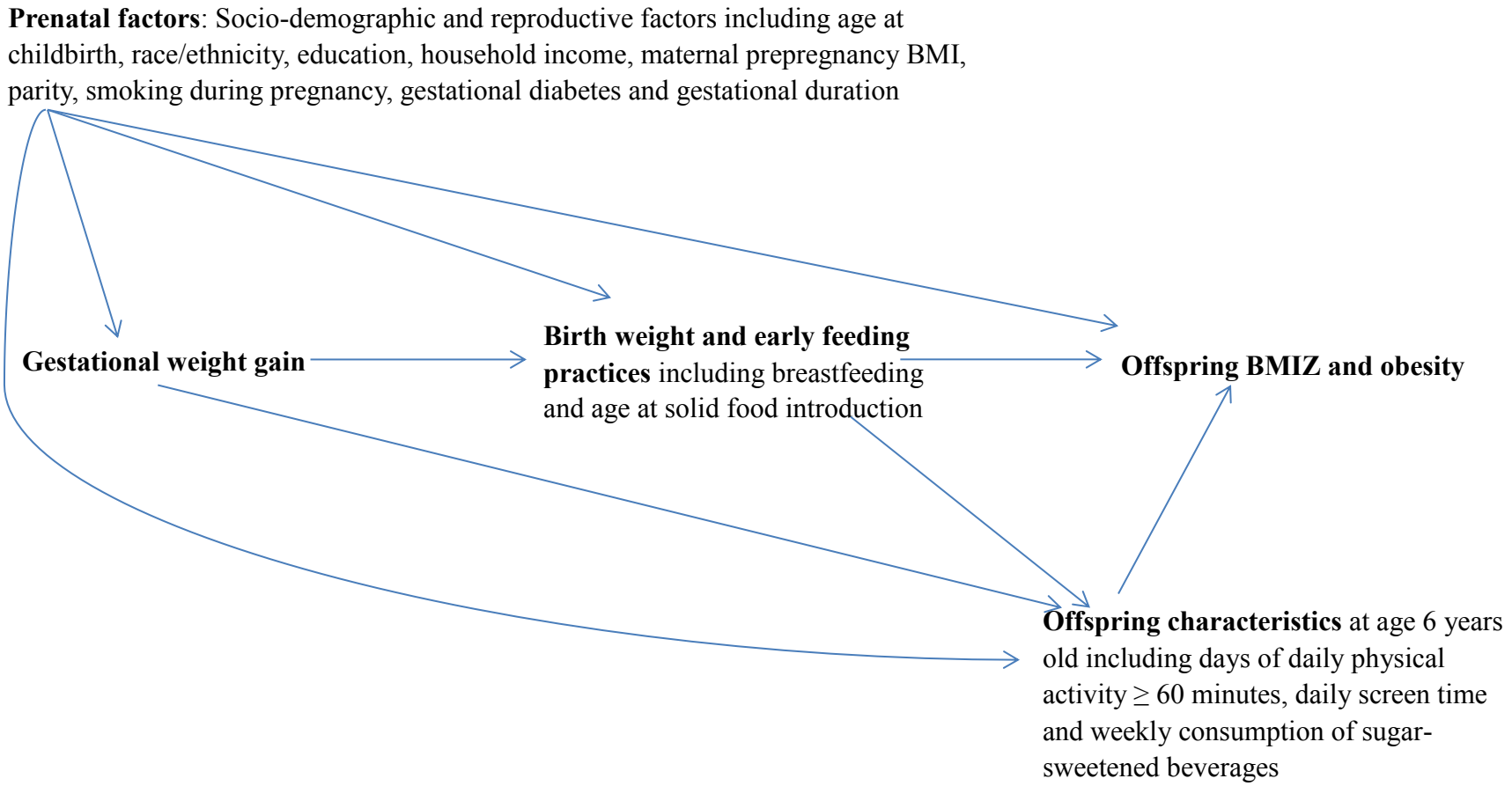

Figure 4.5: Directed Acyclic Graphs depicting possible causal pathways for gestational weight gain, offspring BMIZ and obesity at age six years

CHAPTER 5

[2]GROWTH TRAJECTORIES OF BODY MASS INDEX DURING THE FIRST YEAR OF LIFE AND THEIR DETERMINING FACTORS

[2] JX Liu, JH Liu, EA Frongillo, NS Boghossian, B Cai and LJ Hazlett. To be submitted to *Pediatrics*

Abstract

Little is known about trajectories of body mass index (BMI) in the first year of life and the determinants of these trajectories. We used the data from the Infant Feeding Practices Survey II restricting to infants with at least two BMI measurements (n=2,320). Latent class growth analysis was used to identify distinct BMI trajectories using BMI values at birth, 3, 5, 7 and 12 months of age. Using multinomial logistic regression models, we examined the prenatal and early life predictors for the identified BMI trajectories. Three BMI trajectories were identified during the first year of life: "low-stable" (81.6%), "high-stable" (15.6%), and "rising" (2.8%) trajectories. Boys (adjusted odds ratio (AOR): 1.52; 95% CI: 1.20-1.93) and infants born to overweight mothers (AOR: 1.36, 95% CI: 1.02-1.81), Hispanic mothers (AOR: 1.92, 1.20-3.07), non-Hispanic Black mothers (AOR: 3.06, 1.83-5.14) and mothers who smoked during pregnancy (AOR: 1.48; 1.00-2.22) were more likely to have high-stable versus low-stable trajectory. Infants born to non-Hispanic Black mothers (AOR: 3.20; 1.03-9.97) were more likely to have rising trajectory versus low-stable one. Full adherence to the guidelines of the American Academy of Pediatrics for both breastfeeding exclusivity and duration significantly reduced the risk of infants being in the rising (AOR: 0.28; 0.08-0.92) versus the low-stable trajectory. Our findings suggest that distinct BMI trajectories are evident among children during the first year of life. Infants born to overweight mothers, minority mothers, and those who smoked during pregnancy had high-stable or rising BMI trajectories in early life and those who were breastfed according to guidelines were protected from being in the rising trajectory.

Child growth in early life has been recognized as a critical factor contributing to lifetime health in various populations.(Law 2005, Fisher et al. 2006, Eriksson et al. 2001, Perng et al. 2016) Increased growth following intrauterine growth retardation, known as catch-up growth, has long been associated with increased risks for obesity(Ong et al. 2000a) and insulin resistance.(Soto et al. 2003, Milovanovic et al. 2014) However, catch-up growth only affects a small fraction of all births and does not accurately summarize the variations in the rates of infancy growth in the population. Some infants might experience different growth patterns which also predispose them to long-term health risks. For example, rapid growth (defined as weight-for-age-z score 0.67 standard deviation) has been widely studied and linked to obesity later in life.(Baird et al. 2005) However, prior studies assessed weight at two time points and ignored the dynamic patterns of weight change over time. Assessing infant growth using just two time points may provide biased results particularly if the growth patterns are non-linear.

In recent years, latent growth modelling approaches have received more attention due to advances in statistical software and analytical packages. This method is particularly useful to identify homogeneous subpopulations with similar growth patterns.(Jung and Wickrama 2008, Østbye, Malhotra, and Landerman 2010) Studies focusing on characterizing trajectories of body mass index (BMI) using the data from prospective cohort studies have recently proliferated and have identified distinct BMI trajectories in early childhood through modelling raw BMI(Pryor et al. 2011, Ventura, Loken, and Birch 2009, Magee, Caputi, and Iverson 2013a, van Rossem et al. 2014), BMI Z score (Haga et al. 2012, Ziyab et al. 2014, Carter et al. 2012, Giles et al. 2015a), BMI percentage(Lane, Bluestone, and Burke 2013) and a dichotomous indicator for

being overweight or obese(Li et al. 2007a, Mustillo et al. 2003). Although BMI Z score is optimal for assessing a child's static weight status in a single occasion, the best scales for measuring weight changes are raw BMI or BMI percentage.(Cole et al. 2005, Hall and Cole 2006) To our knowledge, few studies have used raw BMI or BMI percentage. Therefore, evidence is limited regarding identifying growth BMI trajectories using appropriate BMI measure in early life, an emerging new focus of research interest.

Infant growth does not happen in isolation and distinct BMI growth patterns during infancy might contribute to future risks of adverse health consequences.(Barker 1995a) Therefore, it is critical to identify modifiable risk factors for these BMI growth trajectories. Even though factors regulating human growth during infancy are not well understood, potential determinants for growth trajectories of BMI during early childhood have been suggested from previous literature relating to both maternal characteristics and infant early life factors.(Pryor et al. 2011, Magee, Caputi, and Iverson 2013a, Haga et al. 2012)

Data specifically focused BMI growth trajectories during the first year of life are limited, and the roles of potential determining factors on infant BMI trajectories are unclear. We conducted this study to identify distinct growth trajectories of BMI among children during their first year of life and to examine the relative influence of potential determining factors on the identified trajectories.

SUBJECTS AND METHODS

Study population

Data came from the Infant Feeding Practice Survey II (IFPS II), a longitudinal survey of U.S. mothers of healthy singletons who were recruited in their third trimester and followed throughout the first year of their baby's life. During the follow-up, a total of 10 mail questionnaires were sent to mothers at approximately 1, 2, 3, 4, 5, 6, 7, 9, 10.5, and 12 months after the infant's birth. The design of the IFPS II was described in details elsewhere.(Ding et al. 2006) In brief, IPFS II data collection was conducted by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) between 2005 and 2007 through a consumer-opinion mail panel of about 500,000 households. In order to qualify for the IFPS II study, mothers had to be at least 18 years old with gestational duration of at least 35 weeks and newborns' birth weight of at least 2.25 kg. The response rates for each postnatal questionnaire varied from 63% to 83%. Figure 1 demonstrates the flowcharts to derive analytical sample for this study.

Exposures—potential determining factors

Maternal socio-demographic factors

Maternal race/ethnicity, marital status, education level and household income were collected in the demographic questionnaire. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic and non-Hispanic others. Marital status was categorized as yes or no. Education level was categorized as high school or less, some college and college graduate or higher. Household income was expressed as the percent of federal poverty level (FPL). It is the ratio of annual family income to the

appropriate poverty-threshold values used by the U.S. Census Bureau.The United States Census Bureau. https://www.census.gov/hhes/www/poverty/index.html. Accessed on May 1, 2016.

