GESTATIONAL WEIGHT GAIN AND THE ASSOCIATION WITH OFFSPRING GROWTH AND OBESITY

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ABSTRACT

Pediatric obesity is a key public health concern in the United States. We studied the association between gestational weight gain (GWG) and offspring growth and obesity risk across three developmental periods thought to be associated with obesity in later life. Mother-child pairs from the Maternal Health Practices and Child Development pregnancy cohort and were followed from <26 weeks gestation to 16 years postpartum. GWG was calculated as a ratio of observed to expected gain based on the 2009 Institute of Medicine GWG guidelines and women were classified as gaining below, within, or above the guidelines as inadequate, adequate, and excessive, respectively. We also studied GWG z-scores which account for prepregnancy BMI and are uncorrelated with gestational length. At birth, 8, 18, and 36 months, offspring weight-for-age z-scores (WAZ) were calculated, as well as body-mass-index-for-age z-scores (BMIZ) at these ages and 10 and 16 years. In accordance with current recommendations, z-scores were calculated based on the 2006 WHO growth standards for children <24 months and the 2000 CDC growth references for children ≥24 months. Child obesity was defined as a BMI ≥95th percentile at 36 months, 10 and 16 years. Compared to adequate, excessive GWG was associated with heavier weight at birth, slower infant growth, and greater risk for obesity at 36 months. At 10 and 16 years, higher GWG was associated with a greater risk of adolescent obesity. Inadequate GWG was associated with lower weight at birth and rapid weight gain from birth to 18 months, but not obesity risk. Children with rapid infant weight gain were more likely to be obese at 10

and 16, but not 3 years. GWG may exert a lasting influence on child growth and may lead to persistent obesity in this low-income sample of black and white mothers and their children. Limiting excessive GWG may impact the intergenerational cycle of obesity, making the findings of this dissertation relevant to public health.

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PREFACE

This dissertation is the direct result of collaboration with a number of outstanding researchers who offered their time and expertise. First and foremost, I would like to acknowledge and thank my dissertation and academic mentor, Lisa Bodnar, for her commitment to this project, and to me as a doctoral student. Lisa is an exceptional educator and has encouraged me to avail myself to diverse educational opportunities as well as to strive for the best in doctoral coursework, extracurricular scholarly pursuits, and the completion of this dissertation.

I am so fortunate to have been able to learn from a talented dissertation committee whose insightful suggestions and deep understanding of multiple aspects of epidemiologic research were essential to a quality research project. My committee has challenged me to consider different aspects of my data in order to strengthen my understanding and sharpen my epidemiologic, research, and analytic skills which will serve me well beyond the program.

Finally, I would like to thank my friends and family for their support which was key to the completion of this dissertation. My sisters, Erin and Sara, and my brother-in-law, Tad, always find a way to make me to smile, laugh, and to not take myself too seriously. My parents, Peter and Deana, taught me work hard, to value my education, and they continue to inspire me by demonstrating those traits each day. Last but not least, Jon, the love of my life: your support and encouragement throughout this process was fundamental to keeping a positive outlook, retaining my sanity, and to completing this degree.

1.0 INTRODUCTION

1.1 BACKGROUND

Pediatric obesity is one of the most important public health concerns in the United States. In 2009-2010, 12.5 million U.S. children and adolescents (2-19 years) were obese (1). Children with rapid weight gain in infancy and children who are obese during early childhood and adolescence are more likely to be obese as adults. Obesity in each of these periods is thought to be driven by early-life factors. One contributor may be maternal weight gain during pregnancy. Gestational weight gain (GWG) has risen over the past 20 years in the U.S. (2), and some evidence suggests that excessive GWG is associated with a greater risk of infant and child obesity. Studies have been inconsistent, and little work has been done to study pattern of GWG, direct measures of adiposity, and high-risk populations.

The goal of this project is to explore the role of total and pattern of gestational weight gain (GWG) in the development of obesity at three critical periods during child development. We will use data from the Maternal Health Practices and Child Development Study (1982-85), a prospective cohort of 763 low-income, black and white mother-child pairs followed from 20 weeks gestation to 22 years. Gestational weight gain was self-reported by mothers at approximately 20 weeks, 30 weeks, and at delivery. Offspring weight and height were measured along with rich psychological, social, medical, and behavioral data at 18 months, 3 years, and 16

years. Retention was >70% at each study visit. The study will be an efficient use of previously collected data to study our research questions.

1.2 RESEARCH AIMS

The goal of this project is to explore the role of total and pattern of gestational weight gain (GWG) in the development of obesity at three critical periods during child development. We will use data from the Maternal Health Practices and Child Development Study (1982-85), a prospective cohort of 763 low-income, black and white mother-child pairs followed from 20 weeks gestation to 22 years. Gestational weight gain was self-reported by mothers at approximately 20 weeks, 30 weeks, and at delivery. Offspring weight, height, and skinfold thickness were measured along with rich psychological, social, medical, and behavioral data at 18 months, 3 years, and 16 years. Retention was >70% at each study visit. The study will be an efficient use of previously collected data to study our research questions.

The specific aims of this project were as follows:

1) To determine the association between GWG and longitudinal growth over the first 36 months, as well as the risk of rapid infant weight gain from birth to 18 months.

We will study total GWG above, below, and within the 2009 Institute of Medicine GWG guidelines. Longitudinal infant growth will be studied as the average change in infant weight-for-age Z-score (WAZ) based on WHO sex- and age-adjusted growth charts. Rapid infant weight gain from 0 to 18 months will be measured as a change >0.67 standard deviations in WAZ.

We hypothesize that excessive total GWG will be associated with faster growth over the first 36 months as well as a higher risk of rapid infant weight gain.

2) To determine the association between total and pattern of GWG and the risk of childhood obesity at 36 months.

Early childhood obesity will be defined as ≥95th percentile of body mass index-for-age based on sex-specific CDC growth charts. We will study both prevalent and incident obesity. Prevalent obesity will be measured as the percent of obesity at the 36-month follow-up. Incident obesity will be measured as obesity at 36 months among a subgroup of children who were not obese at 18 months.

We hypothesize that excessive total GWG and excessive early-pregnancy GWG will be associated with prevalent and incident obesity at 36 months.

3) To determine the association between total GWG and the risk of childhood obesity at 10 and 16 years.

We will study both prevalent and incident obesity. Prevalent obesity will be measured as the percent of obesity at the 10-year follow-up and 16-year follow-up. Incident obesity will be measured as obesity at 16 years among a subgroup of children who were not obese at 10 years.

We hypothesize that excessive total GWG will be more strongly associated with incident obesity at 16 years.

2.0 LITERATURE REVIEW

2.1 INTRODUCTION

2.1.1 Public health importance of childhood obesity

Childhood obesity is a major public health problem that affects 1 in 10 infants and toddlers aged 6 to 23 months and 1 in 6 children and adolescents aged 2 to19 years in the U.S. (1). From 1971 to 2000, obesity prevalence rates more than doubled for preschoolers and adolescents, more than tripled for children 6 to 11 years (3), and have since plateaued for all age groups (1).

Childhood obesity is associated with insulin resistance, diabetes mellitus, hypertension, asthma, altered pubertal timing, depression, unhealthy eating behaviors, and substance use (4). Additionally, obesity in childhood tracks into later life (5-7) and is associated with related comorbidities in adulthood (8-10). Intriguing data suggest that childhood adiposity may predict adulthood morbidity, independent of adult BMI (11, 12). This persistent effect of early-life obesity highlights the importance of primary and secondary prevention.

Treatment of obesity in infancy, early childhood and adolescence may reduce risk of adulthood obesity and associated morbidities (13), but this impact may be limited (14, 15) because obesity is resistant to treatment. Primary prevention efforts are critical to reducing

obesity rates (13). However, a deeper understanding of the causes of childhood obesity is needed for interventions to be most effective.

2.1.2 Etiology of childhood obesity remains obscure.

A positive energy balance is the most accepted theory of the cause of obesity (16). For adults, weight maintenance occurs when energy balance is zero, and weight gain occurs when energy intake is greater than energy expenditure. In children, a slight positive energy balance is necessary to sustain normal child growth, but a substantial positive energy balance will cause a gain of excess fat (3). Inadequate physical activity and excess caloric intake each contribute to the energy surplus. While other postnatal factors, such as insufficient sleep (17, 18) and gene-environment interactions (19, 20) may exaggerate the energy imbalance, further increasing the risk for childhood obesity, a growing body of evidence suggests that Intrauterine exposures may also play a role (21).

The goal of this study is to explore the role of maternal weight gain in pregnancy – a modifiable intrauterine factor – in the development of obesity. We will study GWG in relation to measures of child obesity during three critical periods: infancy, early childhood and adolescence. Nutritional status during these developmental stages in a child's life is thought to alter metabolism and physiology, and increase the risk of persistent adult obesity and its complications (22, 23). While each of these critical periods reflects a change in growth pattern, it is yet unclear which of these periods is relatively most important in adult obesity (10).

2.1.3 The intrauterine environment may reflect a critical period of obesity development.

The 'fetal origins of disease' hypothesis posits that fetal alterations in maternal-fetal nutrition lead to permanent developmental changes (24). The fetus may adapt to in-utero insults for a developmental advantage (25). These changes may include altered structure and function of fetal organs and tissues, when these systems are still 'plastic'. In later life, these formerly advantageous changes may incite postnatal disease. This general theory became popularized through the Barker Hypothesis, which suggests that low birth weight, a marker of poor in-utero growth, is associated with various diseases in late life, including obesity (21, 24, 26, 27). In contrast, high birth weight as a marker of fetal overnourishment is also associated with later life obesity (21). Taken together, this suggests a U-shaped relationship between in-utero nutrition and risk for adulthood obesity (25, 28). However, studies using birth weight as a proxy for the intrauterine environment have failed to find a U or J-shaped risk for adulthood obesity but instead find a positive linear association with BMI (29, 30). In contrast, many studies find a negative linear association between birth weight and direct measures of central obesity in adulthood after adjusting for current weight (21, 31). Far fewer data support a U-shaped association between maternal nutrition and childhood obesity (23, 32). In a recent study, a U-shaped association between total pounds of gain and child's BMI Z-score became linear after adjustment for prepregnancy BMI (**Figure 1** (33)). In fact, a positive, linear relationship between total GWG and childhood weight has been detected in several studies controlling for confounding by prepregnancy BMI (34-37) and in a study of GWG pattern (38).