Maternal reproductive and prenatal factors

Maternal age at childbirth, smoking during pregnancy, and gestational diabetes were self-reported by women using the prenatal questionnaire. In this study, we coded maternal age as 18-24, 25-34 and 35-43. Smoking status during pregnancy was determined by the questions "*how many cigarettes on average they smoked per day*?" when the women were pregnant. If the answer was 0, women were categorized as non-smoker; otherwise they were categorized as smokers. Gestational diabetes was defined as yes or no for this pregnancy. Gestational duration was categorized as < 37 weeks or 37 weeks. Maternal pregravid weight and height were self-reported by mothers in the prenatal questionnaire. BMI was calculated by dividing weight in kilograms by the square of height in meters. Furthermore, maternal pregravid BMI was categorized as mothers with underweight (BMI<18.5), normal weight (BMI: 18.5-24.99), overweight (BMI: 25.0-29.9), or obese (BMI 30.0). Maternal gestational weight gain was self-reported by women when the infant was approximately 3 weeks old. The question regarding maternal GWG was asked as "*how much weight did you gain during this pregnancy in pounds*?" Then we converted the unit in pounds to kilograms (1 pound=0.453 kilograms). Due to the fact that total GWG varies by gestational age, we calculated the GWG adequacy ratio according to the 2009 Institute of Medicine (IOM) guidelines(Yaktine and Rasmussen 2009) and women were further categorized as

inadequate, adequate, and excessive. The detailed calculation procedures by maternal pregravid status are provided elsewhere.(Bodnar et al. 2010, Liu et al. 2014)

Offspring's early life factors

Infant feeding practices were collected using postnatal survey questionnaires during the first year of life. Based on breastfeeding initiation, duration and exclusivity data, we expressed breastfeeding information as adherence to breastfeeding guidelines which was created according to the 2005 American Academy of Pediatrics (AAP) breastfeeding guidelines(Sharma, Dee, and Harden 2014): never initiated breastfeeding, initiated breastfeeding but did not exclusively breastfeed for ≥4 months, adhered to exclusivity for ≥4 months but breastfeeding duration <12 months, and adhered to both exclusive breastfeeding for ≥4 months and breastfeeding ≥12 months.(Lin, Tu, and Zhu 2005, Schwalfenberg, Genuis, and Rodushkin 2013) Age at solid food introduction, categorized as <4, 4 to <6, and ≥ 6 months, was estimated as the midpoint between the child's age when the mother reported no solid food consumption and when she first reported her child had consumed solid foods in the previous 7 days based on of postnatal survey questionnaires completed by the mother monthly until infants reached 7 months and then completed at 9, 10 and 12 months. . Infant sex and birth weight, categorized as low birth weight (<2500 grams), normal birth weight (2500-3999 grams) and high birth weight (≥4000 grams), were reported by the mothers in the neonatal questionnaire. .

Outcome—BMI trajectory during the first year of life

Through postnatal questionnaires, the mothers were asked to provide their infant's weight and length as measured at their most recent doctor's visit and their infant's age at

the time of birth and ages of 3, 5, 7 and 12 months. BMI was calculated by dividing an infant's weight in kilograms by the square of length in meters. Sex-and age-specific BMI Z scores were calculated using SAS programs developed for infants according to the 2006 WHO Growth Charts.The Centers for Disease Prevention and Control. A SAS Program for the 2006 WHO Growth Charts. http://www.cdc.gov/ nccdphp/ dnpao/ growthcharts/resources/sas.htm. Accessed on January 11, 2016. According to WHO recommendationsThe Centers for Disease Prevention and Control. A SAS Program for the 2006 WHO Growth Charts. http://www.cdc.gov /nccdphp/dnpao/growthcharts /resources/sas.htm. Accessed on January 11, 2016., BMI Z scores (<-5 or >5) were considered as biologically implausible and were deleted from the analysis. The repeated measurements of BMI were used in growth mixture modeling (GMM) to identify distinct BMI trajectories during the first year of life. The detailed information regarding GMM was presented below.

Statistical analyses

First, GMM(Jung and Wickrama 2008) was used to identify group-based growth trajectories using serial measurements of BMI at birth, 3, 5, 7 and 12 months. In this analysis, the aim was to capture unobserved subpopulations (latent groups) of infants who share similar trajectories during their first year of life. GMM is a mixture of conventional growth models commonly used to classify individuals into distinct groups based on the individual growth trajectory patterns, where the mixture corresponds to latent trajectory classes.(Jung and Wickrama 2008, Muthén and Muthén 2000, Muthén 2004)

The conventional growth model is a random effects model,(Raudenbush and Bryk 2002) which uses a single mean trajectory to describe the growth trajectories of all individuals and allows growth factors (i.e., intercept, slope and quadratic coefficient for a quadratic curve) to vary across individuals, that is, the growth factors are allowed to be random. In contrast, GMM allows for different groups of individual trajectories to vary around different mean curves, resulting in separate growth models for each latent class, with each having its unique estimates of growth factors. GMM, often called a person-oriented approach with a focus on describing the relationships among individuals,[31] ideally fits our goal of classifying individuals into different groups based on their individual response patterns. To avoid convergence and overall model instability problems, we consider a mixture of random intercept growth models (i.e., the intercept is random and the other growth factors are nonrandom) and set the intercept variances as equal across all latent classes. M-plus version 5.1 was used for all GMM analyses.(Muthén and Muthén 2010)

We first examined the functional shapes of trajectories by fitting both linear and quadratic models with different numbers of latent classes (Table 1). The results showed that quadratic models had much smaller Bayesian information criteria (BIC) values across all models. Therefore, the rest of the analyses were based on the quadratic curve assumption. We next started with the 2-class model and kept adding an extra class until the best fitting model was found. Here the best fitting model was the model with the lowest BIC value and a significant p-value for the Lo-Mendell-Rubin (LMR) likelihood ratio test. The LMR compared the current model against the model with one less class, and a significant p-value indicates that the current model was better.(Lo, Mendell, and

Rubin 2001) Other criterion we used to select a better model included high entropy value, the interpretability of the number of classes, and no smaller total count in a class. [9]

After identifying BMI trajectories, multinomial logistic regression models were used to quantify the relative influences of potential determining factors on the distinctness of the identified BMI trajectories. Due to the small number of women within underweight category (n=68), we combined these women with women in the normal weight category before pregnancy. We created a special category for missing covariates. This procedure was performed using SAS version 9.4. $P<0.05$ was defined as significant level.

RESULTS

The study sample consisted of half boys (49.4%) and half girls (50.6%). The combined sample was used to estimate the overall BMI trajectories during the first year of life in order to increase statistical power. Table 1 compared the goodness-of-fit indices among models with different shape and different number of classes. The model 3 has relative smaller BIC with a significant LMR p-value and reasonable value of entropy. Hence, we used the three-class model as our final model to compute class memberships.

Three trajectories of BMI during the first year of life were identified and labeled as "low-stable" (81.6% of infants), "high-stable" (15.6%) and "rising" (2.8%) trajectories (Figure 1). The low-stable trajectory could be visualized as a low rate of BMI increase from birth until 7 months then a relatively flat BMI throughout the remaining of their first year of life. Infants classified in the high-stable trajectory as compared with low-stable group had a much higher rate of increase in the first 7 months of life and then decrease modestly between month 7 and month 12. The rising trajectory had similar rate of increase in the

first 3-4 months as low stable group but maintained the same rate of increase throughout the first year of life. Due to its stable increase, this curve crossed with low stable at month 3 and with high-stable at month 9.

We found that maternal race/ethnicity, marital status, education, household income, smoking during pregnancy, adherence to breastfeeding guidelines and child's sex were significantly related to BMI trajectories in bivariate analyses (Table 2). Children born to non-Hispanic white mothers were more likely to be in the low-stable BMI trajectory, while children born to non-Hispanic black mothers were more likely to be in the high-stable or rising BMI trajectory. Additionally, children born to Hispanic mothers tend to be in the high-stable trajectory. Children born to married mothers were less likely to be in the high-stable BMI trajectory. Moreover, mothers with higher educational level and higher household income level were more likely to have children in the low-stable BMI trajectory. Mothers who did not smoke during pregnancy and those who had longer duration of breastfeeding were also more likely to have children in the low-stable BMI trajectory. Compared with boys, girls were more likely to be in the low-stable trajectory.

After adjusting for maternal age at delivery, GWG, marital status, education, parity, gestational diabetes and infant's birth weight, maternal risk factors for infants being in the high-stable versus low-stable trajectory included being born to an overweight mother (adjusted odds ratio (AOR): 1.36, 95% CI: 1.02-1.81), a Hispanic mother (AOR: 1.92, 1.20-3.07), non-Hispanic black mother (AOR: 3.06, 95% CI: 1.83-5.14), and a mother who smoked during pregnancy (AOR: 1.48, 1.00-2.22) (Table 3). Additionally, children's risk factors included being born preterm (less than 37 weeks of gestation) (AOR: 2.26, 1.42-3.61) and being a male (AOR: 1.52; 1.20-1.93). Risk factors for infants being in the

rising versus low-stable trajectory included being born to a non-Hispanic black mother (AOR: 3.47, 1.24-9.72). Full adherence to the guidelines of the American Academy of Pediatrics for both breastfeeding exclusivity and duration was associated with lower odds of the infant being in the rising (AOR: 0.17, 0.05-0.57) compared to the low-stable trajectory. Maternal household income measured as the percentage of federal poverty level larger than 350% was associated with lower odds of the infant being in the rising BMI trajectory (AOR: 0.25, 0.15-0.85) versus in the low-stable category.

DISCUSSION

Infancy is a critical period of child development due to the occurrence of rapid weight gain and altered adiposity, which might shift a child's growth trajectory towards a more obese phenotype in childhood and this can further track into adulthood. Few studies have examined the heterogeneity of BMI trajectory throughout the first year of life and characterized the potential determining factors. In our study, the majority of the children in the sample had a similar BMI trajectory in infancy (81.6%), which was labeled as low-stable BMI trajectory, while 15.6% of children had a high-stable BMI trajectory and a smaller percentage of children (2.8%) were in the rising BMI trajectory. This study provided useful information on the infancy at which two distinct BMI trajectories emerged during the first year of life accounting for twenty percent of children.

A number of studies have attempted to identify the distinct BMI trajectory among childhood using latent class analysis. These studies mainly came from developed countries, namely the Netherlands,(van Rossem et al. 2014) Japan,(Haga et al. 2012) UK,(Ziyab et al. 2014) Australia,(Giles et al. 2015a, Magee, Caputi, and Iverson 2013a)

Canada(Carter et al. 2012, Pryor et al. 2011, Tu et al. 2015) and U.S.A.(Lane, Bluestone, and Burke 2013, Ventura, Loken, and Birch 2009, Li et al. 2007a, Mustillo et al. 2003) Age ranges covered in these studies varied and three studies examining the BMI trajectory commenced from birth.(Giles et al. 2015a, van Rossem et al. 2014, Haga et al. 2012) The number of trajectories identified varied from three to six, but in most cases four trajectories were found. In addition, even though previous studies demonstrated that raw BMI or BMI percentage is preferred over BMI Z score for studying weight changes in children; few studies(Pryor et al. 2011, Ventura, Loken, and Birch 2009, Magee, Caputi, and Iverson 2013a, van Rossem et al. 2014) have utilized raw BMI. To the best of our knowledge, the current study is the first to identify latent BMI trajectories during infancy using raw BMI.