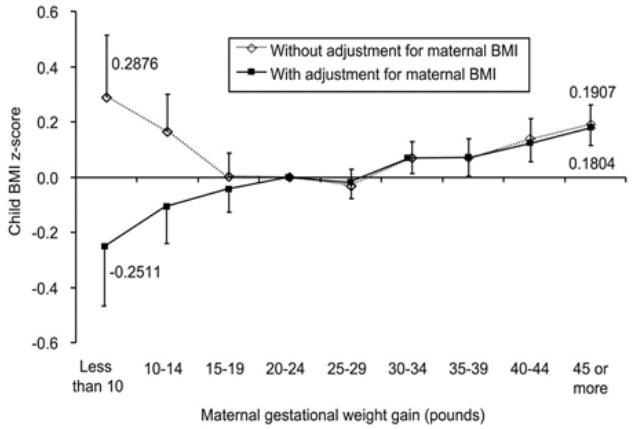


Figure 1. Association of GWG and child BMI Z-score adjusted for confounding by maternal BMI

Much of the literature linking the in-utero environment to long-term offspring obesity is rooted in a series of studies on pregnancies during the 1944-1945 Dutch famine. Since the famine lasted only seven months, women experienced malnourishment at various stages of pregnancy, affording researchers the ability to explore the long-term impact of nutritional patterns during gestation (39). The Dutch famine studies have suggested that undernutrition in late pregnancy is associated with smaller neonatal body size (40, 41) but in early pregnancy, undernutrition has been associated with adulthood obesity (particularly centrally-located) and cardiovascular disease (39, 42-45). To our knowledge, there are no studies of childhood obesity in the Dutch famine cohort. The available epidemiologic data on inadequate prenatal nutrition and childhood obesity are limited and inconsistent. In one study, pregnant Indian women consumed fewer calories (~1800 cal d^{-1}) and had smaller, shorter and thinner infants compared with a UK cohort (~2400 cal d^{-1}), but infants had similar subscapular fat (46), suggesting deficits in lean mass but preserved fat mass. In a comprehensive review, several studies used birth weight as a proxy of intrauterine nutrition (31) and suggest that the consistent positive

association between birth weight and later BMI may be driven by lean body mass, rather than fat mass. The inconsistency in findings may be due to the level of nutritional deprivation, use of birth weight to indirectly represent maternal nutrition, or postnatal overfeeding to compensate for famine or small birth size (47, 48). The association between insufficient in-utero nutrition and offspring weight may be explained by prenatal smoking (23) or socio-economic position (31), each of which is associated with deficits in fetal growth, yet obesity in childhood (49).

Today in developed countries, maternal overnutrition is more common, as is childhood obesity, yet data are just beginning to be published on this potential association. Most of the literature relating maternal nutritional status and child weight is based in work linking gestational diabetes mellitus (GDM) to fetal hyperinsulinemia, subsequent fetal overgrowth, and infants born large-for-gestational age (2). Long-term studies have been mixed on whether GDM affects offspring weight into childhood and adolescence (50-53). Since GDM is a metabolic disorder leading to fetal overnutrition, and is more likely among heavier women who have higher energy reserves, an association with offspring long-term weight is plausible. Unlike maternal starvation, very little is known about the timing of overnourishment and the health consequences for offspring (2), but recent data suggest an association.

Summary: Studies from GDM pregnancies and pregnancies during the Dutch famine suggest a U-shaped association between maternal nutrition and offspring obesity. Studies of maternal weight gain support a U-shaped association with offspring BMI when unadjusted for confounding by prepregnancy BMI, but after adjustment, this association was positive in a number of studies. Data are inconsistent in studies using proxies of maternal nutrition such as birth weight and infants of GDM pregnancies. Birth weight and GDM are consistently, positively associated with later offspring BMI, but later body composition is less clear. Studies

of birth weight suggests that fat tissue is preserved at the expense of lean tissue, yet studies of GDM pregnancies suggest a consistent, positive association with fat mass. It is thus unclear whether maternal nutrition and offspring adiposity are associated. Further work in this area is warranted.

2.1.4 The intrauterine environment may impact obesity development during three critical periods: infancy early childhood, and adolescence

Critical periods for obesity development are energetically costly and may be biologically protected against weight loss, in order to promote growth and development. Changes in body composition and body fat distribution occur during each critical period. The physiologic changes that permit fat deposition may be a naturally-occurring process in which the body stockpiles energy reserves in order to support developmental periods (54, 55). The propensity for adulthood obesity may be more likely in a child 'overly-protected' against weight loss during these periods.

The physiologic alterations driving body composition changes may be programmed in early life. Maternal metabolism may condition fetal regulatory mechanisms to be hypervigilant, thus 'overprotecting' against weight loss, which may be exaggerated during these biological states. Alternatively, high fat accrual may result from a mechanism in which there is a failure to limit energy reserves, such as increased appetite.

2.1.4.1 Infancy.

Neonatal and infant fat may be biologically protected in order to fuel brain development (56). Human neonates have large brains and have relatively high body fat (15%) compared with other mammals (57, 58). High fetal fat may serve as a buffer to anticipated energy deficits when transitioning from placental nutrition to breastfeeding (59). At approximately 6 months, fat deposition peaks at 25% body fat (57, 60) which may protect against energy deficits during weaning (56).

2.1.4.2 Early Childhood.

Less literature speculates why the second changing growth pattern, adiposity rebound (AR), may be a biologically protected state, perhaps because AR is a relatively new concept (61). Taking place during early childhood (ages 5-7), AR is traditionally defined as a nadir of body mass index on the child growth curve chart (61, 62). The rapid increase in body mass index following the nadir is thought to be an accrual of fat, rather than lean tissues or height (62-64), though recent work suggests otherwise (65). Fat accrual in early childhood may be necessary to cue or support adrenarche, a poorly understood period of child brain development occurring in middle childhood. In adrenarche, the adrenal glands begin to produce dihydroepiandrosterone (DHEA), the most abundant steroid in humans, and a prohormone for sex steroids. It is thought that DHEA binds to dendrites in the brain (66), acts as a neurosteroid, and is associated with prepubescent social and cognitive development (67). Fat deposition in this period may protect childhood brain development.

2.1.4.3 Adolescence.

Adolescence may be a biologically protected state in order to improve reproductive success, especially in girls. Women may require fat stores to support the energy-demanding state of pregnancy made possible by puberty. Changes in body fat composition and distribution are drastic during the pubertal transition. These changes include (1) predominantly the deposition of fat-free mass (95% of weight gain in boys, 85% in girls) (68), (2) an increase in total body fat among girls, but not boys (55), demonstrated by an increase in total body fat from ~17% to ~24% in girls, but a decrease among adolescent boys (69, 70), (3) a shift in body fat from the extremities toward the trunk (71) and increases in central fat deposition (to a greater extent in boys (~5-fold increase) than girls (~3-fold increase)) (69), (4) a non-linear increase in BMI for both sexes, (5) a dynamic shift in triceps skinfold thickness distribution, dependent on sex (72). Adiposity during these three critical periods may be driven by biological mechanisms supporting the energy needs for upcoming periods of physiologic and evolutionary importance—such as brain development and reproduction. Fat accrual is a normal physiologic process during infancy, early childhood, and adolescence, but may be exaggerated by maladaptive in-utero adaptations.

2.1.5 Gestational weight gain (GWG) is a modifiable in-utero exposure that may be associated with child obesity.

The 2009 Institute of Medicine Committee to Reevaluate Gestational Weight Gain Guidelines ((2), **Table 1**), identified evidence-based ranges of weight gain that attempt to optimize maternal and offspring risks associated with low and high gain. Weight gain below the recommended ranges is associated with increased risk of small-for-gestational-age birth, preterm birth, and

neonatal death while gain exceeding the ranges is associated with infant overgrowth, gestational diabetes, and maternal postpartum weight retention (2). When the revised guidelines were published in 2009, there was little data on child obesity in relation to GWG to inform the recommendations. The 2009 IOM Committee called for further research on the association between GWG and offspring obesity to inform future evidence-based guidelines. Our study will directly address this research gap at three critical periods of development thought to predict adulthood obesity risk.

Table 1. Gestational Weight Gain Recommendations, IOM 2009

Prepregnancy BMI (kg/m^2)		Total weight gain (lb)	Rate of weight gain 2^{nd} & 3^{rd} trimester (lb/wk) [1]
Underweight	< 18.5	28 – 40	1.0 (1.0 – 1.3)
Normal weight	18.5 – 24.9	25 – 35	1.0 (0.8 – 1.0)
Overweight	25.0 – 29.9	15 – 25	0.6 (0.5 – 0.7)
Obese	≥ 30	11 – 20	0.5 (0.4 – 0.6)

[1]Calculations assume a first-trimester weight gain of 1.1-4.4 lb (0.5-2.0 kg)

Excessive GWG is common in U.S. pregnancies. While no nationally-representative data exist to study trends in GWG in the United States, a number of large U.S. databases suggest that women increasingly gain outside of the IOM GWG guidelines. Pregnancy Risk and Monitoring System (PRAMS) population-based surveys from 1993-2003 suggested that a majority of women gained outside the 1990 Institute of Medicine GWG guidelines (2). Absolute weight gains are lower as BMI increases, but because recommended ranges for gestational weight gain

decrease with increasing BMI, more women gain in excess of the guidelines. Underweight women tended to gain inadequately, yet normal weight, overweight, and obese women gained in excess (2). Data on federally funded program enrollees in the Pregnancy Nutrition Surveillance System (PNSS) supported these findings (2).

In a normal, healthy pregnancy, dynamic physiologic fluctuations promote weight gain to build essential maternal and fetal tissues (73). Maternal insulin resistance is one of several adaptations that sustain a constant supply of glucose for the fetus. Since insulin does not cross the placenta, but glucose does, the fetus must make insulin in order to uptake glucose. In women with ample energy reserves, such as overweight women or those gaining excessive weight during pregnancy, the fetus may become more severely insulin resistant or resistant for a longer time, when presented with persistently high glucose levels (74, 75). This pathway may lead to fetal fat accumulation (76), and a propensity for fat accrual postnatally (77). The associations between gestational diabetes and large-for-gestational age birth (78) and childhood adiposity (79) offer strong evidence to support this theory. However, it remains unclear whether less extreme maternal metabolic dysfunction impacts offspring adiposity in the short- and long-term (80).

2.2 GESTATIONAL WEIGHT GAIN AND OFFSPRING WEIGHT

2.2.1 Neonates (<4 weeks)

There is a strong, consistent finding across populations between excessive GWG and large-for-gestational-age infants (LGA) (78, 81). However, LGA does not provide information on infant fat mass. Since excess maternal GWG and high maternal pregravid BMI are likely to jointly

contribute to fetal fat accrual, it is important to measure infant body composition, but data are limited. Only one study described the effect modification of maternal prepregnancy BMI on the association between GWG and a direct measure of neonatal body composition (82). Hull and colleagues found that among overweight women, maternal weight gain in excess of the 2009 IOM guidelines was associated with higher neonatal fat mass as measured by air displacement plethysmography, in a multi-ethnic Manhattan hospital sample of healthy, full-term infants (n=306). Yet for women with pregravid obesity, there was no association between excess gain and infant fat measures. These data, which agree with others' findings (83), underscore the importance of accounting for prepregnancy weight. In an urban Canadian sample, women who gained excessive weight according to the 2009 IOM guidelines had infants with caliper-measured suprailiac skinfold thicknesses that were higher, on average, as compared to those who gained adequately (84). Air displacement plethysmography was also used in a small study (n=38) of Chicago-area women and found that excessive GWG was associated with a mean fat mass 175 grams higher than gain within the guidelines (p=0.009), but fat-free mass was not different by GWG category (85). In a larger (n=948) British sample, dual X-ray absorptiometry (DXA) was used to measure fat mass in 564 neonates (36). After adjusting for sex, gestational age at measurement, and infant length, GWG above the 2009 IOM was associated with an increase in neonatal fat mass compared with GWG within the recommended range. In support of these studies, a high total GWG (>18 kg) was positively associated with subscapular and triceps skinfold thicknesses in a large (n=7945) sample of Australian mother-infant pairs (86). Collectively, these results support a positive association between excessive GWG and neonatal fat mass.

A noteworthy approach was taken to study the timing and amount (also referred to as 'pattern') of GWG in relation to infant fat (84). Among 172 healthy, nonsmoking women, four mutually exclusive patterns of GWG were studied based on adequacy of the 2009 IOM in two periods of pregnancy: early (<20 weeks gestation) and late (≥20). Women who gained excess weight in both early and late pregnancy (n=61) had infants with a higher BMI compared with infants of women who gained adequately in both periods (n=33). Skinfolds were higher for children of women who gained excess weight in both periods as compared to women who gained adequately in both periods. However, there were no differences between gain specific to early pregnancy. The four groups were not compared for neonatal body fat and instead were collapsed to two groups based on the gain in early pregnancy. Compared to women who gained adequate weight in early pregnancy (early and late adequate; early adequate and late excess), those who gained excess weight in early pregnancy (early and late excess; early excess and late adequate) had infants with higher percent body fat after adjusting for prepregnancy BMI. This comparison suggests that too much GWG in early pregnancy may influence infant adiposity, but it is unclear whether the gain in early pregnancy alone drives this association, or if instead it is predominantly driven by the group of women with excess gain in both periods. Higher GWG in early pregnancy may be the result of greater fat stores rather than fetal growth (2). These data suggest that intervention in early pregnancy may restrict premature GWG, and may be an effective approach to prevent early-life risk factors.

Table 2. Summary of literature linking GWG to neonatal fat mass

First author	Sample	Birth years	GWG measure	Adiposity measure	Result
Hull (82)	306 New York, NY	2002-06	Measured, IOM categories	Fat mass	+
Crozier (36)	564 United Kingdom	1998-03	Measured, IOM (1990) categories	Fat mass	+
Tikellis (86)	7,945 Australia	1988-95	Recalled, Total amount of gain	Supscapular skinfolds[1] Triceps skinfolds[2]	+[12]
Sewell (83)	220 Cleveland, OH	1990-00	Recalled, Total amount of gain	% body fat	+
Josefson (85)	38 Chicago, IL	unknown	Measured, IOM categories	Fat mass	+
Davenport (84)	172 Ontario, Canada	1995-07	Measured, IOM categories, timing of GWG	% body fat[1] BMI[2] Supriliac skinfold[3]	+[123]

2.2.2 Infancy (1 to 24 months)

The literature on GWG and attained infant weight or adiposity in the first 24 months is mixed. In contrast to a majority of the literature on GWG and offspring weight (87), two small U.S. studies found a negative association between total amount of GWG and infant weight (88, 89). Higher GWG was associated with a decrease in WLZ at 2 and 3 months based on the 2006 WHO standards in a small U.S. sample (n=40), but there were no associations at birth, 2, or 4 weeks, and no association at any age for infant WAZ or BMIZ (89). Similarly, a 5-lb increase in total GWG was associated with a lower likelihood of infant BMI ≥84th percentile (based on within-study norms) at 14 months after adjustment for mother's usual nonpregnant weight and child's BMI at a previous study visit (e.g., BMI at 10 months was adjusted for BMI at 7 months), but there were no associations at 1, 4, 7, or 10 months (88). Yet in a French birth cohort total

amount of GWG was associated with higher infant weight at 1 and 3 months (unadjusted for age and sex) after adjusting for prepregnancy BMI (90). Similarly, GWG ≥85th percentile based on internal standards was associated with higher child weight at birth, and higher WHO-based weight at 3, 6, and 9 months, but was unassociated at 12, 18, or 24 months in a Chinese sample (91).

Two studies of attained infant weight (92, 93) classified GWG according to standards from the Institute of Medicine based on prepregnancy BMI. In a large (n=38,539) Chinese sample of term deliveries using prepregnancy BMI specific to Chinese populations (94), a positive association with child weight was observed across several ages during infancy in a (92). Excessive GWG was associated with a higher age and sex-adjusted weight at birth, 3, 6, 9, and 12 months based on the 2006 WHO standards. At 12 months, the children of women who gained in excess of the guidelines had a higher likelihood of a WHO-based WLZ ≥95th percentile (odds ratio (95% CI): 1.31 (1.23, 1.40)) compared with women whose gain met the guidelines. Women who gained inadequate weight had children with a reduced likelihood for WLZ ≥95th percentile at 12 months (0.85 (0.75, 0.96)) compared to adequate. Models were adjusted for a number of confounders, but did not include prepregnancy BMI, so residual confounding cannot be excluded. In a study of 266 Iranian women and their term-born children, inadequate GWG was common (34%) and no children had a CDC-based BMI ≥95th percentile at 24 months (93). Women who gained inadequately had infants with lighter weights at 12 and 24 months compared to higher categories of gain, though there were no differences in child weight among women who gained excessive or adequate weight.

Total GWG ≤30 weeks gestation was not associated with DXA-measured percent truncal, peripheral, or total body fat in a random subsample of a large prospective study of Dutch 6

month-olds after controlling for gender, gestational age at delivery, length, and age at assessment (95). Interestingly, fetal growth in the intrauterine environment 20-30wk was measured using ultrasound and was positively associated with a change in infant fat and lean mass >0.67SD at 6 months, but fetal growth ≥30wk was unassociated with body composition at 6 months, after adjustment. These results suggest that infant growth is partially determined in early life, but the direct association between GWG and infant growth must be studied. Yet in a small (n=47) U.S. sample, there was a trend for higher category of GWG to be associated with higher trunk fat at 12 months and no association was observed between GWG and infant lean mass (96).

Results are also mixed for studies on weight gain or growth. Growth velocities indicate growth dynamics as well as the timing of growth. In contrast, achieved weight and length embody both prenatal and postnatal effects. Thus, instantaneous growth will be more informative in studying prenatal exposures.

Among infants <6 months, GWG was positively associated with continuous measures of infant growth in two studies that did not apply a growth standard (90, 96) as well as a study that did (97). In a sample of women from two French prenatal clinics (n=1,418), total amount of GWG was associated with linear weight- and length-growth velocities (grams/day) from 0 to 1 month, but the effect diminished from 0 to 3 months. Yet an analysis of a small Oklahoma sample found that a higher category of the 2009 IOM GWG guidelines was associated with a borderline trend for a faster rate of infant growth from 0 to 3 months (96). In a North Carolina sample of term-born, healthy infants, severely excessive GWG (≥200% of the 2009 IOM) was associated with faster increases in CDC-based WAZ and WLZ from 0 to 6 months as compared to adequate GWG, however, there was no association with the risk of rapid infant weight gain (WAZ 0 to 6 mo >0.67 SD) (97). Similarly, there was no association between total amount of

GWG and rapid infant weight gain (WAZ 0 to 24 mo. >0.67 SD) based on the UK growth charts in a subsample of the ALSPAC pregnancy cohort (98).

Few analyses of GWG and offspring weight have been conducted using a longitudinal approach. In a longitudinal analysis of the PIN cohort (North Carolina), severely excessive GWG (≥200% of the 2009 IOM) was associated with persistently higher weights and faster infant growth from 0 to 36 months using CDC-based WAZ, but not WLZ compared with GWG within the guidelines (37). In contrast, Li and colleagues conducted a series of cross-sectional analyses of a large sample of Chinese mother-child pairs and found a significant trend for the children of women with higher categories of 2009 IOM GWG to have smaller increases, and thus slower growth, in WHO-based measures of WAZ and WLZ from 0 to 3 months, 3 to 6 months, and 0 to 12 months (92). The children of women who gained less weight in pregnancy had larger increases in WAZ and WLZ during each of these periods. Thus, the available literature on WHO-based child growth directly contradicts work that compares child growth to the CDC standard.

While the literature in the first 24 months is largely mixed, this age of development is thought to be important to later obesity. In a study of the development of child obesity (≥95th percentile) by age 12, nationally-representative, racially-diverse U.S. data of 1,739 children were used to identify three growth trajectories of child BMI (99). Li and colleagues found that mothers with a total amount of GWG ≥45 lb. were more likely than mothers gaining 25-35 lb. to have children with early-onset overweight (diverging at 2 yr) after adjusting for prepregnancy BMI, birth weight and other factors. However, total amount of maternal weight gain was unassociated with late-onset overweight (diverging at 6 yr). This finding implies that in early life, the GWG-child growth association may be particularly influential.

Summary: Of the twelve studies on early infant weight, the results are mixed and may be due poorly-defined measures of GWG or the varied measures of infant size and growth. Two studies using IOM-based GWG and CDC-based age and sex-adjusted measures of growth (WAZ, LAZ, WLZ) from 0-6 months and 0-3 years found that excessive GWG was associated with higher infant size and faster growth over time. In contrast, in two of three studies where infant growth measures were based on the WHO standard, women who gained excess weight had infants who were larger at each assessment, yet grew slower 0-3, 3-6, and 0-12 months. Whether the chosen growth standard explains these differences remains unclear. Rapid weight gain during infancy (RWG) is thought to be a crude marker of infant obesity and may be a risk factor for later life obesity; yet the relationship between GWG and RWG has only been reported in two publications, and results were mixed. GWG in excess of 200% of the IOM recommendations was positively associated with rapid growth (RWG) from 0-6 months, but in another report, total GWG was not associated with RWG in the first 24 months. These mixed results may be due to inherent differences in growth over age ranges covered.

BMI is meant to reflect total body fat, yet the three studies of body fat this do not suggest a clear direction of the associations. No relationship was detected in three of six studies using total gain (confounded by gestational age and prepregnancy BMI) or in four studies using unstandardized measures of anthropometry or body composition. This underscores the importance of using well-defined measures of GWG and child outcome, accounting for known confounders.