Of the potential determining factors that we considered, the most important ones that differentiated between BMI trajectories during the first year of life were maternal race/ethnicity, household income, maternal pregravid weight, smoking status during pregnancy, breastfeeding practices, duration of gestation, and infant's sex. These determining factors have not been consistently reported among previous studies. In terms of maternal race/ethnicity, our findings show that children born to mothers being non-Hispanic black or Hispanic had higher odds of being in the high-stable and rising BMI trajectories as compared with those born to non-Hispanic white mothers. This finding was partially in line with a recent study(Martinson, McLanahan, and Brooks-Gunn 2015) examining maternal racial disparity in offspring BMI trajectories from ages 3 to 9 years, and another study by Li and coworkers.(Li et al. 2007a) Both studies suggested that non-white children having significantly steeper BMI growth trajectories than white children.

Our study identified higher household income as a protective factor for being in the rising BMI trajectory. Moreover, prior studies reported other socio-economic factors such as maternal or parental education as determining factors for offspring's BMI trajectory.(Magee, Caputi, and Iverson 2013b) Previous studies also reported that multiparous mothers had higher odds of their children being in the high-stable BMI trajectory compared with primiparous mothers. An Australian study(Giles et al. 2015a) found that parity (≥1 previous child) was a significant predictor of *accelerating trajectory* of BMIZ from birth until 3.5 years old.

Emerging evidence suggests that prenatal environments may have long-term effects on offspring's health. However, studies on the influence of maternal prenatal factors on their offspring BMI trajectory are limited. Our study found that a mother who smoked during pregnancy was associated with an increased risk of their children being in the high-stable BMI trajectory compared with non-smoking mothers. This finding is largely consistent with previous findings that children born to mothers who smoke during pregnancy have an increased risk of obesity in their life. (Li et al. 2007a, Ziyab et al. 2014, Carter et al. 2012, Haga et al. 2012, Magee, Caputi, and Iverson 2013a) Additionally, mothers who were overweight before pregnancy had an increased odds of children being in the high-stable BMI trajectory as compared with mothers who were under/normal weight. This finding was supported by Giles and co-workers who modelled BMIZ score using serial measures across birth, 6, 9 and 12 months, 2 and 3.5 years among 556 children. Giles et al. reported that maternal obesity in early pregnancy is the most important factor differentiating factor for BMIZ trajectories. Regarding to the role of GWG, our data did not find gestational weight gain (GWG) during pregnancy meeting IOM guidelines as a

significant factor contributing to the divergence of the BMI trajectories during infancy. In contrast to our findings, Li and his colleagues(Li et al. 2007a) reported that total GWG larger than 20.43 kg was a risk factor associated with *early onset overweight* trajectory from age 2 years followed up until 12 years.

Our findings together with data from other studies(Li et al. 2007b, Giles et al. 2015b) further highlight the potential role of child's male gender in the BMI trajectory. However, due to the relatively small sample size, we were not able to analyze the sample separately for boys and girls. In spite of numerous studies on the associations of breastfeeding with single measures of obesity in childhood and later in life, its effects on the BMI trajectory in a developmental perspective are not well-studied. On the basis of comprehensive measures of breastfeeding, our study found that adherence to breastfeeding guidelines was associated with reduced odds of being in the rising BMI trajectory in comparison to the reference trajectory. This finding was consistent with the finding from a study modelling BMI trajectories using a dichotomous indicator for being overweight.(Li et al. 2007a) Studies also have shown that children with longer duration of breastfeeding were less likely to be in the rising weight patterns.(Oddy et al. 2014, Carling et al. 2015) Children's age at solid food introduction has been related to obesity in later life. Of note, our study did not observe a significant association of age at solid food introduction with children's BMI trajectory in their first year of life. Future longitudinal studies with large sample size are warranted to confirm these findings.

Previous studies have proposed several factors that explain the potential links between maternal pre-and perinatal factors such as maternal high pregravid BMI, excessive GWG and smoking during pregnancy and adverse health outcomes. The underlying biological

or behavioral etiology that would explain the differential trajectories of BMI during the first year of life is unclear. It is possible that the differentiation of BMI trajectories during the first year of child's life stem from genetic, maternal conditions and behavioral socio-demographic factors, as well as their interactions. The findings from our study and others suggest that that the BMI trajectory separated early in life. The complex determinants of early child growth need to be further investigated with large sample sizes. There is particular interest to elucidate the contribution of intrauterine programming through unfavorable maternal features such as maternal smoking during pregnancy, and high pregravid BMI.

The IFPS II data has proved to be a valuable resource for many researchers, and its main strengths include the longitudinal prospective design with serial measures of body size during infancy, rich information collected and careful assessment on infants' feeding patterns. Our data also have several potential limitations. First, the sample, although well distributed throughout the U.S., is not nationally representative of the U.S. population. Hence, the findings could not be generalized to the whole U.S. population. A second limitation was that all data were self-reported by the child's mother. No medical records were examined to verify weight, height, health status, or other medical characteristic for children. Third, longitudinal attrition across postnatal questionnaires in the IFPS II study(Senanayake 2013) might introduce potential bias. Finally, the sample size is relatively small and the small number of participants in the rising BMI trajectory did not allow us to perform separate analysis for boys and girls. Future cohort studies with a large sample size should explore this possible gender difference.

CONCLUSION

This prospective longitudinal study suggests that distinct BMI trajectories are evident as early as infancy during their first year of life. Several maternal risk factors were associated with the high-stable BMI trajectory including overweight before pregnancy, smoking during pregnancy, breastfeeding practices and household income. Moreover, maternal race/ethnicity was positively associated with BMI trajectories. The identified BMI trajectories during the first year of life are not necessarily evidence of obesity. Rather, different BMI trajectories might be an important early sign of future health because of their association with underlying differential characteristics.

Table 5.1 Indices of goodness-of-fit for latent class growth analysis solution

Model	Model fit	2 classes	**3 classes**	4 classes	5 classes
Linear	BIC	35898	**35860**	35871	35883
Quadratic	BIC	33711	**33561**	33493	33485
	Entropy	0.718	**0.733**	0.552	0.598
	LMR p-value	0.0000	**0.0000**	0.0346	0.3054
	Smallest prop.	0.1615	**0.0276**	0.0228	0.0194

Table 5.2 Basic maternal and infant characteristics according to the identified BMI trajectories

Characteristics (n, %)	Total sample (n=2322)	BMI trajectory group			P value
		Low-stable (n=1895)	High-stable (n=363)	Rising (n=64)	
Maternal Characteristics					
Age (year),					
18-24	452(19.5)	353(18.7)	85(23.4)	14(21.9)	
25-34	1473(63.5)	1206(63.7)	226(62.3)	41(64.1)	0.187
35-43	395(17.0)	334(17.6)	52(14.3)	9(14.1)	
Race					
Non-Hispanic White	1947(83.9)	1630(86.1)	269(74.1)	48(75.0)	
Non-Hispanic Black	87(3.8)	54(2.9)	28(7.7)	5(7.8)	
Hispanic	122(5.3)	92(4.9)	27(7.4)	3(4.7)	<0.001
Others	164(7.1)	117(6.2)	39(10.7)	8(12.5)	
Married,%	1791(77.2)	1474(77.9)	266(73.3)	51(79.7)	0.046
Education, %					
High school or less	404(18.5)	315(17.6)	76(23.2)	13(22.4)	
Some college	845(38.8)	688(38.4)	133(40.6)	24(41.4)	0.038
College graduate or Higher	930(42.7)	790(44.1)	119(36.3)	21(36.2)	
Income (% of poverty threshold)					
<185%	892(38.5)	715(37.8)	143(39.4)	34(53.1)	
185-350%	848(36.6)	688(36.3)	138(38.0)	22(34.4)	0.047
>350%	580(25.0)	490(25.9)	82(22.6)	8(12.5)	
Parity,%					
Primiparous	695(29.9)	583(30.8)	97(26.7)	15(23.4)	0.157
Multiparous	1627(70.1)	1312(69.2)	266(73.3)	49(76.6)	
Maternal smoking,%					
Yes	193(8.4)	145(7.7)	41(11.3)	7(11.1)	0.048
No	2119(91.7)	1742(92.3)	321(88.7)	56(88.9)	
Prepregnancy BMI status, %					
BMI<25 kg/m2	1046(45.6)	866(46.3)	154(43.3)	26(40.6)	0.256
BMI: 25.0-29.9 kg/m2	634(27.7)	499(26.7)	114(32.0)	21(32.8)	
BMI ≥30 kg/m2	612(26.7)	507(27.1)	88(24.7)	17(26.6)	
Gestational Weight Gain, %					
Inadequate	404(17.4)	318(16.8)	72(19.8)	14(21.9)	
Adequate	805(34.7)	671(35.5)	115(31.7)	19(29.7)	0.390
Excessive	1111(47.9)	904(47.8)	176(48.5)	31(48.4)	
Gestational diabetes, %	149(6.5)	117(6.2)	28(7.8)	4(6.3)	0.744

Adherence to breastfeeding guideline,%					
Never initiated breastfeeding	313(13.5)	246(13.0)	53(14.6)	14(21.9)	
Initiated breastfeeding, did not exclusively breastfeed for ≥4 months	1556(67.0)	1260(66.5)	252(69.4)	44(68.8)	0.044
Adherence to exclusivity for ≥4 months, breastfeeding duration<12 months	102(4.4)	83(4.4)	17(4.7)	2(3.1)	
Adherence to both exclusivity for ≥4 months and breastfeeding for ≥12 months	351(15.1)	306(16.2)	41(11.3)	4(6.3)	
Offspring Characteristics					
Infant gender, %					
Boy	1147(49.4)	902(47.6)	214(59.0)	31(48.4)	<0.001
Girl	1175(50.6)	993(52.4)	149(41.1)	33(51.6)	
Infant's birth weight, g					
Birth weight<4000, %	2043(88.0)	1662(87.7)	324(89.3)	57(89.1)	0.678
Birth weight >=4000,%	279(12.0)	233(12.3)	39(10.7)	7(10.9)	
Age at solid food introduction					
<4 months	1040(46.6)	824(45.4)	186(53.0)	30(46.7)	
4 to <6 months	1019(45.7)	846(46.6)	146(41.6)	27(42.2)	0.060
≥6 months	173(7.8)	147(8.1)	19(5.4)	7(10.9)	

Abbreviations: BMI, body mass index; Data are presented as number (percentage) of children. P value determined using chi-square test or analysis of variance F test.

Table 5.3. Results from adjusted multinomial logistic regression of the association between prenatal and early life factors with high-stable and rising BMI trajectories in comparison to low-stable trajectory among 2320 children

Variable	High-stable Adjusted OR (95% CI)	Rising Adjusted OR (95% CI)
Prepregnancy BMI status		
BMI<25 kg/m2	1 (reference)	1 (reference)
BMI: 25.0-29.9 kg/m2	**1.36 (1.02,1.81)**	1.30 (0.70, 2.42)
BMI ≥30 kg/m2	0.99(0.72, 1.35)	0.91(0.47, 1.79)
Gestational Weight Gain		
Inadequate	1.20 (0.85, 1.71)	1.53 (0.74, 3.18)
Adequate	1 (reference)	1 (reference)
Excessive	1.11 (0.84, 1.47)	1.22 (0.65, 2.29)
Adherence to breastfeeding guideline		
Never initiated breastfeeding	1 (reference)	1 (reference)
Initiated breastfeeding, did not exclusively breastfeed for ≥4 months	0.94 (0.66, 1.34)	0.58 (0.30, 1.13)
Adherence to exclusivity for ≥4 months, breastfeeding duration<12 months	1.23 (0.65, 2.35)	0.32(0.07, 1.52)
Adherence to both exclusivity for ≥4 months and breastfeeding for ≥12 months	0.84(0.51, 1.39)	**0.17(0.05, 0.57)**
Age (year),%		
18-24	1.14 (0.82, 1.58)	1.05 (0.51, 2.14)
25-34	1 (reference)	1 (reference)
35-43	0.81 (0.57, 1.14)	0.86 (0.40, 1.84)
Race/ethnicity,%		
Non-Hispanic White	1 (reference)	1 (reference)
Non-Hispanic Black	**3.06(1.83, 5.14)**	**3.47 (1.24, 9.72)**
Hispanic	**1.92 (1.20, 3.07)**	1.07 (0.32, 3.59)
Others	2.08 (1.34, 3.22)	2.16 (0.87, 5.34)
Married or cohabiting,%		
Yes	1.24 (0.87, 1.75)	1.80(0.80, 4.03)
No	1 (reference)	1 (reference)
Education, %		

	1.49 (1.02, 2.17)	1.03(0.46,
High school or less		2.32)
	1.18 (0.88, 1.50)	1.00 (0.52,
Some college		1.92)
College graduate or Higher	1 (reference)	1 (reference)
Income (% of poverty threshold),%		
<185%	1 (reference)	
	1.22 (0.91, 1.62)	0.71 (0.39,
185-350%		1.28)
	1.26 (0.88, 1.81)	**0.35 (0.15,**
>350%		**0.85)**
Gestational age		
	2.26(1.42, 3.61)	0.44(0.06,
<37 weeks		3.25)
37 weeks		
Parity,%		
Primiparous	1 (reference)	1 (reference)
	1.37 (1.01, 1.85)	1.08 (0.55,
Multiparous		2.12)
Maternal smoking		
	1.48 (1.00, 2.22)	1.12 (0.44,
Yes		2.82)
No	1 (reference)	1 (reference)
Gestational diabetes		
	1.31 (0.82, 2.07)	1.01 (0.35,
Yes		2.92)
No	1 (reference)	1 (reference)
Sex		
	1.52 (1.20, 1.93)	1.04 (0.62,
Boy		1.75)
Girl	1 (reference)	1 (reference)
Birth weight		
	1.04 (0.71, 1.52)	1.12(0.49,
Birth weight<4000, %		2.57)
Birth weight >=4000,%	1 (reference)	1 (reference)

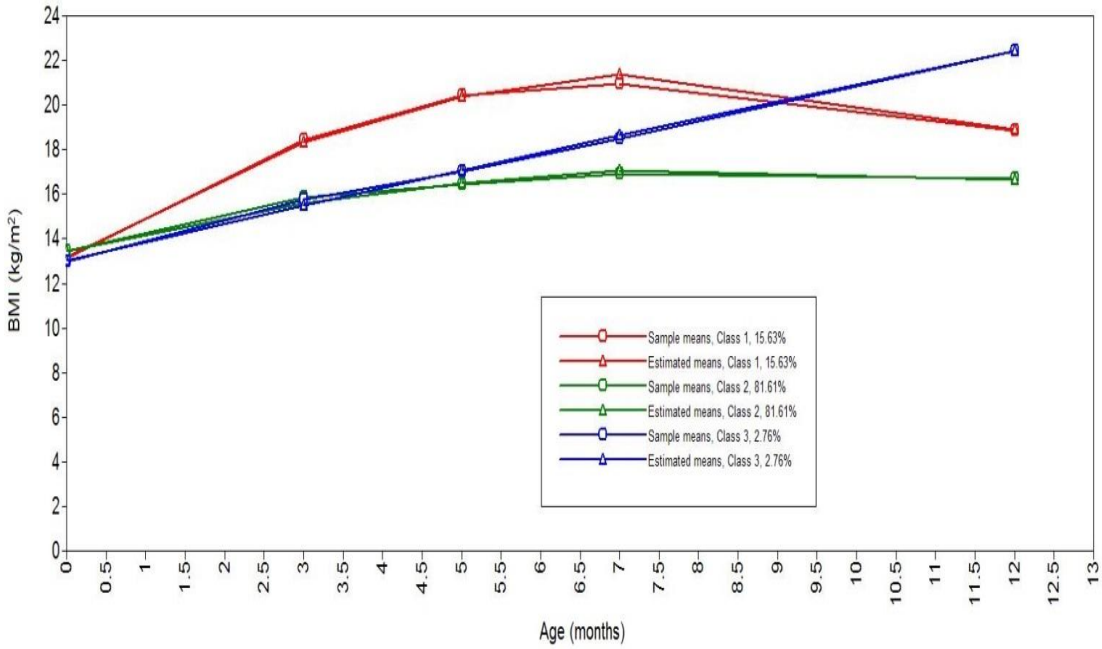

Figure 5.1. The identified body mass index (BMI) trajectory groups among 2322 infants from the Infant Feeding Practices Survey II study, 2005-2007. Square lines represent observed values, and triangle lines represent expected values. Red line corresponds to high-stable trajectory; green line corresponds to low-stable trajectory and blue line corresponds to rising trajectory.

CHAPTER 6

[3]BODY MASS INDEX TRAJECTORIES DURING THE FIRST YEAR OF LIFE AND CHILDHOOD OBESITY AT SIX YEARS OLD

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Abstract

Background and objective: Empirical evidence on the relationship between the BMI trajectories in early life and obesity later in life is limited. This study aimed to assess BMI trajectories during infancy and the risk of obesity at 6 years old.

Methods: We used data from the Infant Feeding Practices Survey II (IFPS II) and its Year Six Follow-Up study (Y6FU). We included 1,169 children with at least two measures of BMI during their first year of life and with information on height and weight at age 6. Latent class growth analysis was used to identify distinct trajectories of BMI and multiple logistic regression analyses were used to assess the association of the identified trajectories with obesity at age 6.

Results: Three distinct trajectories of BMI were identified during first year of life: low-stable (80.2%, n=938), high-stable (16.9%, n=198) and rising (2.8%, n=33). Overall, 11% of children were obese at 6 years old. The percentages of obesity in children at age 6 classified in the low-stable, high-stable and rising BMI trajectory groups were 9.6%, 17.2% and 9.1%, respectively. Compared to those in the low-stable trajectory, the adjusted odds ratio for obesity at age 6 was 1.79 (95% confidence interval 1.13 to 2.84) in children with high-stable growth trajectory and 0.84 (0.26 to 2.72) in children with the rising growth trajectory.

Conclusion: Children with high-stable BMI trajectory during the first year of life had increased risk for obesity at age 6. This finding suggests that a child's BMI trajectory during the first year of life provides additional information regarding his or her risk for obesity at school ages. Obesity prevention program should start as early as infancy and should monitor pay special attention to those children with sub-optimal growth trajectories in infancy.

INTRODUCTION

Population health as measured by life expectancy and burden of disease is compromised by the obesity epidemic and its pervasive feature of being not immune to age, ethnicity and socioeconomic status in a disproportionate way.(Ng et al. 2014, Wang and Beydoun 2007) As a complex multisystem disorder, obesity affects almost every organ system with both short- and long-term health consequences, with the most significant ones being cardiovascular diseases, (Fuster et al. 2016, Ortega, Lavie, and Blair 2016) musculoskeletal disorders (Wearing et al. 2006) and cancers of the endometrium, breast and colon. (Calle and Kaaks 2004, Bianchini, Kaaks, and Vainio 2002) Main contributors to obesity involve lifestyle-related factors and genetic factors. (Li et al. 2016, Voortman et al. 2016, Hu 2008b)

Since the late 1980s when Dr. Barker et al. proposed the fetal origins of disease hypothesis,(Barker 1995b) researchers have increasingly focused on the early determinants of obesity, which might help curb the current obesity epidemic and further

provide cost-effective interventions for those at the highest risk for obesity.(Frongillo and Lampl 2011b) Infants who are born small for gestational age and those who experience catch-up growth and/or adiposity rebound around the age of school entry are at increased risk of developing childhood obesity.(Ong et al. 2000b, Morrison et al. 2010, Rolland-Cachera et al. 2006, Taylor et al. 2005)

The risks for most obesity-related diseases depend on both the age at onset of obesity and the duration of obesity.(Abdullah et al. 2011, Power and Thomas 2011, Boney 2012) Differences in obesity can be detected as early as infancy. Infants usually experience rapid growth during the first year of life, thus infancy may present an opportunity to detect upward deviations from normal child growth identifying children who might be at higher risks for childhood obesity.

Growth trajectories of body mass index (BMI) might capture the dynamic physiological process. Linking the BMI trajectories in early life with the risk of obesity later in life may offer new perspectives on how to improve obesity prevention strategies. To the best of our knowledge, only one study conducted in Australia(Giles et al. 2015a) examined the relationship between growth trajectories of BMI from birth to age 3½ years and the development of obesity at age 9. This study found that in comparison to intermediate trajectory group, the children in the high trajectory group and accelerated trajectory group have increased odds of being obese at 9 years old. This study provides information relating growth trajectory of BMI in early life to the development of

childhood obesity; however whether BMI trajectories during the first year of life can actual predict obesity risk is currently unexamined.

The Infant Feeding Practices Study II (IFPS II) linked with its Year Six Follow Up study presented a unique data source to investigate the association of BMI trajectories during the first year of life with the risk of obesity at age 6. We hypothesized that compared with children who are not in the fast growing BMI trajectory during the first year of life, those in the fast growing BMI growth trajectory had a greater risk for obesity in childhood.

SUBJECTS AND METHODS

Study population

IFPS II is a longitudinal survey conducted by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) between 2005 and 2007. A total of 4,902 pregnant women were recruited during their 7th month of pregnancy throughout the United States and followed up throughout their infants' first year of life at approximately monthly intervals. Details of subjects' recruitments and their follow-ups have been published previously.(Fein et al. 2008) During 2012, FDA and CDC conducted the Year 6 Follow-Up (Y6FU) study through a single questionnaire in a sub-sample (n=1,542) of IFPS II mother-child pairs when the children reached six years old. The original purpose of the Y6FU study was to examine infant feeding practices and their long-term health consequences. To qualify for the Y6FU study, mothers had to have

completed the Neonatal questionnaire in the IFPS II study and not subsequently been excluded due to death of mother or the infant, a diagnosed condition likely to affect feeding, or undeliverable mail. The detailed information regarding to the study design and method for IFPS II and Y6FU are provided elsewhere. (Fein et al. 2014a) In this study, we included 1,169 mother-child pairs after excluding those if the children from both IFPS II and Y6FU had missing data on height, weight, or biologically implausible values (BIV) of BMI. The cutoff value of BIV for BMI was defined according to CDC criteria.[21] The specific sample size of study participants excluded and included at different time points within the IFPS II and Y6FU studies are provided by Figure 6.3.