Table 3. Summary of literature linking GWG to infant adiposity and weight gain

First author Ages assessed	Sample	Birth years	GWG measure	Adiposity measure	Result
Ay (95) 6 mo	252 Netherlands	2002-06	Measured, total amount of gain	% body fat	null
Sowan (88) 1, 4, 7, 10, 14 mo	630 Iowa	1988-96	Recalled, total amount of gain	BMI (within-study norms)	null 1, 4, 7, 10 mo - 14 mo
Li (99) 0-12 yr diverge 2 yr	1,739 Multiple sites, US	1984-90	Recalled, total amount of gain	BMI (2000 CDC)	+ diverge 2 yr
Deierlein (37) 0-36 mo	476 North Carolina	2001-05	Measured, IOM categories	WAZ[1], WLZ[2] (2000 CDC)	+[1] null[2]
Deierlein (97) 0-6 mo	363 North Carolina	2001-05	Measured, IOM categories	WAZ[1], WLZ[2] (2000 CDC) Rapid infant weight gain[3] (WAZ>0.67 SD)	+[12] null[3]
Ong (98) 0-24 mo	848 United Kingdom	1991-92	Measured, total amount of gain	Rapid infant weight gain (WAZ >0.67 SD) (1990 UK)	null
Regnault (90) 0-1, 0-3 mo	1,418 France	2003-05	Measured, total amount of gain	Weight velocity (grams/day)	+ 1, 3 mo null 0-1, 0-3mo
Anderson (89) 2 wk, 1, 2, 3 mo	40 Athens, GA	2005-08	Recalled, IOM (1990) categories	Fat mass[4] WAZ[1], WLZ[2], BMIZ[3] (2006 WHO)	null 2wk[1234], 1mo[14], 2mo[124], 3mo[14] - 1mo[23],2mo[3], 3mo[23]

Table 3 continued.

Chandler-Laney (96) 0-3, 12 mo	47 Oklahoma City, Oklahoma	unknown	Recalled, IOM categories	Weight velocity[5] (grams/day) Fat mass[4]	+[45]
Li (92) 3, 6, 9, 12 mo	38,539 Tianjin, China	2009-11	Measured, IOM categories	WAZ[1], WLZ[2], BMIZ[3] (2006 WHO)	Attained weight + 3, 6, 9, 12 mo Change in weight - 0-3, 3-6, 0-12 mo + 6-12 mo
Liang (91) 3, 6, 9, 12, 18, 24 mo	317 Hefei, China	2008	Measured, total amount of gain	WAZ (2006 WHO)	+ 3, 6, 9 mo null 12, 18, 24 mo
Ahmadi (93) 12, 24 mo	266 Tehran, Iran	2004-08	unknown (medical records), IOM (1990) categories	BMI (2000 CDC)	null 12, 24 mo

2.2.3 Early childhood (2 to 5 years)

The most convincing evidence for an association between GWG and adiposity in early childhood comes from six modern, prospective pregnancy cohorts of predominantly white women from the US (34, 100), UK (36), the Netherlands (101), and Germany (102, 103) with data at specific child ages.

First, an analysis of 1,044 Boston, MA mothers (Project Viva), every 5-kg increase in net GWG [total gain – birth weight] was associated with a 52% increase in the odds of child obesity at age 3 years (BMI≥95th vs. <50th percentile) after adjustment for parental BMI, birth weight, maternal glucose tolerance, breastfeeding duration, and other covariates (34). Similarly, net GWG was positively associated with a 28% increase in summed triceps and subscapular skinfold thickness as well as a 75% increase in systolic blood pressure. In fully-adjusted multinomial logistic regression models, both adequate and excessive GWG (1990 IOM) were associated with greater odds of a high child BMI compared with inadequate GWG. There was no evidence of an interaction on the multiplicative scale by prepregnancy BMI.

The results from Oken's study were confirmed in a similarly-sized (n=948) UK cohort (36). Crozier and colleagues studied the association between DXA-measured specific adiposity and the total GWG to 34 weeks with ranges adjusted to the 2009 IOM recommendations for each BMI category. Offspring from term births (≥37 wk) were studied longitudinally from birth to 6 years. After adjustment for birth weight, excessive GWG was not associated with fat mass at 4 years (OR=1.15 (95% CI: 0.97, 1.36), but was associated with fat mass at 6 years (1.30 (1.07, 1.57)) compared with adequate GWG. Children of women who gained inadequately had higher fat mass at 4 (1.16 (0.94, 1.42)) and 6 (1.17 (0.94, 1.46)) years than GWG within the

recommendations, but these differences did not reach statistical significance. The U-shaped association between GWG and fat mass is likely to be negatively confounded by prepregnancy BMI, since heavier women tend to gain less weight (2), but also tend to have children with higher adiposity (6). With adjustment for pregravid BMI, the association at 4 years may be positively associated and the association at 6 years may be stronger.

Unlike Oken's study, three papers reported heterogeneity in the association between GWG and child BMI by maternal prepregnancy weight (100-102), while another (103) did not find evidence of effect modification, yet stratified models regardless and concluded that their study was underpowered.

In a nationally-representative US birth cohort (n=3,600), Hinkle and colleagues found an interaction between total amount of GWG and prepregnancy BMI category for child's BMI at 5 years (100). Among normal weight and overweight women, GWG above the midpoint of the IOM recommendations was associated with an increase in child BMI z-score, but there were no associations among underweight or obese women. In addition, the authors use d a path analysis to determine whether the total effect of gestational weight gain was direct or indirectly related to child's BMI at 5 years. The direct effect of gestational weight gain on child's BMI Z-score was not mediated through birth weight among women with normal prepregnancy body mass index. This suggests that the association between gestational weight gain and childhood weight may be causal, similar to a study of 7-year olds (104).

In support of this US study, maternal prepregnancy body mass index modified associations in three European samples. In a large (n=5,674) population-based prospective cohort study of pregnant women and their children in the Netherlands (101), every 4.7 kilogram increase in maternal weight gain was associated with offspring body mass index z-score at ages

1, 2, 3, and 4 years in the overall sample, though these estimates were not adjusted for prepregnancy BMI. Among lean women, every 4.7 kilogram increase in GWG was associated with an increase in child BMI at ages 1, 2, 3, and 4 years, but there were no associations among overweight or obese women. Two large retrospective birth cohort studies of German women and their children (102, 103) found a positive association between GWG and child weight among lean women but not among underweight, overweight, or obese women. In a combined dataset from three German cohorts, Beyerlein and colleagues found that among normal weight women, excessive GWG was associated with a 28% increase in the odds of childhood overweight (95% CI: 1.02, 1.61), compared with adequate after adjustment (102). GWG was not associated with child overweight among underweight, overweight, or obese women. The use of combined datasets complicates interpretation since the ascertainment of the exposure and outcome differs. Yet sensitivity analyses specific to each study population did not meaningfully change estimates, making it more likely that the reported association is real. Ensenauer and colleagues found that compared to adequate, excessive GWG was associated with a 29% increase in the likelihood of child's BMI ≥90th percentile (95% CI: 1.01, 1.66), and a 35% increase in the likelihood of a waist circumference ≥90th percentile (95% CI: 1.11, 1.65), after adjusting for covariates (103). In addition, they used spline terms for GWG and found that the likelihood for child BMI ≥90th percentile and waist circumference ≥90th percentile was flat for GWG <12 kilograms, but the likelihood increased for GWG ≥12 kilograms. While the authors reported that no effect modification was evident, they gave stratified results by prepregnancy BMI, finding that among overweight women, excessive GWG was associated with child BMI [OR (95% CI): 1.75 (1.14, 2.80)], but not waist circumference [1.07 (0.75, 1.55)], compared with adequate GWG. No

associations between GWG category and child weight were observed among underweight women or obese women.

Differences in gestational length were addressed by adjusting for gestational age as a confounder (34) or by restricting the gestational age studied (100), but residual confounding by length of gestation likely exists. Crozier and colleagues studied total weight gain based on classification at 34 weeks' gestation rather than final weight at delivery. Despite these limitations, there were consistent positive associations reported by three studies in moderately-sized population-based data; for all, GWG measures accounted for EMM by prepregnancy BMI included several covariates in models, and two studies used directly-measured childhood adiposity.

The most convincing data rebuking an association is based on an elegant analysis using the Collaborative Perinatal Project (CPP), a large, racially-diverse prospective pregnancy study (105) in which women were studied across two recorded pregnancies (n=5,917; n=2,758 sibling-pairs). A sibling analysis compares and contrasts estimates when controlling for unmeasured confounding by shared familial traits such as genetics and environment. Two multivariable linear regression models were compared: 1) a conventional model clustered by siblings, and 2) a fixed-effects model comparing siblings of the same family. In population average (conventional) models adjusting for prepregnancy BMI, each 5-kg increase in GWG was associated with BMI Z-score at 4 years (β=0.07 (95%CI: 0.04, 0.01)), but in fixed effects models conditioned on the mother, the effect was no longer significant (-0.03 (-0.08, 0.02)). Consistent results were found for category of the 2009 IOM. The authors did not find an interaction between prepregnancy BMI and GWG when entering the cross-product term to the model. Thus, the authors concluded that the association with child weight is highly confounded by shared familial traits, such as

genetics or lifestyle factors, and suggested that child obesity is not due to intrauterine exposures. Further, adjustment for birth weight in fixed models did not attenuate the association for GWG or prepregnancy BMI; consequently, the authors concluded that birth weight is not a mediator. Branum and colleagues are not the only authors of a compelling study to include results with and without adjustment for the mediating effect of birth weight (34, 36, 92, 97, 102, 103, 106-108). Yet methodologists argue that including a potential mediator in a model does not remove it's effect (109) and worse, may bias estimates (110). From the outset, we believe that birth weight may lie on the causal path and thus we will not consider it in models and report statistics from the literature that are unadjusted for birth weight when available.

Two additional sibling analyses that were conducted in older offspring (106, 108) dispute Branum's study. In a study of 42,133 women and their 91,045 offspring born from 1989 to 2005, there were available birth records and child weight from public schools in Arkansas (108) (Table 5). With every 1-kilogram increase in GWG, there was an 0.02 increase in child BMI in 6-18 year-olds (95% CI: 0.01, 0.03), and the odds of child overweight increased by 0.7% (1.003, 1.012). Lawlor and colleagues studied Swedish men and their brothers (birth years: 1973-1988) in a total of 136,050 Swedish families (106) (Table 6). BMI data for 18-year old men were obtained from linking data from military records, birth records and the Swedish housing census. The authors reported that among lean women, the positive association between GWG and offspring weight is driven by shared familial characteristics (genetics, environment). Yet for overweight women, the positive association is driven by both shared familial characteristics as well as the intrauterine environment.

The sibling analyses by Branum, Ludwig, and Lawlor may disagree because of the ages of the siblings studied. One possibility is that both Ludwig and Lawlor used larger, more

modern samples with a higher prevalence of child overweight/obese (39.4% and 21.1%) than children in the CPP, these studies were better powered to detect differences between pregnancies after the inherent control for strong confounders, distinctive of a sibling analysis. Further, since births in the CPP data took place in an era when GWG was restricted (1959-65), the association between obesity and GWG may be different than the association observed in more modern data capturing the start of the obesity epidemic (1973-88) or thereafter (1989-05). The mixed results of these similarly-designed studies compels further work in this area in order to determine whether a causal association truly exists. While our observational data will not inform causality, we will be able to adjust for a number of known confounders of the shared maternal-child environment, which may confirm the positive findings.