Outcome measures

The outcome of interest is the occurrence of obesity at 6 years old. Both weight and height for children at age 6 years were measured and reported by their mothers according to instructions included in the Y6FU questionnaire. Detailed information is provided elsewhere. (Fein et al. 2014b) BMI was calculated as weight (kg) divided by height (meters) in square. Obesity was defined as BMI ≥ the 95th percentile of the CDC sex-specific BMI-for-age growth charts from 2000.The Centers for Disease Prevention and Control. A SAS Program for the 2000 CDC Growth Charts. http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. Accessed on Novermber 11, 2015.

Exposure measures

The main exposure was the identified BMI trajectories during the first year of life. The weight and length measurements used for infancy were obtained through postnatal questionnaires in IFPS II at the time of birth and ages 3, 5, 7 and 12 months. At each questionnaire, the mothers were asked to report the values of these measurements from the most recent doctor's visit and the date at the measurement. Infants' BMI was calculated by dividing an infant's weight in kilograms by the square of length in meters. BMI trajectories were modeled among infants with at least 2 measures of BMI. The detailed modelling method regarding to the identification of BMI trajectories during infancy is presented in the statistical section below.

Confounding variables

Covariates related to maternal demographic, pre-and peri-natal characteristics were collected through questionnaires in IFPS II. These include mother's age at childbirth, race/ethnicity, educational level, household income presented as federal poverty level per the U.S. Census BureauThe United States Census Bureau. https://www.census.gov/hhes/www/poverty/index.html. Accessed on November 16, 2015.l, prepregnancy BMI, gestational weight gain during pregnancy, smoking status during pregnancy, gestational diabetes, gestational age and parity. Covariates for children's characteristics were obtained through neonatal and postnatal follow-up questionnaires including gender, birth weight, age at solid food introduction, and

breastfeeding practices. Age at solid food introduction was defined as the infant's age when any solid food was first reported on any of the monthly surveys. We created a new combined variable to measure the adherence of the 2005 breastfeeding guidelines recommended by the American Academy of Pediatrics (AAP), [24] which took into account the breastfeeding initiation, duration and exclusivity. This new variable had four categories: never initiated breastfeeding, initiated breastfeeding but did not exclusively breastfeed for ≥4 months, adhered to breastfeeding exclusivity for ≥4 months but did not adhere to breastfeeding duration guideline (<12 months), and adhered to both exclusivity (≥4 months) and duration guidelines (≥12 months). (Sharma, Dee, and Harden 2014, Schwalfenberg, Genuis, and Rodushkin 2013) Covariates for children's characteristics at 6 years old included days of doing physical activity in a typical week for a total of at least 60 minutes, daily hours of watching television and weekly consumption of sugar-sweetened beverages.

Statistical Analyses

The maternal and their offspring's characteristics were provided by child's obesity status at age 6. Continuous variables were presented as means with standard deviation (SD) while categorical variables were presented as percentages. P-values were calculated using analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables.

We used latent class growth analysis (LCGA) models to identify subgroups within the IFPS II cohort of infants who were followedup during their first year of life (n=1169). The LCGA method is particularly useful for analyzing developmental trajectories since it extends traditional methods through a semiparametric, group-based modelling strategy and allows to simultaneously estimatemultiple trajectories instead of focusing on the overall population mean.(Jung and Wickrama 2008, Nylund, Asparouhov, and Muthén 2007) Using LCGA method, subgroups of children reflecting heterogeneous growing patterns within the whole population can be identified and each subgroup shared a similar underlying growth BMI trajectory. We fitted both linear and quadratic models with different number of latent classes to examine the functional shapes of BMI trajectories. Model fit was assessed using the Bayesian Information Criterion (BIC), Entropy, Lo-Mendell-Rubin (LMR) likelihood ratio test, and the sample size of children identified in the trajectory within the smallest proportion. Based on the final model, the posterior probability was calculated for each infant belonging to each of the trajectories. The trajectory group was assigned according to the greatest posterior probability. These models were fit using M-plus version 5.0.

To estimate the association of BMI trajectories with obesity risk at age 6, BMI trajectory group was included as an exposure variable in logistic models. We used logistic regression models to estimate odds ratio (OR) and its 95% confidence intervals (CIs) of BMI trajectory during infancy and obesity risk at age 6 years. In Model 1, we

provided the estimated OR and its 95% CI without adjusting for any covariates. In Model 2 , we adjusted for maternal demographic, pre-and peri-natal factors including age at childbirth (18-24, 25-34, 35), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and others), education (high school or less, some college, college graduate or higher), household income as percent of poverty level (<185%, 185-350%, >350%), maternal prepregnancy BMI (kg/m^2) ((<18.5, 18.5-24.9, 25.0-24.9 and ≥30), gestational weight gain during pregnancy according to the 2009 weight gain guidelines (inadequate, adequate and excessive), parity (primiparous or multiparous), smoking during pregnancy (yes or no), gestational diabetes (yes or no) and infant early life factors including birth weight for gestational age (SGA, AGA and LGA), adherence to breastfeeding recommendations (never initiated breastfeeding; initiated breastfeeding but did not exclusively breastfeed for ≥4 months; adhered to exclusivity for ≥4 months but breastfeeding duration <12 months; and adhered to both exclusivity for ≥4 months and breastfeeding ≥12 months), and age at solid food introduction ((<4 months, 4 to <6 months, and ≥6 months). In model 3, we additionally adjusted for children characteristics at age six including days of daily physical activity ≥ 60 minutes (<3 days and ≥3 days), daily screen time (< 60 min and ≥ 60 min) and weekly consumption of sugar-sweetened beverages (0, 1 time and ≥2 times) based on model 2. Model 3 was performed as traditional mediation analysis because we suspected that the additional adjusted variables might lie on the pathway of infant BMI trajectory during the first year of life and risk of obesity at age 6 years.

To examine the utility of the predictive role of BMI trajectories on the risk of obesity later in life, we additionally presented sensitivity and specificity analyses and a population attribution risk (PAR) calculations for our data. These statistical analyses were performed using the SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC). All the tests were two-sided at a significant level of 0.05.

RESULTS

The sample characteristics of mothers and their offspring were displayed by obesity status (Table 1). Approximately, 11% of children were obese at 6 years old. Obese children were more likely born to mothers who were non-Hispanic black or Hispanic mothers, not married, less educated and overweight or obese before pregnancy. These children were also more likely to come from families with low household income. Additionally, children whose birth weight was large for gestational age were more likely to be obese at age six and children who consumed higher number of sugar-sweetened beverages at age six were more likely to be obese.

Trajectories of BMI during the first year of life were examined among 1,169 children with 2 or more BMI measurements. Three distinct BMI trajectories during the first year of life were identified (Figure 6.1). First, 80.2% (n = 938) of infants had a low-stable trajectory that they experienced a steady rate of increase in BMI from birth until 7 months but its rate of growth was almost flat after 7 months. Second, 16.9% (n = 198) of infants experienced a high-stable trajectory, in which their growth pattern was similar to

low-stable group, but its rates of increase was higher and the decrease after month 7 was more pronounced. Lastly, 2.8% (n =33) of infants experienced a rapid increase in BMI and this linear increasing trend was maintained throughout their first year of life (rising trajectory). Moreover, the maternal and children's characteristics by three identified BMI trajectories are presented in Table 6.2.

The relationship between BMI trajectories during the first year of life and obesity at 6 years differed significantly between those who experienced high-stable BMI trajectory and those who experienced low-stable BMI trajectory (17.2% vs. 9.6%; P=0.0019), but not between those who experienced rising BMI trajectory and those who experienced low-stable BMI trajectory(9.6% vs. 9.1%, P=0.90) (Figure 6.2). Moreover, children with a high-table BMI trajectory during infancy had a high prevalence of obesity at age 6 years

The odds of obesity at 6 years old by BMI trajectories during the first year of life were presented in Table 3. In comparison with children in the low-stable BMI trajectory during their first year of life, children in high-stable trajectory had significantly greater odds of being obese at 6 years old (OR:1.97; 95% CI: 1.28-3.01) in unadjusted analysis. After adjusting for covariates in Model 2, this association persisted (adjusted OR (AOR): 1.79; 95% CI: 1.13-2.84). In the sensitivity analysis demonstrated in Models 3, the significant relationship of high-stable BMI trajectory with childhood obesity at 6 years

remained after adjusting for potential intermediates from both early life and age 6 years. The corresponding AORs were 1.76(1.11, 2.80) and 1.82 (1.14, 2.89), respectively.

The sensitivity and specificity of BMI trajectories (high-stable vs. low-stable) predicting childhood obesity at age 6 were 0.27 and 0.84, respectively (Table 6.4). The positive and negative predicted values were 0.17 and 0.90. The population attributable risk was 0.12 (Table 6.4).

DISCUSSION

In this study, we identified 3 distinct BMI trajectories among infants during their first year of life. These trajectory patterns can be described as low-stable, high-stable and rising. We found that children who exhibited high-stable BMI trajectory during their infancy had the greatest odds of being obese at age six. Notably, 16.9% of children had experienced a high-stable BMI trajectory during their first year of life. These findings support our hypothesis that rapid BMI growth trajectories during the first year of life increase the risk of obesity later in life. Hence, our findings provide a unique insight into growing BMI patterns as early as in infancy and suggest that heterogeneous pattern in BMI trajectories might exist in pediatric population.

Almost all of previous studies have examined rapid growth (usually measured as rapid weight gain between two time points) during the first year of life in the pediatric population and have found a positive association between rapid growth and obesity later in life. Dubois and his colleague(Dubois and Girard 2006) showed that rapid growth

defined as in the highest quintiles of monthly weight gain between birth and 5 months of age, is associated with increased risk of childhood obesity at 4.5 years (AOR: 3.9, 95% CI: 1.9-7.9). Rooney and his colleague(Rooney, Mathiason, and Schauberger 2011) defined rapid weight gain as weight gain larger than 2 lbs per month during the first 4 months and reported associations with increased risk of obesity in childhood around age 5 (adjusted OR: 2.17 and 95% CI: 1.26-3.73) and in adolescence around age 14 (AOR: 1.63, 95% CI: 1.05-2.53). One study(Stettler et al. 2003) used weight-for-age Z scores increase larger than 1 SD between birth and 4 months to define rapid weight gain, and found that rapid weight gain in children in the first 4 months was positively linked to obesity at age 20. Another study (Hui et al. 2008)conducted in Hong Kong defined accelerated infant growth as a change greater than 0.67 in weight Z score standardized using WHO growth standard and found that accelerated infant growth was associated with higher childhood BMIZ at age 6. Jones et al.(Jones-Smith, Fernald, and Neufeld 2007) using a sample from Mexico defined accelerated growth as positive change in BMIZ between birth and age 1 year using WHO growth standard and reported its positive association with obesity at age 4 to 6 years. Another study found that rapid growth defined as the highest quartiles of weight-for-length Z score at month 6 was positively associated with childhood obesity at age 3 years.(Taveras et al. 2009) To date, growing evidence from observational studies among diverse populations largely suggests that rapid growth between two time points during infancy is positively associated with childhood obesity.

With the advances in statistical modelling methods and availability of statistical software, recent studies have started to link distinct infant growth trajectories of BMI and childhood obesity or obesity later in life. To the best of our knowledge, our study is one of the few which examined the association of BMI trajectories with obesity later in life and showed that children with high-stable BMI trajectories experienced increased odds of obesity at age 6. Another Australian study(Giles et al. 2015a) using LCGA identified 4 trajectories: low, intermediate, high, and accelerate. This study found that in comparison to intermediate trajectory group, the children in the high trajectory group and accelerated trajectory group had 4.26 (95% CI: 2.50-7.26) and 15.36 (95% CI: 5.24-45.05) times higher odds of being obese at 9 years old. Furthermore, our study is the first one to conduct the sensitivity-specificity and PAR analyses in terms of the predictive role of BMI trajectories in childhood obesity. Our data suggest that the accuracy of BMI trajectories to predict childhood obesity (i.e., to identify children with obesity at age 6) is low because both the sensitivity and positivity predicted value were low. The sensitivity of 0.27 means that being in the high-stable trajectory identified only 27% of children with obesity at age 6, and the positive precited value of 0.17 means that only 17% of children in the high-stable trajectory were obese at 6 years. in terms of sensitivity whereas is relatively high in specificity. The PAR analyses provide further evidence on the cautious use of BMI trajectories for the prediction of future obesity risk in childhood because only 12% of obesity at age 6 years was attributable to early BMI trajectories.

Several mechanisms are proposed to explain the link between early rapid growth in BMI trajectory and future obesity risk. Intrauterine environment plays an important role in programming their child's metabolic risks.(Young, Johnson, and Krebs 2012, Alfaradhi and Ozanne 2011) The programming process might differ according to parental characteristics such as maternal adiposity, weight gain during pregnancy, nutritional and hormonal status, smoking during pregnancy, pregnancy complications, and other lifestyle factors like physical activity. Epigenetic process might also play a role in the early life origins of obesity.(van Dijk et al. 2015, Sookoian et al. 2013) For example, animal models have demonstrated gene specific alternations in DNA methylation after maternal exposure to a high fat diet. (Aagaard-Tillery et al. 2008) Human studies have shown that children who experienced gene methylation changes in DNA extracted from umbilical cord tissue have an increased risk of childhood obesity.(Godfrey et al. 2011) Another explanation relates to infant feeding practices and appetite regulation. Studies have shown that the infants' gut is highly permeable and susceptible to hormones in human milk.(Ballard and Morrow 2013) These hormones contained in human milk such as insulin, leptin, and adiponectin may elicit endocrine effects and regulate infant appetite and weight gain.(Savino, Liguori, et al. 2009, Savino, Fissore, et al. 2009) Moreover, different maternal characteristics such as obese and non-obese might affect milk composition and imparts differential programming effects to their offspring.(Desai et al. 2014)

This study has several strengths. The longitudinal nature of IFPS II study with repeated measures of infant anthropometrics provides a unique opportunity to examine BMI trajectories during their first year of life. The Y6FU study provides additionally valuable opportunity to examine the long-term impact of BMI trajectories during infancy on childhood obesity at 6 years old. Moreover, the latent class modelling method used in our study provides a clear description of different BMI growing patterns existing among pediatric population rather than the overall means. This finding extends previous studies by showing that some children are more likely to experience rapid increases of BMI during their first year of life, which place them at high risk level of obesity later in life. This suggests that obesity prevention programs should start as early as infancy. Additionally, the comprehensive information from IFPS enabled us to control for many potential confounders. Notably, our study is the first one providing the information of prediction of identified BMI trajectories during the first year of life on obesity later in childhood including sensitivity-specificity and PAR analyses. However, the limitations of this study are worth to be noted. Although the study population is a geographically diverse in the U.S, it is a not nationally representative sample. Hence, the trajectory groups identified may not be generalizable and the associational findings might not be generalized to other populations either. Children' heights and weights were measured by their mothers, so child obesity at age 6 may be prone to measurement errors.

In conclusion, differential BMI trajectories during the first year of life were identified in our study population and the rapid BMI growing trajectory increased the

odds of childhood obesity at 6 years. Exposure to a faster growth trajectory in infancy might exert long-lasting adverse health consequences. This finding suggests that a child's BMI trajectory during the first year of life provide additional information regarding his or her risk of development of obesity later in life. Therefore, the identification of growth trajectories using BMI is conceptually of great importance because it might help identify the sub-groups of children with sub-optimal growth trajectories and provides an opportunity to promote and improve obesity prevention strategies in the sub-group. However, our findings from sensitivity-specificity and PAR analyses provide evidence of being cautious to make a claim for the utility of BMI trajectories as a predictor for future obesity risk. Hence, additional research is needed to examine the utility of specific BMI trajectories during the first year of life in obesity risk and to clarify the underlying mechanisms.

Table 6.1. Study sample characteristics by obesity status at age 6 years-old

		obesity at age 6 years		
	overall (N=1169), %	Yes (n=127)	No (n=1042)	
Maternal/family characteristics				
Maternal age at delivery				
18-24	149 (12.8)	20(15.8)	129(12.4)	
25-34	776(66.4)	86(67.7)	690(66.3)	0.319
≥35	243(20.8)	21(16.5)	222(21.3)	
Race/ethnicity				
Non-Hispanic white	1016(86.9)	105(82.7)	911(87.4)	
Non-Hispanic black	37(3.2)	10(7.9)	27(2.6)	
Hispanic	52(4.5)	9(7.1)	43(4.1)	0.002
Others	64(5.5)	3(2.4)	61(5.9)	
Marital status				
Yes	965(88.3)	94(74.0)	871(83.6)	0.027
Education				
High school or less	166(14.3)	34(26.8)	132(12.7)	
Some college	408(35.1)	48(37.8)	360(34.5)	<0.001
College graduate or higher	556(47.8)	40(31.5)	516(49.8)	
Household income as percent of poverty level,%				
<185%	387(33.1)	57(44.9)	330(31.7)	
185-350%	449(38.4)	42(33.1)	407(39.1)	0.011
>350%	333(28.5)	28(22.1)	305(29.3)	
Parity				
Primiparous	228(28.9)	32(25.2)	306(29.4)	0.378
Multiparous	810(69.3)	94(74.0)	716(68.7)	
Perinatal characteristics				
Mother's prepregnancy BMI				
Underweight (<18.5)	31(2.7)	0	31(3.0)	
Normal weight (18.5-24.9)	486(41.6)	28(22.1)	458(44.0)	
Overweight(25.0-24.9)	319(27.3)	42(33.1)	277(26.6)	<0.001
Obese(≥30)	217(27.1)	55(43.3)	262(25.1)	
Weight gain during pregnancy				
Inadequate	185(16.6)	22(18.6)	163(16.3)	
Adequate	319(28.5)	25(21.2)	294(29.4)	0.173
Excessive	614(54.9)	71(60.2)	543(54.3)	
Maternal smoking during pregnancy				
Yes	75(6.4)	12(9.5)	63(6.1)	0.143
Gestational age (weeks)	39.3(1.2)	39.4(1.2)	39.3(1.2)	0.591
Gestational diabetes	92(7.9)	15(11.8)	77(7.4)	0.324
Child's characteristics during their first year of life				

Sex				
Boy	579(49.5)	63(49.6)	516(49.5)	0.985
Girl	590(50.5)	64(50.4)	526(50.5)	
Birth weight for gestational age				
Small for gestational age	80(6.9)	7(5.5)	73(7.0)	
Appropriate for gestational age	952(81.5)	96(75.6)	856(82.2)	0.024
Large for gestational age	136(11.6)	24(18.9)	112(10.8)	
Age at solid food introduction				
<4 months	486(41.6)	65(51.2)	421(40.4)	
4 to <6 months	567(48.5)	50(39.4)	517(49.6)	0.114
≥ 6 months	94(8.0)	9(7.1)	85(8.2)	
Adherence to breastfeeding recommendations				
1	155(13.3)	20(15.8)	135(13.0)	
2	762(65.2)	87(68.5)	675(64.8)	0.368
3	54(4.6)	4(3.2)	50(4.8)	
4	198(16.9)	16(12.6)	182(17.5)	
Child's characteristics at age six years-old				
Days of daily physical activity≥ 60 min				
<3 days	163(13.9)	21(16.5)	142(13.6)	0.565
≥3 days	1003(85.8)	106(83.5)	897(86.1)	
Daily screen time				
<60 min	254(21.7)	20(15.8)	234(22.5)	0.112
≥60 min	901(77.1)	104(81.9)	797(76.5)	
Weekly consumption of sugar-sweetened beverages				
0	221(18.9)	15(11.8)	206(19.8)	
1 time	784(67.1)	86(67.7)	698(67.0)	0.032
≥ 2 times	161(13.8)	26(20.5)	135(13.0)	

Table 6.2 Basic maternal and infant characteristics according to the identified BMI trajectories

Characteristics	Total sample (n=1169)	BMI trajectory group			P value
		Low-stable (n=938)	High-stable (n=198)	Rising (n=33)	
Maternal Characteristics					
Age (year),					
18-24	149(12.8)	118(12.6)	25(12.6)	6(18.2)	
25-34	776(66.4)	616(65.7)	137(69.2)	23(69.7)	0.507
35-43	243(20.8)	203(21.7)	36(18.2)	4(12.1)	
Race					
Non-Hispanic White	1016(86.9)	831(88.6)	158(79.8)	27(81.8)	
Non-Hispanic Black	37(3.2)	24(2.6)	10(5.1)	3(9.1)	
Hispanic	52(4.5)	37(3.9)	14(7.1)	1(3.0)	0.017
Others	64(5.5)	46(4.9)	16(8.1)	2(6.1)	
Married,%					
Yes	965(84.9)	783(85.4)	155(82.9)	27(84.4)	0.120
No	171(15.1)	134(14.6)	32(17.1)	5(15.6)	
Education, %					
High school or less	404(18.5)	315(17.6)	76(23.2)	13(22.4)	
Some college	845(38.8)	688(38.4)	133(40.6)	24(41.4)	0.063
College graduate or Higher	930(42.7)	790(44.1)	119(36.3)	21(36.2)	
Income (% of poverty threshold)					
<185%	387(33.1)	301(32.1)	69(34.9)	17(51.5)	
185-350%	449(38.4)	365(38.9)	73(36.9)	11(33.3)	0.171
>350%	333(28.5)	272(29.0)	56(28.3)	5(15.2)	
Parity,%					
Primiparous	338(29.4)	271(29.4)	60(30.9)	7(21.9)	0.833
Multiparous	810(70.6)	651(70.6)	134(69.1)	25(79.1)	
Maternal smoking,%					
Yes	75(6.4)	51(5.5)	22(11.2)	2(6.1)	0.012
No	1090(93.6)	884(94.6)	175(88.8)	31(93.9)	
Prepregnancy BMI status, %					
<25	517(44.8)	432(46.7)	73(37.6)	12(36.4)	0.090
25.0-24.9	319(27.7)	236(25.5)	71(36.6)	12(36.4)	
≥30	317(27.5)	258(27.9)	50(25.8)	9(27.3)	
Gestational Weight Gain, %					
Inadequate	185(16.6)	149(16.5)	29(15.7)	7(22.6)	
Adequate	319(28.5)	273(30.3)	41(22.2)	5(16.1)	0.075
Excessive	614(54.9)	480(53.2)	115(62.2)	19(61.3)	
Gestational diabetes, %					
Yes	92 (7.9)	69(7.4)	20(10.1)	3(9.1)	0.783