Two US studies used medical record data and measures based on the 2009 IOM GWG guidelines, but did not find associations with child obesity at 4 or 5 years (111, 112). A large (n=3,302) retrospective study of labor and delivery records from 2004 to 2007 were linked to well-child visits at approximately 4 years of age, within the Christiana Care Health System in Delaware, US (112). Among term infants, excessive GWG was not associated with child's BMI Z-score [Beta (95% CI): 0.051 (-0.039, 0.140)], compared with adequate after adjustment for covariates. A pregnancy cohort in the Midwest did not find an association between GWG and child's BMI at 4-5 years (n=359) (111), but this may be due to a biased measure of GWG adequacy. Since maternal weight gain was based on a first prenatal visit (mean: 10.3 weeks) subtracted from the weight just prior to delivery (gestational age not reported), the total amount of weight is likely to be underestimated, resulting in an underestimation of excessive GWG, perhaps giving biased estimates.

Associations were not identified between total GWG and child BMI between 2 and 5 years in a large US WIC-birth certificate linked database that studied rate of net gain [(total GWG – birth weight) / gestational length] (113), a small US prenatal clinic (total gain>net gain for normal weight women (114)), or a small Polish prenatal sample (total GWG>75th percentile) (115)). Five of these seven null studies had serious limitations in the methods used to classify GWG (111-115). Interestingly, a large US of health system enrollees found a positive association between net gain [total GWG – birth weight] and child's BMI Z-score at 4 years [Beta (95% CI): 0.0116 (0.0058, 0.0174)] (112).

Two unique analyses tested whether the pattern of GWG impacts child weight (116, 117). In a cohort of U.S. births from 1959 to 1968, researchers found that each 1-kg increase of measured GWG in the first trimester was associated with an increase in the odds for child overweight (BMI≥85th percentile) at 5 years (OR=1.05 (95% CI: 1.02, 1.09)) (116). This effect was more strongly associated with BMI among offspring of underweight women (1.10 (1.04, 1.18)), was weaker for normal weight (1.04 (1.02, 1.07)), and was unassociated for overweight women (1.02 (0.94, 1.05). In contrast to the finding for the first trimester, there was no association between GWG in the second and third trimesters and odds of child overweight, which tend to agree with other reports (38, 84, 104). More gain in early pregnancy may be the result of greater fat stores rather than fetal growth (2). These data suggest that early intervention to restrict early gain may be the most effective approaches to prevent early-life factors of child obesity. In contrast to the finding by Margerison-Zilko and colleagues, a retrospective study of 6,665 German schoolchildren and their mothers found that measured gain in the third trimester specifically contributed to the risk of child's overweight (117). von Kries and colleagues found that women who gained non-excessive weight in the third trimester (based on the 2009 IOM) had

children with a 31% lower risk of obesity (95% CI: 0.59, 0.82) as compared to the children of women who gained late excess weight, regardless of their gain in earlier pregnancy. It is unclear why these results differ, and it may be due to the definition of 'early' pregnancy. von Kries' study collapsed the first and second trimester to be designated as 'early'. This definition of early encompasses biologically different periods, in which there are a wide range of developmental achievements for the fetus as well as different rates of fat accumulation and other pregnancy components for the mother. Further, von Kries' study does not compare all weight gain groups to a common idealized referent group of non-excessive gain in both early and late pregnancy. Additional research is necessary must be done to determine how these maternal weight gain groups compare with regard to child's risk for overweight.

Summary: The results of previous studies on ages 2-5 are mixed, but this may be partially explained by a differential effect based on timing of GWG. Excess total gain may be due to high gain in a specific period or over the entire gestation; in contrast, high gain in a specific period may not result in classification above the IOM. In the proposed analysis, we will contribute to knowledge by studying both total GWG and the timing of GWG in relation to child obesity. In addition, we will add to the literature by studying whether an effect between GWG and child obesity differs by pregravid maternal weight.

Table 4. Summary of literature linking GWG to early childhood adiposity

First author Ages assessed	Sample	Birth years	GWG measure	Adiposity measure	Result
Crozier (36) 4, 6 yr	948 United Kingdom	1998-03	Measured, IOM (1990) categories	Fat mass	+ 4, 6 yr
Oken (34) 3 yr	1,044 Boston, MA	1999-02	Recalled, IOM (1990) categories, net gain	BMI[1] Summed skinfolds[2]	+[12]
Ensenauer(103) 5.8 yr	6,837 Germany	2003-05	Measured, IOM categories	BMI[1] Waist circumference[2]	+[12]
Whitaker (113) 2, 3, 4 yr	8,494 Ohio	1992-96	Measured, net gain	BMI	null 2, 3, 4 yr
Olson (114) 3 yr	208 New York	1995-97	Recalled, net gain	BMI	null
Ehrenthal (112) 4 yr	3,302 Delaware	2004-07	Recalled, total amount of gain, net gain	BMI	null
Durmus (101) 4 yr	5,674 Netherlands	2002-06	Recalled, total gain at 30 wk	BMI	+
Branum (105) 4 yr	5,917 Multiple sites, US	1959-66	Measured, IOM categories	BMI	+ conventional null FE (sibling)
Rooney (111) 4-5 yr	359 Midwestern US	1988-90	Measured, IOM (1990) categories	BMI	null
Hinkle (100) 5 yr	3,600 Multiple sites, US	2001	Recalled, IOM categories, total amount of gain	BMI	+

Table 4 continued.

Margerison-Zilko (116) 5 yr	3,015 Oakland, CA	1959-68	Measured, rate of net gain *timing of GWG	BMI	+ early null mid & late
Jedrychowski (115) 5 yr	312 Poland	2001-04	Measured, total gain ≥19kg	WLZ	null
von Kries (117) 5.8 yr	6,665 Germany	2003-05	Measured, IOM categories *timing of GWG	BMI	null early-mid + late
Beyerlein (102) 5-6 yr	6,254 Germany	1996-01 1997-99 2000-01	KOPS- Recalled, IOM LISA- Measured, IOM Ulm- Measured, IOM	BMI	+

2.2.4 Prepuberty (6 to 12 years)

Eleven of the thirteen studies of prepubertal children found an association between GWG and child adiposity. Only one of these studies reported on child pubertal status in which 47% of the sample was classified as pre- or early puberty (33). The Growing Up Today Study consisted of 11,994 healthy US adolescents aged 9-14 years who were predominantly white, breastfed beyond 6 months, and had normal-weight mothers who were nonsmokers and had normal glucose tolerance in pregnancy (33). Child overweight (BMI 85th-<95th percentile) was common (13%) while only 7% of children were obese (BMI≥95th percentile). Excessive GWG (>1990 IOM) was associated with a 42% increase in the odds of child obesity (95% CI: 1.19, 1.70), a 27% increase in the odds for child overweight (95% CI: 1.12, 1.44), and a 14% increase in BMI Z-score (95% CI: 0.09, 0.18) compared to GWG within the 1990 IOM guidelines. There was no evidence that maternal prepregnancy BMI modified associations. A limitation of this study is its reliance on self-reported weight and height, which might be misreported by adolescents, especially during growth spurts (118, 119). Our study will avoid this potential bias by using measured weight, and height data at all ages, including adolescence.

A rigorous analysis of the 2009 GWG guidelines was conducted in a sample from the ALSPAC pregnancy cohort (birth years 1991-1992) based in the United Kingdom (38). In 5,154 mothers with term born infants (37 to 44 weeks), women who gained in excess of the IOM had 9 year-old offspring with higher BMI, waist circumference, fat mass, systolic blood pressure, and a number of blood lipids including HDL, ApoA1, leptin, triglyercides, CRP, and IL-6 as compared to women whose gain was within the guidelines. As compared to the same referent, excess gain was associated with an increased odds for child overweight/obese BMI (Odds Ratio (95%

Confidence Interval): 1.73 (1.45, 2.05) based on the International Obesity Task Force standards (120) and an increased odds for waist circumference ≥90th percentile (121) (1.36 (1.19, 1.57)) based on British reference charts (122). In contrast, gain below the guidelines was associated with a protective effect against overweight/obese BMI and elevated central adiposity (0.80 (0.67, 0.96); (0.79, 0.69, 0.90), respectively. Models were adjusted for prepregnancy BMI, smoking during pregnancy, as well as other factors. However, IOM category was not associated with a difference in diastolic blood pressure, non-HDL,or adiponectin.

Similar results were reported from other studies using the 1990 IOM (35, 111). In a small sample (n=450) from three states in the Midwestern US, excess GWG was associated with a 73% increase (95% CI: 1.06, 2.80) in the risk of adolescent BMI ≥85th percentile (9-14 years) as compared to gain within the IOM (111). However, these results were unadjusted for prepregnancy BMI and used maternal weight at the first visit as a proxy for prepregnancy weight, which systematically overestimates prepregnancy BMI, and underestimates GWG. In an analysis of CPP participants that did not study sibling pairs, the association between GWG and child BMI at 7 years was estimated among term births (n=10,226) (35). Only 5.7% of children were classified as obese (BMI≥95th percentile). Excess maternal weight gain (>1990 IOM) was associated with a 48% increase in the odds of child overweight (95% CI: 1.06, 2.06) compared with adequate GWG, after adjustment for prepregnancy BMI, maternal smoking, and other factors. Women who gained excess weight and had a prepregnancy BMI <19.8 kg/m2 had 7 year-olds more likely to be overweight (OR: 3.36 (95% CI: 1.01, 11.16), while the association among heavier women (BMI ≥19.8) was less strong (OR: 1.59 (95% CI: 1.14, 2.23). In contrast to these findings between IOM-measured GWG and child BMI at specific ages, findings for fat mass were inconsistent. A small sample of Caucasian women from a UK prenatal clinic

recorded DXA-measured fat mass for offspring at 9 years. Compared with women gaining inadequately (<1990 IOM), there was no association between the few women gaining excessively (>1990 IOM) and child fat mass (123).