No	1074(92.1)	866(92.6)	178(89.9)	30(90.9)	
Adherence to breastfeeding guideline,%					
Never initiated breastfeeding	155(13.3)	116(12.4)	31(15.7)	8(24.2)	
Initiated breastfeeding, did not exclusively breastfeed for ≥4 months	762(65.2)	608 (64.8)	134(67.7)	20(60.6)	0.163
Adherence to exclusivity for ≥4 months, breastfeeding duration<12 months	54(4.6)	44 (4.7)	8(4.0)	2(6.1)	
Adherence to both exclusivity for ≥4 months and breastfeeding for ≥12 months	198(16.9)	170(18.1)	25(12.6)	3(9.1)	
Offspring Characteristics					
Infant gender, %					
Boy	579(49.5)	443(47.2)	118(59.6)	18(54.6)	0.006
Girl	590(50.5)	495(52.8)	80(40.4)	15(45.5)	
Infant's birth weight, g					
SGA	80(6.9)	66(7.0)	12(6.1)	2(6.1)	0.969
AGA	952(81.5)	762(81.3)	162(81.8)	28(84.9)	
LGA	136(11.6)	109(11.6)	24(12.1)	3(9.1)	
Age at solid food introduction					
<4 months	486(42.4)	384(41.8)	89(45.4)	13(39.4)	
4 to <6 months	567(49.4)	458(49.9)	94(48.0)	15(45.5)	0.525
≥6 months	94(8.2)	76(8.3)	13(6.6)	5(15.2)	
Days of daily physical activity≥60 min,%					
<3 days	163(14.0)	127(13.6)	32(16.3)	4(12.1)	0.169
≥3 days	1003()	810()	164()	29()	
Daily screen time,%					
<60 min	254(22.0)	211(22.6)	31(16.4)	12(36.4)	<0.001
≥ 60 min	901(78.0)	722(77.4)	158(83.6)	21(63.6)	
Weekly consumption of sugar-sweetened beverages,%					
0	221(19.0)	174(18.6)	39(19.9)	8(24.2)	
1 time	784(67.2)	640(68.3)	124(63.3)	20(60.6)	0.208
≥ 2 times	161(13.8)	123(13.1)	33(16.8)	5(15.2)	

Abbreviations: BMI, body mass index; Data are presented as number (percentage) of children. P value determined using chi-square test or analysis of variance F test.

Table 6.3. The odds ratios (OR) and 95% confidence intervals (95% CI) of BMI trajectories during infancy and obesity risk at age six.

BMI trajectories	Model 1	Model 2	Model 3
Low-stable	reference	reference	reference
High-stable	1.97(1.28, 3.01)*	1.79(1.13, 2.84)*	1.82(1.14,2.89)*
Rising	1.08(0.34, 3.38)	0.84(0.26, 2.72)	0.96(0.30,3.09)

*indicates $p<0.05$.

Model 1: Unadjusted model;

Model 2: Adjusted for maternal socio-demographic and reproductive factors including age at childbirth, race/ethnicity, education, household income, maternal prepregnancy BMI, parity, smoking during pregnancy, gestational diabetes and infant early life factors including birth weight for gestational age, adherence to breastfeeding recommendations and age at solid food introduction.

Model 3: Model 2+additionally adjusted for children characteristics at age six including days of daily physical activity ≥ 60 minutes, daily screen time and weekly consumption of sugar-sweetened beverages.

Table 6.4 Sensitivity-specificity and population attributable risk of identified BMI trajectories and obesity at age six.

	Count	obese	not obese	%obesity
rising	33	3	30	9.09
high-stable	198	34	164	17.17
low-stable	938	90	848	9.59
Total	1169	127	1042	
Sensitivity	0.27			
Specificity	0.84			
Positive predictive value		0.17		
Negative predictive value		0.90		
Population attributable risk		0.12		

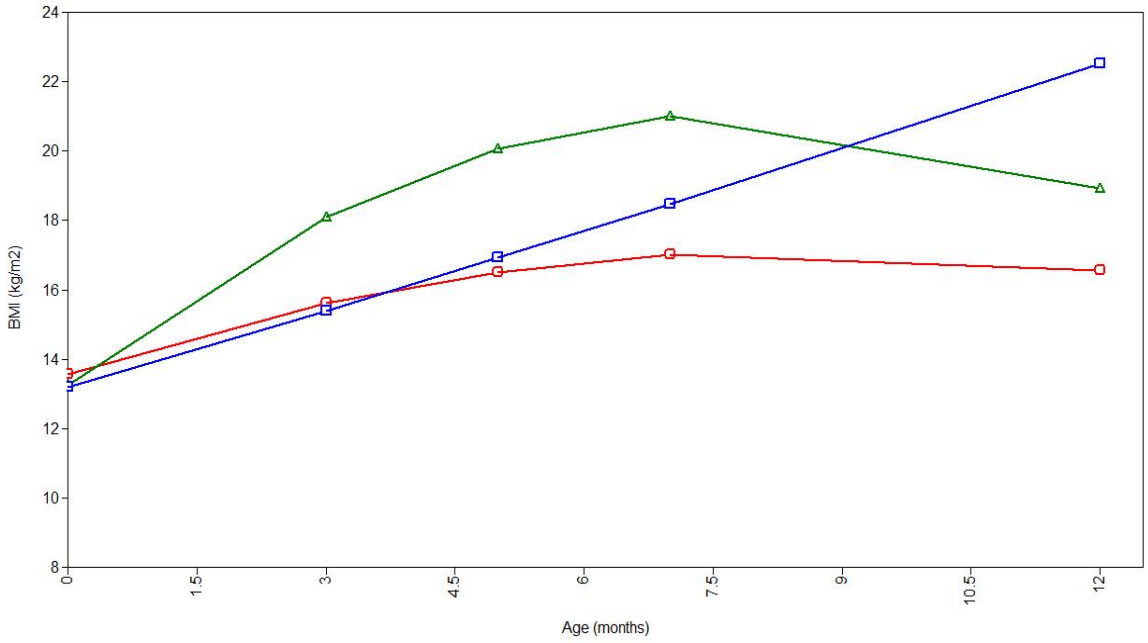

Figure 6.1: Body Mass Index (BMI) trajectories during the first year of life. Red line indicates low-stable, blueline indicates high-stable and green lineindicates rising.

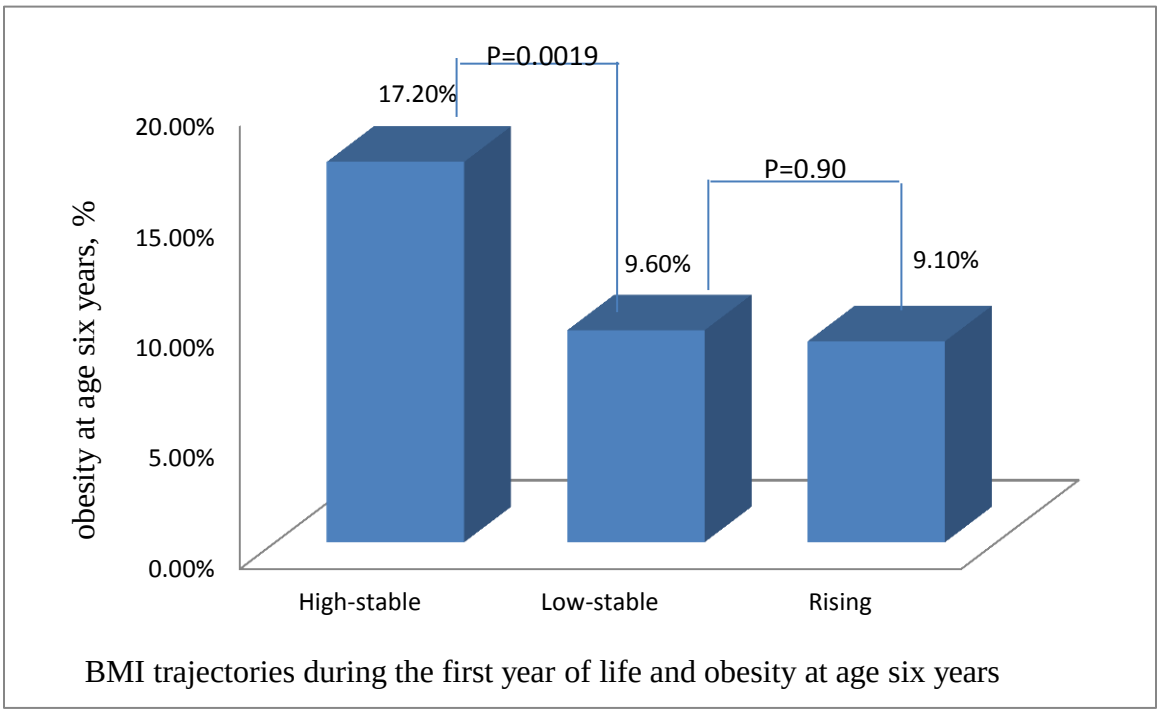

Figure 6.2: The percentage of obesity at age 6 by BMI trajectories during the first year of life. P values were calculated using chi-square test from unadjusted logistic regression.

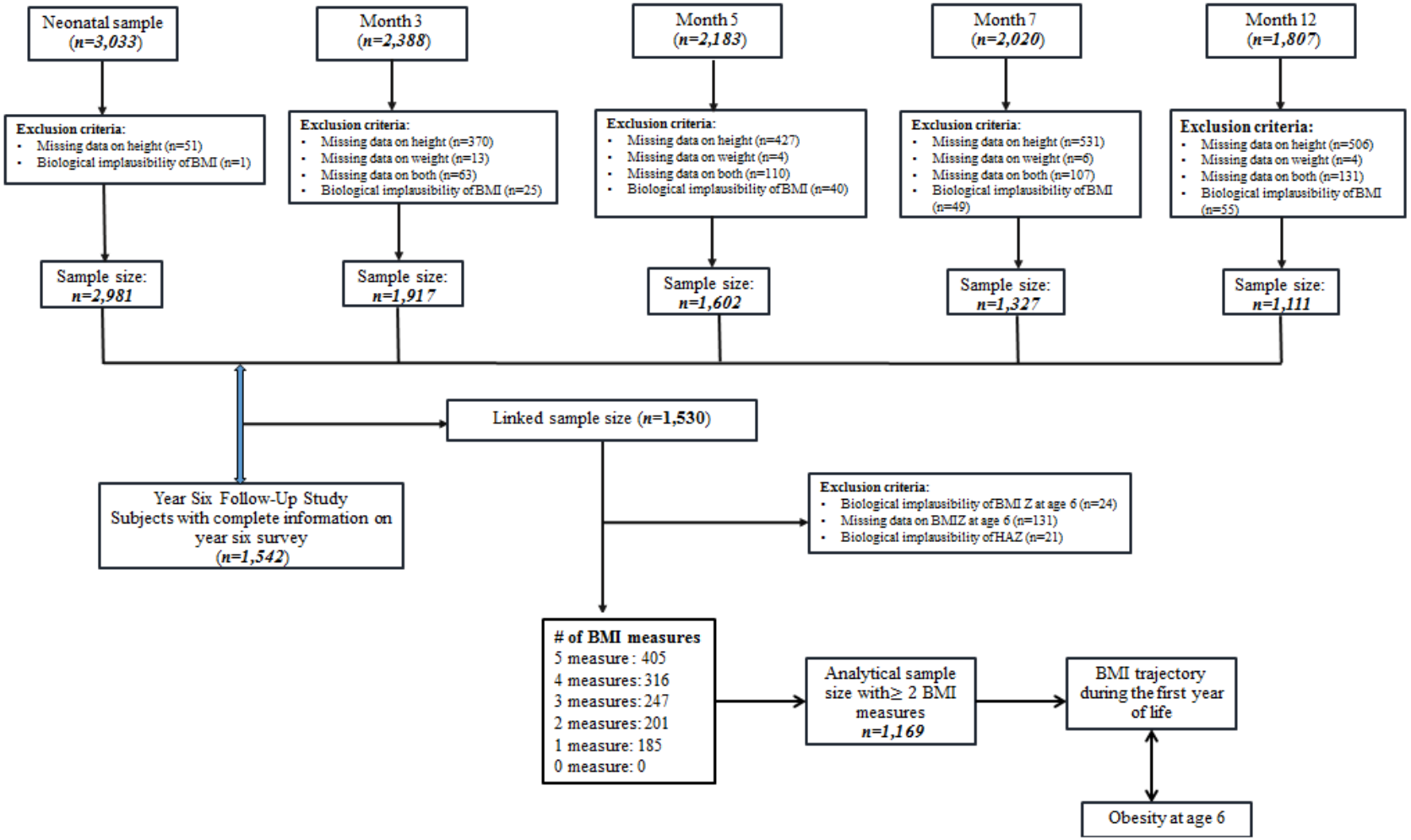

Figure 6.3: the flowchart of study participants.

CHAPTER 7

SUMMARY AND CONCLUSION

This dissertation encompasses three studies using the data from a birth cohort study of Infant Feeding Practices Survey II (IFPS II) and its Year Six Follow-Up (Y6FU) study. Study one examined the associations of maternal pre-pregnancy BMI and GWG with offspring BMIZ and the risk of obesity at age 6. Study two identified BMI trajectories during the first year of life and assessed the potential influences of prenatal factors (i.e. pre-pregnancy BMI and GWG) and early-life factors (i.e., breastfeeding) on the identified BMI trajectories. Study three examined the association of the BMI trajectories in the first year (identified in study two) with the risk of obesity among children at age 6. The following sections summarize the key findings from each study, acknowledge strengths and limitations, discuss future research directions and public health implications.

Summary of Key Findings

Study one found that 11% of children were obese at age six years old. Maternal excessive weight during pregnancy significantly increased their offspring' risk for being obese and this positive relationship was strengthened among mothers who were normal weight before pregnancy. No associations were found between inadequate weight gain during pregnancy and offspring's obesity. This study also examined the associations of meeting the 2009 IOM recommendations on gestational weight gain and offspring BMIZ

across the distribution of BMIZ using quantile regression methods. We found that children born to mothers who gained excessive weight during pregnancy had higher BMIZ and the magnitudes of association were heterogeneous across offspring's BMIZ distribution. Also the associational patterns were different in subgroups by maternal pre-pregnancy BMI. Positive association was more pronounced in the upper tail of the offspring BMIZ distribution among normal weight mothers who gained excessive weight compared to those born to mothers who gained adequate weight during pregnancy. No associations were observed among overweight and obese mothers. In contrast, children born to obese mothers who gained inadequate weight gain had lower BMIZ at the certain percentiles of the BMIZ distribution.

In study two, three BMI growth trajectories during the first year of life were identified using Latent Class Growth Analysis. These trajectories were labelled as "low-stable" (81.6%), "high-stable" (15.6%), and "rising" (2.8%). We examined the correlates of the identified BMI trajectories. Of the potential determining factors, the primary ones that differentiated between BMI trajectories during the first year of life were: maternal race/ethnicity, household income, maternal pregravid weight, smoking during pregnancy, breastfeeding practices, duration of gestation, and infant's sex. In study three, we linked the identified BMI trajectories during the first year of life with childhood obesity at age 6. Our results suggested that in comparison to children in "low-stable BMI trajectory", those who exhibited "high-stable BMI trajectory" during infancy had higher odds of being obese at age six (adjusted odds ratio (OR): 1.79; 95% confidence interval (CI): 1.13, 2.84). These findings supported our hypothesis that rapid fasting growing BMI growth trajectories during the first year of life increases the risk of obesity later on in life.

This study provided evidence that infant growing patterns during early life are important factors to be considered for future childhood obesity risk.

Study strengths

The IFPS II data have proved to be a valuable resource for researchers, and its main strengths include the longitudinal prospective design with multiple measures of infants' weight and height during the first year of their life, careful assessment on infants' feeding patterns, and a relatively large national sample mother-infant dyads recruited during pregnancy and being followed up to 6 years after delivery. Moreover, the comprehensive information from IFPS II enabled us to examine both prenatal, early life, and childhood risk factors and to control for many potential confounders. Furthermore, the longitudinal design of IFPS II with repeated measures of infant's weight and height allows us to identify the underlying BMI trajectories during the first year of life. The latent class growth modelling method enables us to identify the latent BMI growth trajectories among pediatric population in infancy rather than using overall means among the whole population. Also, we are able to examine the correlates of these identified BMI trajectories from both prenatal and early life factors. The Y6FU study provided additionally valuable opportunity for us to examine the links of maternal gestational weight gain and infant BMI trajectories with childhood obesity at 6 years old.

Study limitations

This dissertation has some limitations as well. First, although the study population is well distributed throughout the United States, it is not a nationally representative sample of the U.S. population due to its sampling frame and the response rates. Hence, these findings are not generalizable to the entire U.S. population. Another limitation is

that all data were self-reported by the child's mother. No medical records were examined to verify these self-reported data. Hence, reporting error might have occurred. However the recall period in our study was relatively short and it is unlikely that the misclassification of exposure/outcome depended on outcome/exposure given the longitudinal design of this study. Based on non-differential misclassification, the reporting errors would usually bias the association of GWG-BMIZ/obesity toward to the null even though this case is not always true since other factors such as the value of the true relative risk, exposure prevalence are also involved. Third, longitudinal attrition resulting from the varying response rates across postnatal questionnaires in the IFPS II study and Y6FU might introduce potential bias. Actually, lost to follow-up is an important issue to be considered in any cohort studies including our study due to its potential threat to study validity. A simulation study has shown that the magnitude of bias depends on different levels of loss to follow-up and missing mechanism. The authors reported no important bias for the 5 to 60% of subjects who were lost to follow-up if missing mechanism is completely at random (MCAR) or missing at random (MCR). However, a small proportion of subjects lost to follow-up would result in bias if missing not at random. The response rate in our study ranged from 64.5% to 87.6%, a relatively high follow-up rate. In the second study, we used the latent class growth analysis method to identify BMI trajectories during the first year of life, and M-plus software handles missing data by the standard approach of MAR under maximum likelihood method to estimate parameters of interest. Nevertheless, compared with the nationally representative National Survey of Family Growth, the mothers in the IFPS II sample tended to be older, more highly educated, of higher income, white, and less likely to be smokers. Moreover,

children of respondents in comparison to non-respondents of Y6FU study were more likely to be breastfed for a longer duration and did not participate in the Special Supplemental Nutrition Program for Women, Infants, and Children. However, no differences were found in terms of infant sex, initiation of breastfeeding, and birth weight or gestational age.

Future research directions

Based upon our research, future studies are warranted to better understand the influence of maternal weight gain and the risk of childhood obesity/BMIZ. In particular, how does the moderating role of maternal prepregnancy BMI influence these associations? Moreover, due to the small number of underweight women in our study, future studies in this category are needed to provide better estimates of weight gain and childhood obesity. In our studies, we identified three distinct BMI trajectories during the infants' first year of life. Since the method we used, latent class growth analysis, is data-driven, the small sample size of "rising trajectory" might cause unstable findings due to the large range of confidence intervals and hence future studies with large sample size are needed. A large nationally representative sample with excellent follow-up and high responses rates would also allow for evaluating gender difference in BMI growing trajectories, which in turn could help identify gender-specific correlates of the growth trajectories.

Public health implications

The global epidemic of pediatric obesity and its clinical and public health consequences have attracted the interest of policy makers, researchers, pediatricians and

the general public. Despite several years of attention and efforts from the whole society, concerns about the epidemic of childhood obesity and its lasting impact on our nation's health remain high. Finding effective prevention strategies and solutions continue to be a challenge to researchers and pediatricians. If parents and pediatricians could recognize children at high-risk of later obesity based on a distinct BMI growth trajectory during postnatal visit in early infancy, these children could be targeted for obesity prevention programs. Targeted obesity prevention strategies are likely to be more efficacious and cost-effective than providing treatment for obesity once developed. The results of this study, however, suggest that, although early BMI trajectories are associated with obesity in later childhood, the accuracy of prediction is much too low to be useful in identifying children at risk of late obesity.

Enlightened by the "fetal origin hypothesis" proposed by Dr. David Barker in the late 1980s, risk factors for childhood obesity can begin before a child is born. Using the unique data sources from IFPS II linked to its Y6FU study, our results emphasize that maternal excessive weight gain during pregnancy is an important risk factor for their offspring obesity status or BMIZ, especially among those who had normal weight before pregnancy. These findings suggest that maternal weight status before pregnancy plays an important role of moderating the maternal GWG-obesity and BMIZ association. Preconception counselling and intervention efforts targeting overweight or obese women are needed to assist these women in lowering their BMI before conception. Another important aspect for pregnant women is to inform them about the importance of gaining adequate weight during pregnancy.

Our findings suggest that heterogeneous patterns in BMI trajectories might exist in the pediatric population, and may be modified by maternal factors such as overweight before pregnancy, smoking during pregnancy and race/ethnicity along with infant early life factors such as breastfeeding. Our findings of higher risk of being obese in school age of 5-6 years among those who experienced the "high-stable BMI" growing trajectory provide evidence that monitoring BMI trajectory in early infancy can provide an important early sign of childhood obesity. Obstetricians and gynecologists should emphasize the importance of mother's health behaviors such as smoking and maternal weight before pregnancy on the risk of obesity for their baby, specifically targeting women in high-risk ethnic groups. Finally, policy makers might be made aware of the role maternal and early infant life factors might play on the children's' BMI growth.

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