In contrast to these studies, a number of others have examined a range of child ages which span >1 critical period (99, 104, 124-127), only one of which used measures of GWG that account for inherent confounding by prepregnancy BMI and gestational age (124) and only three had available data on prepregnancy BMI (99, 104, 124). In a racially and socio-economically diverse sample of U.S. births (n=4,496) born from 1972-2000 found that excessive GWG (>2009 IOM) was associated with a 27% increase in the odds of child overweight between the ages of 2 and 20 years (95% CI: 1.10, 1.48) compared with adequate GWG (124) in models adjusted for prepregnancy BMI. Margierson-Zilko and colleagues stratified models by prepregnancy BMI and found a positive association between the total amount of GWG and the risk of child overweight (≥85th percentile) among normal weight women, but no other weight group. However, associations approached significance among all weight groups, particularly overweight women, but estimates did not reach significance, which may have been due to a relatively non-overweight sample, underpowering estimates. Further, the study concluded that the current weight gain recommendations for overweight and obese women may be too high to prevent child overweight, similar to another study (128). In a study of the Dutch National Birth Cohort, total amount of GWG was associated with an increase in offspring BMI z-scores in 5 to 8 year-olds in crude models, as well as models adjusted for prepregnancy BMI, maternal smoking, and child weights at previous periods (birth, 5 months, 12 months) (104). However, since obesity tends to track over time, the adjustment for previous child weight may be considered adjusting for an intermediate variable and does not reveal information about the causal path. The only

longitudinal analysis including any data on the ages of middle childhood was introduced in a previous section (99). Neither crude nor adjusted models found associations between high total GWG (>45 lb; 35-44 lb) and the late-onset child obesity group (diverging at 6 years and obese by 12 years) identified by the data-driven models when compared with lower gain (25-34 lb). The study did not test for effect modification.

The remaining studies that encompassed a range of child ages used total amount of GWG and did not have prepregnancy BMI data available, instead using current maternal BMI as a proxy or to estimate pregravid weight (125-127, 129).

Dello-Russo and colleagues studied a sample of 16,224 European 2-9 year-olds in the IDEFICS cohort (125). There was a trend for the association between tertile of self-reported GWG and child BMI z-score, waist circumference z-score, and sum of triceps, subscapular skinfold thicknesses, and measures of blood pressure after adjusting for a number of covariates, including maternal current BMI, prenatal alcohol or smoking, gestational diabetes, gestational hypertension, breastfeeding duration. However, after adjustment for child's current BMI or waist z-score GWG was no longer associated with child's blood pressure. The risk for child obesity was 33% higher (95% CI: 1.09, 1.62) for children of mothers with GWG in the highest tertile (interquartile ratio (IQR): 18-24 kg) as compared to GWG in the lowest tertile (IQR, 8-11 kg) after adjustment for current maternal BMI. These categories do not take into account maternal prepregnancy BMI and the referent gain in this study is considered too little gain for underweight and normal weight women. Similarly, a community-based Portuguese sample (n=4,845) found that GWG ≥16 kg was associated with a 27% increase in the odds for obesity (95% CI: 1.01, 1.61) among 6-12 year-olds as compared with gain <9 kg, after adjustment for current maternal BMI (129).

Data from the KiGGs study, a large (n=10,784) cross-sectional health survey of German children and adolescents aged 3-17 years, was used in two analyses in which the authors report that maternal BMI modified associations between GWG and child weight (126, 127). Kleiser et al., used maternal current weight as a proxy for pregravid weight and found that GWG >20kg was associated with child obesity among mothers who were normal weight at their child's 3-17 year assessment (OR: 2.81 (95% CI: 1.6, 5.0) compared with gain ≤20kg, yet there was no association among overweight mothers (0.71 (0.3, 1.6)) (126). In another analysis of these data, to the researchers attempted to account for prepregnancy BMI using an unvalidated estimation technique in child's age multiplied by 0.08 (a constant estimated using a linear model of child's age as the dependent variable and maternal current BMI as the independent variable) was subtracted from maternal current BMI. High GWG (>17kg, 11-17 ref) was associated with an increased odds of child overweight among women with an estimated normal prepregnancy weight, while no associations were observed among underweight, overweight or obese women.

Only two studies examined the pattern of GWG and the association with prepubertal weight. A path analysis studied total and rate of weekly GWG for an association with child obesity in 5-8 year-olds in the Danish National Birth Cohort (104). Multiple mediators were studied (middle and late periods of GWG and child weights at birth, 5 months, and 12 months). Both the direct and total effects of early GWG were associated with child weight. There was a positive total effect for rate of gain in the first 20 weeks' gestation on child BMI Z-score at 5-8 years as well as for 20-32 weeks, but not ≥32 weeks. A large population-based pregnancy cohort (ALSPAC, UK) was used to study GWG pattern and a number of cardio-metabolic measures in 5,154 9-year old children born at term (38). After adjustment for prepregnancy weight, GWG in the previous period, and other covariates, every 400g/week increase in maternal weight between

0-14 weeks' gestation was associated with higher child BMI, waist circumference, fat mass, systolic & diastolic blood pressures, leptin, triglycerides, IL-6, CRP, and lower HDL-C, and ApoA1 in the 9-year old child. This trend was strongest among women who maintained a high total weight GWG (>500g/wk) over the entire pregnancy. GWG between 14-36 weeks was only associated among women maintaining high gains for the entire pregnancy. There was no evidence that prepregnancy BMI modified these effects in the work by Anderson, Fraser or Margerison-Zilko (2010), in contrast to previous findings (116) suggesting an interaction should be explored in subsequent analyses.

Summary: Of thirteen studies on GWG and prepubertal adiposity, eleven found positive associations; eleven used BMI despite its' well-documented limitations, yet support an association. Only three studies (38, 123, 125) used measures of childhood fat and had mixed results: the association between total GWG and fat mass was not associated when stratified by child sex, but high gain overall and specific to early pregnancy was associated with fat mass and a number of related metabolic markers. Our study is limited to the use of BMI. It must be clarified whether GWG pattern is associated with direct measures of child weight, and to answer this, we will study pattern of GWG. In addition, these results must be confirmed in datasets with diverse populations and a higher prevalence of child overweight since most of the data on prepubertal weight is based on racially-homogenous samples with limited information on socioeconomic status. The dataset we will use is half-black, half-white and predominantly low-income.

Table 5. Summary of literature linking GWG to prepubertal adiposity

First author Ages assessed	Sample	Birth years	GWG measure	Adiposity measure	Result
Gale (123) 9 yr	216 United Kingdom	1991-92	Measured, IOM (1990) categories	Fat mass	null
Fraser (38) 9 yr	5,154 United Kingdom	1991-92	Recalled, IOM 2009 rate of gain *timing of GWG	BMI[1] Waist circumference[2] Fat mass[3]	+ early & mid[123] null late[123] + overall
Dello Russo (125) 2-9 yr	12,775 Multiple sites, Europe	1998-06	Recalled, total amount of gain	BMI[1] Waist circumference[2] Summed skinfolds[3] Blood pressure[4]	+[1234]
Li (99) 0-12 yr diverge 6 yr	1,739 Multiple sites, US	1984-90	Recalled, total amount of gain	BMI	null diverge 6yr
von Kries (127) 3-17 yr	10,784 Germany	1986-03	Recalled, total amount of gain	BMI	+
Kleiser (126) 3-17 yr	10,021 Germany	1986-03	Recalled, total amount of gain	BMI	+
Margerison-Zilko (124) 2-20 yr	4,496 Multiple sites, US	1972-00	Recalled, IOM categories	BMI	+
Andersen (104) 5-8 yr	9,969 Netherlands	1996-02	Recalled, total amount rate of gain *timing of GWG	BMI	+ early & mid null late + overall

Table 5 continued.

Wrotniak (35) 7 yr	10,226 Multiple sites, US	1959-66	Measured, IOM (1990) categories	BMI	+
Moreira (129) 6-12 yr	4,845 Portugal	1994-06	Recalled, total amount of gain	BMI	+
Rooney (111) 9-14 yr	450 Midwestern US	1988-90	Measured, IOM (1990) categories	BMI	+
Oken (33) 9-14 yr	11,994 Multiple sites, US	1982-87	Recalled, IOM (1990) categories	BMI	+
Ludwig (108) 6-18 yr	91,045 Arkansas	1989-05	Recalled, total amount of gain	BMI	+

2.2.5 Postpuberty (12 to 18 years)

Relatively few articles have focused on GWG and the risk of obesity during or beyond puberty. In a birth cohort from the Midwest region of the US, the IOM GWG categories were studied in relation to BMI ≥85th percentile in 19-20 year-olds (111). Gain in excess of the 1990 IOM was associated with a 2-fold increase in the risk of overweight at 19-20 years (95% CI: 1.18, 4.14), though this risk was unadjusted for pregravid weight. No association was observed for gain below the recommendations. However as discussed in the above section, this study used weight measured at the first study visit as a proxy for prepregnancy weight, which may have biased estimates.

Two additional studies examined the total amount of GWG in relation to BMI of 18 year-old offspring (28, 106). In a large (n=35,826) retrospective US study of mothers and daughters, total GWG was U-shaped in the association with offspring obesity after adjustment for maternal prepregnancy BMI, and maternal history of diabetes, as well as other factors (28). Compared to a weight gain of 15-19 pounds, total amount of GWG <10 lb, 10-14 lb, as well as gain 30-39 lb. and >40 lb. were each associated with an increased odds for obesity after adjustment. The study found a multiplicative interaction between maternal overweight (BMI ≥25 kg/m2) and category of GWG. Among normal weight mothers, GWG 10-14 lb. was associated with an increased risk of obesity in the daughter, while among overweight mothers, GWG in both extremes (<10 lb and >40 lb) were each associated with increased offspring obesity risk. These findings were unlike many other studies reporting effect modification by prepregnancy BMI. While stratification by prepregnancy BMI partially accounts for its' influence, residual confounding cannot be excluded. It is possible that the use of a confounded measure of GWG resulted in the remaining U-shape among overweight women. Indeed, other studies (33, 38) report that the positive

association among lower maternal weight gains is eliminated after adjustment for prepregnancy BMI. Further, in this study, mothers recalled GWG 36-56 years postpartum, after the development of offspring obesity, which may have led to inaccurate reporting and recall bias. In addition to this study, an analysis of 18 year-old siblings (described previously), found that among overweight women GWG was associated with offspring BMI in conventional and fixed-effects models accounting for shared maternal-child factors; for lean women, it appeared that the association was attenuated in fixed-effects models (106).

Only one study focused on the timing of GWG and postpubertal weight. In a large Finnish birth cohort, total weight gain >7.0 kilograms during the first 20 weeks of pregnancy was associated with a 46% increase in the odds of an overweight BMI (95% CI: 1.16, 1.83) and a 39% increase in a waist circumference ≥85th percentile compared to 3.0 to <5.0 kilograms of gain and after adjustment for prepregnancy body mass index (130). GWG in later pregnancy was not studied. It is yet unclear whether the timing of GWG is differs over the course of pregnancy in its relation to child weight. Some women may gain disproportionately higher weight in early pregnancy, but less later, or vice versa, and these changes may contribute to child weight in different ways. Our study will fill this research gap by examining for an interaction between different gain amounts in early and late pregnancy.

Table 6. Summary of literature linking GWG to postpubertal adiposity

First author Ages assessed	Sample	Birth years	GWG measure	Adiposity measure	Result
Laitinen (130) 16 yr	6,637 Finland	1985-86	Recalled, total gain *timing of GWG (early only)	BMI[1] Waist circumference[2]	+ early[12]
Lawlor (106) 18 yr	136,050 Sweden	1973-88	Measured, net gain	BMI	Overweight + conventional + FE (sibling) Lean + conventional null FE (sibling)
Stuebe (28) 18 yr	35,826 Multiple sites, US	1946-64	Recalled, total gain	BMI	U
Rooney (111) 19-20 yr	453 Midwestern US	1988-90	Measured, IOM (1990) categories	BMI	+

2.2.6 Adulthood (≥18 years)

Only five studies on GWG and adult offspring weight have been conducted. Gain above the 1990 IOM was weakly associated with the odds of overweight and obese BMI at 21 years an Australian prospective study (131). There were no associations between category of IOM and offspring blood pressure. The authors reported that there was no statistical evidence for effect modification on the multiplicative scale.

Four studies examined the total amount of GWG and the association with child weight. In an Israeli cohort (n=1,400), every 1-kilogram increase in GWG was associated with a faster a 0.11 kg/m2 increase in offspring BMI between 17 and 32 years, after adjustment for maternal prepregnancy BMI, offspring genetic scores, as well as other maternal and child covariates, including BMI at 17 years, and caloric intake and physical activity at 32 years (132). This study also found no evidence of effect modification by prepregnancy BMI for change in child's weight. In another analysis of this cohort, total GWG was linearly associated with offspring BMI, waist circumference, systolic blood pressure, and triglycerides at 32 years (107). GWG was correlated with percent body fat, waist circumference, BMI, & fat mass index at 27-30 years in a small UK birth cohort (133). Finally, in a Danish birth cohort, an unknown source of total GWG was studied from birth to 42 years (134). By 42 years, total GWG was not associated with overweight or obesity, however a linear trend was suggested (p=0.095 and p=0.003, respectively). Researchers are unsure how GWG was ascertained, which raises questions of accuracy and the potential for bias (135).

Summary: Five studies examined GWG and BMI in adult offspring, suggesting a positive association. Mamun and colleagues were the only to study IOM GWG categories based on measured maternal delivery weights. Two studies of an Israeli birth cohort provide compelling

evidence for an association between GWG and child weight waist circumference, as well as child weight gain beyond adolescence, after taking into account a number of hypothesized confounders as well as markers of genetic risk. Analyses on total and pattern of GWG and fat mass should be extended to studies in adulthood offspring.

Table 7. Summary of literature linking GWG to adulthood adiposity

First author Ages assessed	Sample	Birth years	GWG measure	Adiposity measure	Result
Reynolds (133) 27-30 yr	276 United Kingdom	1967-68	unknown (medical records), total amount of gain	BMI[1] Percent body fat[2] Waist circumference[3] Fat mass[4]	+[1234]
Hochner (107) 32 yr	1,400 Israel	1974-76	Recalled, total amount of gain	BMI[1] Waist circumference[2]	+[12] +
Lawrence (132) 17-32 yr	1,400 Israel	1974-76	Recalled, total amount of gain	BMI	+
Mamun (131) 21 yr	2,432 Australia	1981-83	Measured, rate of gain IOM (1990) categories	BMI	+
Schack-Nielsen (134) 42 yr	4,234 Netherlands	1959-61	unknown (‘likely from medical records’), total amount of gain	BMI	null + linear trend

2.3 SUMMARY OF LITERATURE REVIEW

In total, the literature supports a moderate association between IOM-measured excessive GWG and infant growth as well as direct and estimated measures of adiposity across several ages. Beyond birth, there were twelve studies using direct measures of adiposity, nine of which found a positive association between GWG and offspring fatness. The three sibling analysis studies were mixed, with the two larger and more contemporary samples supporting an association between GWG and offspring BMI, independent of shared familial and environmental characteristics. Six analyses on the timing (or 'pattern') of GWG suggest that gain in early pregnancy is associated with child BMI at ages 5 and 7, fat mass at 9 years, and BMI and waist circumference at 16 years; gain in later periods of gestation were less associated. Data were mixed on whether prepregnancy BMI modified the effect of GWG on child weight; several studies reported an interaction yet it is unclear in some whether the finding was supported by statistical evidence or whether results were significant at one level but not another once stratified by BMI. Most of the literature is based on white populations and samples in which the average income is likely to be moderate or high.

Overall impact: The proposed analysis will importantly add to the sparse data on rapid infant weight gain, early childhood and postpubertal adiposity. We will answer important questions on whether total or pattern of GWG is associated measures of BMI and fat mass during these identified critical periods of development, in which fat accrual is thought to be promoted. Our approach will powerfully influence research on GWG and child obesity to focus on nutritional critical periods in pregnancy. Our work on the pattern of GWG may help to inform prenatal counseling by identifying whether weight gain advice should differ over the course of pregnancy, with focus on early weight gain to prevent offspring adiposity. The obesity epidemic

continues among adults and children unabated. Our study of a modifiable risk factor may suggest early pregnancy as an important point for offspring obesity prevention. We will further complement the existing literature by analyzing a racially-diverse, low-income population..

3.0 METHODS

3.1 OVERVIEW OF STUDY DESIGN AND STRUCTURE

We have the unique opportunity to use existing data to study total and pattern of GWG in relation to child obesity in a racially-diverse, low-income population of pregnancies occurring immediately before the obesity epidemic (1982-85). Pregnant women and their offspring were studied longitudinally in the Maternal Health Practices and Child Development (MHPCD) study. The MHPCD has pregnancy data at <20 weeks, <30 weeks, and at delivery, as well as offspring growth data at 18 months, 3 years, and 16 years. Data on prepregnancy body mass index, total and pattern of pregnancy weight gain were self-reported at sequential prenatal interviews. Trained staff measured offspring weight and height using the same calibrated scale.

3.2 DESCRIPTION OF STUDY POPULATION

The Maternal Health Practices and Child Development (MHPCD) is a prospective birth cohort study of pregnant women and their offspring (Nancy Day, PI; AA006666). The original aim of the MHPCD was to study the long-term effects of in-utero exposures to maternal alcohol and marijuana use on several domains of child growth and development (136, 137).

From 1982 to 1985, English-speaking women ≥18 years old and in the 4th or 5th prenatal month were selected at random from an appointment book at an outpatient prenatal clinic at Magee Womens Hospital in Pittsburgh, PA. The clinic served predominantly low-income women. Of the 1,600 women approached, 85% agreed to participate in an initial screening. Two cohorts were selected based on first trimester alcohol or marijuana use. The alcohol cohort included all women who reported drinking three or more drinks per week in the first trimester of pregnancy and a random sample of those reporting less than this amount. Similarly, the marijuana cohort included all women who reported using two or more joints per month in the first trimester of pregnancy and a random sample of those reporting less than this amount. The cohorts were selected in parallel and with replacement, so that women could be in either or both cohorts (60% overlap). The two studies were conducted in parallel, using identical data collection techniques and assessment instruments and took place during the same time and within the same geographic region. Thus, for the proposed analyses, we will use the combined sample from both cohorts (n=829). Women were interviewed regarding socioeconomic characteristics and maternal health behaviors at a mean of 18.9 weeks gestation (SD, 3.1). Subsequent assessments of the women occurred at the 7th prenatal month and at delivery, when their children were also evaluated. A total of 763 women had live, singleton births and the mother-child pairs were eligible for follow-up evaluations that occurred at 8 and 18 postnatal months, and 3, 6, 10, 14, 16, and 22 postnatal years. Attrition at delivery (n=66) resulted from 18 fetal or perinatal deaths, 8 refusals, 16 subjects were missed, 21 moved, 1 infant was placed for adoption, and 2 women had multiples. .

3.3 DEFINITIONS AND ASSESSMENT OF MEASURES

A strength of this study is that rich data were collected for 11 total interview phases. While pregnant, women were interviewed at study enrollment (median, IQR: 19wk, 4) and a second prenatal visit (31wk, 4). Women and their offspring were assessed at delivery (39wk, 2), 8 months, 18 months, 3 years, 6 years, 10 years, 14 years, 16 years, and 22 years. At each interview, women reported demographic, physical, psychological, and substance use statuses; offspring were assessed for physical, cognitive, and behavioral development. In addition, data were collected on many facets of the maternal and child environments. Retention of the original sample remained high for all postnatal time points (≥76%).

3.3.1 Gestational weight gain

Weight gained since becoming pregnant was self-reported at each study visit: visit 1 (median, IQR: 19wk, 4), visit 2 (31wk, 4), delivery (39wk, 2). Various measures of cumulative gestational weight gain have been used in the literature (2). The total amount of GWG is one of the most common measures of pregnancy weight gain, but it is confounded by prepregnancy BMI and gestational length. The rate of GWG (total gain divided by weeks of gestation at delivery) accounts for the length of gestation, but misleadingly assumes that the increase in weight is linear. Net gain (difference between total gain and products of pregnancy (fetal and/or placental weight)) is thought to be a better estimate of maternal fat (106), but is not clinically useful to recommend targeted net gain without equipment to estimate the contributions of each anatomical component of gain. In contrast to these measures, we will study a definition of GWG

based on the 2009 Institute of Medicine (IOM) recommendations (**Equation 1**). The IOM recommends the use of a ratio calculated as observed total weight gain (kg) at the gestational age of delivery divided by the gain expected (recommended) at this same gestational age (37, 138, 139), assuming a fixed linear gain in the first trimester based on prepregnancy BMI. Because the IOM adequacy ratio accounts for prepregnancy BMI and gestational age, it is considered a superior measure to total amount, rate, and net GWG.

GWG adequacy ratio = [observed weight gain] / [expected weight gain] x 100

Equation 1: Gestational weight gain (GWG) adequacy ratio based on the 2009 Institute of Medicine (IOM) guidelines

Further, the IOM suggests the use of three categories of the adequacy ratio that assist in the clinical utility of this measure: inadequate, adequate, and excessive. GWG is considered adequate when GWG falls within recommended weight gain ranges for each BMI category, inadequate when the adequacy ratio is below the recommended range, and excessive when the ratio exceeds the IOM recommendations. In addition to these categories, we will also study percent of the 2009 IOM recommendations as a continuous measure of GWG adequacy. However, since the GWG adequacy may be correlated with gestational age (140) residual confounding may bias studies of GWG and outcomes associated with gestational age such as child growth. Thus, we will additionally study gestational age-based GWG z-scores which are independent of gestational length, thus avoiding this potential bias (141). GWG z-scores are calculated based on prepregnancy BMI and gestational age, though no reference has been published for underweight women or those with gestational ages beyond 40 weeks. Further, the available GWG z-scores for obese women are preliminary. We will utilize those for obese

women as reported, and as a proxy, we will apply the standards for normal weight women to underweight women, and apply standards at 40 weeks to gestational ages of ≥40 weeks. As a sensitivity analysis, we will examine whether our results are consistent between IOM adequacy ratio and GWG z-score, and we will additionally examine a subgroup for whom the standards have been published.

We will also study the timing of GWG, also referred to as pattern of GWG, to determine whether gain during early pregnancy disproportionately contributes to the risk of offspring obesity than gain in later pregnancy. We will study two specific prenatal intervals: early (conception to first prenatal visit: 0 to <26 weeks), and late (from the first prenatal visit to delivery: ≥26 weeks to delivery). We will not use a measure that assumes a linear rate of gain across each period, such as the rate of GWG for early and late pregnancy. Rather, the assumption of linear gain can be avoided in the study of GWG pattern using pattern of GWG adequacy. Pattern of adequacy will be calculated in two separate time periods as a ratio of observed gain within the 'early' or 'late' interval to expected (recommended) gain within the 'early' or 'late' interval. This measure does not assume a linear shape of gain in early pregnancy and will allow us to study the relative contribution of gain outside the guidelines from each period. While some research suggests that weight gain over pregnancy has a sigmoidal shape (2) and this may be handled with flexible curve modeling or calculation of area under the weight gain curve (142), many serial weights are needed for these methods.

3.3.2 Outcomes

Trained study nurses measured infant crown to heel length between 24 and 48 hours after birth and abstracted gestational age and weight at birth from medical records. At approximately 8, 18,

and 36 months, weight and length were measured by study nurses. Exact child age was calculated using the difference between the date of the study visit and the date of birth.

Weight-for-age z-scores (WAZ) will be calculated using the 2006 WHO sex- and age-specific growth standards (143) for children <24 months and the 2000 CDC growth reference for children ≥24 months (144), in accordance with current recommendations (145). The use of z-scores accounts for growth differences in sex and variance in the exact age at assessment. The WHO standard addresses several limitations of the traditional Centers for Disease Control (CDC) growth charts, including the lack of standardized anthropometric measurements across various cross-sectional datasets used to construct the CDC charts. In contrast, the WHO standard is based on longitudinal data from a racially and ethnically diverse population exposed to optimal growth conditions, establishing how infants should grow. The American Academy of Pediatrics and the CDC have recommended that clinicians adopt the 2006 WHO growth references over the accepted CDC growth charts to assess the growth of infants <24 months (145). Despite support for the adoption of the WHO-based z-scores, literature continues to compare growth to the CDC growth reference. The WHO and CDC growth references demonstrate different growth patterns over time with increasing variance for extreme z-scores. This results in a fluctuation between WHO and CDC-based attained z-scores and the changes in z-scores over time (146). In fact, during the first months of life, the CDC reference grades weights as a higher z-score compared to z-score assigned by the WHO growth standard. Yet the CDC grades weights as lower z-scores as compared to the WHO growth standard from approximately 8 to 30 months. As a result, the 2000 CDC growth standard sets a lower standard of weight gain in early infancy and a higher standard of weight gain in later months as compared to the WHO charts (147, 148). In order to

better understand how our WHO-based outcomes compare to CDC-based outcomes from other publications, we will run analyses using both standards.

Growth measures the change in body weight over time. Unlike attained weight, growth is a more informative and dynamic measure of change within a specified period. In the study of obesity development, growth accounts for the initial body size and time to reach a particular weight, while attained weight alone only shows the achievement of obesity, but does not indicate the path to obesity. We will study the change in weight over the first 36 months of infancy to determine whether GWG is associated with faster infant growth. As described above, we will use the current growth chart recommendations for children <24 months and ≥24 months. Next, we will study upward centile crossing (rapid infant weight gain) a dichotomized measure of growth thought to be associated with later obesity (98, 149). To calculate rapid infant weight gain, we will classify those with a change in WAZ >0.67 SD units from birth to 18 months on the 2006 WHO growth standard as having rapid infant weight gain. This unit change is chosen because it corresponds with the crossing of one percentile curve on growth charts (98, 150, 151). Those with a change in WAZ <0.67 SD units will be classified as not having rapid infant weight gain.

Body mass index-for-age z-scores (BMIZ) will also be used at several ages. Trained pediatric study nurses measured offspring weight and height at 0, 8, 18, and 36 months, as well as 10 and 16 years. We will calculate BMI using measured weight (kilograms) divided by measured height (meters) squared. Similar to WAZ, we will compare child BMI to the 2006 WHO growth standard for children <24 months (143) and the 2000 CDC growth charts (144) for children ≥24 months, in accordance with the current recommendations (145) as discussed previously. A switch to the CDC charts is preferred at 24 months because *1)* the methods to

develop the WHO and CDC charts are similar after age 24 months, *2)* the CDC charts can be used continuously through age 19 years, and *3)* transitioning at age 24 months is most feasible because length measurement switches at 24 months from recumbent length to standing height. We will study BMI z-score continuously and categorically. Standard BMI percentile cutoffs will be used to classify offspring as obese (≥95th percentile). BMI is well-known estimate of total body fat, but does not indicate body composition or body fat distribution (152). BMI is a well-accepted and simple measure reported in the literature and used clinically; our analysis will study BMI for comparison to other studies. As a sensitivity analysis, we will run longitudinal models using raw, unstandardized BMI values since the use of z-scores to study growth over time has been questioned due to extreme z-scores having reduced within-child variability (153).

This project will address both prevalent and incident childhood obesity to inform different aspects of our research question, thereby giving a more complete picture of the association between GWG and childhood growth.

Prevalent obesity is defined as the number of children who meet obesity criteria at a time point of interest, regardless of previous obesity status (**Equation 2**).

$$\text{Prevalent obesity}_{(36\ \text{months})} = (\text{Number of children obese}_{(36\ \text{months})}) / (\text{Number of children with obesity data}_{(36\ \text{months})})$$

Equation 2: Prevalent obesity

Since prevalence is a population-level variable and we will use individual-level data, we will not truly study prevalence. In our study, we will evaluate the extent to which total and pattern of GWG are associated with the proportion of children meeting obesity criteria in infancy, childhood, and adolescence. Studying the proportion of obesity will serve as an

estimate of prevalence and it allows us to determine whether GWG contributes to the public health burden of childhood obesity at these ages. This information may be useful to planners of health services in anticipating proportion of exposed children who will need treatment for obesity and related comorbidities. However, since this proportion will not indicate the age of onset, this measure will neither aid prevention efforts nor indicate obesity duration. Prevalent obesity at any age may reflect an innocuous and/or transient growth phase in which a high level of childhood fat may be quickly ameliorated and the child returns to normal size. Indeed, literature supports that obesity in childhood tends to be transient but is persistent at older ages, meaning that as children age, obesity at one point is increasingly predictive of later obesity.

For our proposed project, we will calculate the proportion of obesity as the number of children meeting obesity criteria (≥95th percentile for BMI) at the age of interest, divided by the total number of children with data at that age. The proportion of obesity will be studied at 36 months, 10 and 16 years.

Incident obesity is defined as the number of new-onset cases of obesity at the time point of interest among all of the children who were not obese in the previous study period (**Equation 3**).

$$\text{Incident obesity}_{(36\ mo)} = (\text{Number of children obese}_{(36\ mo)}) / (\text{Number of children with obesity data at current and previous period}_{(18\ \&\ 36\ mo)} \text{ and were not obese at previous period}_{(18\ mo)})$$

Equation 3: Incident obesity

Incident obesity allows us to better understand the etiology of childhood obesity. We will determine whether total or pattern of GWG confers higher susceptibility for obesity development during each critical period. This information may suggest the ages during which it may be most

important for clinicians to implement prevention programs for those at risk. Since obesity is transient in early childhood, incidence may inform whether exposed children may develop obesity at more than one critical period. In later childhood, when obesity is persistent, exposed children may be more likely to remain obese after development, resulting in higher prevalence rates at older ages but low incidence. Incidence models will thus include fewer children and the estimates will be less precise than prevalence models and will limit our study incident obesity in detail at each time point. Our power to study interactions with maternal body mass index and other postnatal factors and adjust for multiple confounders may be limited. In addition, incident obesity will not show how GWG is associated with the total frequency (burden) of obesity at each time point of interest.

We will calculate incident obesity by finding the number of new-onset cases of obesity (≥95th percentile for BMI) at the age of interest, divided by the number of children who were not obese at the previous period (<95th percentile for BMI). We will study incident obesity at 36 months and 16 years. Incident obesity at 36 months will be defined as those with a BMI Z-score ≥95th percentile on the CDC growth charts, among children who did not have an obese BMI Z-score (<95th percentile) on the WHO growth charts at the 18 month visit. Different charts will be used at these ages in accordance with current recommendations for measuring child growth before and after 24 months. Since there is no standardized definition of infant obesity and because it is unclear whether and how the change in reference charts over the two ages will impact the definition of new cases of obesity, the validity of our definition of obesity development may be questionable. Incident obesity at 16 years will be defined as those with a BMI Z-score ≥95th percentile on the CDC growth charts, among adolescents who did not have an obese BMI Z-score (<95th percentile) on the CDC growth chart at the 10 year visit.

We hypothesize that the association between GWG and offspring incident obesity will be stronger than its association with prevalent obesity due to the possibility of an influential critical period. There is very little data to suggest that GWG would uniquely predict obesity development during one critical period over another, so it is difficult to hypothesize the effect size or the timing at which GWG would be most associated with obesity development.

Because the parent study was not designed to study childhood obesity, the time periods available in our data are not ideal for studying incident obesity during the critical developmental windows. To optimally study obesity development, we would need several more time points of data to estimate the age at which children cross the threshold of obesity, and whether/how they remain obese from that point forward or waiver between being obese and non-obese over time. We have obesity measures near the developmental stages of interest, but we are unable to determine whether obesity truly developed near that period or at ages in-between. Nevertheless, our study is important because we will be able to provide an estimate of when the effects of prenatal factors may be most influential on obesity development..

3.3.3 Covariates

(1.) Prepregnancy BMI. Prepregnancy BMI may be both a confounder and an effect modifier in our analyses. Heavier women tend to gain above the guidelines and heavier women tend to have heavier children. Literature suggests that the effect of GWG on child weight is stronger among women who were lean before becoming pregnant, meaning that prepregnancy BMI may also be an important effect modifier. In our analysis, we will consider both roles of prepregnancy BMI by adjusting for confounding by prepregnancy BMI in all multivariable

models, as well as examining whether GWG has a different effect on child size across levels of BMI.

Measurement: Prepregnancy weight and height were self-reported at the first prenatal visit. Maternal prepregnancy BMI will be calculated as weight (kg) divided by height (meters) squared. Women will be classified as underweight (BMI<18.5), normal weight (BMI: 18.5-24.9), overweight (BMI: 25.0-29.9), or obese (BMI≥30.0). Several analyses have shown that adults tend to overestimate their height and underestimate their weight, which can lead to misclassification of body mass index (154, 155). Because the misclassification is unlikely to vary by the outcome (i.e., it is nondifferential) then results may be biased toward or away from the null (156), and without formal quantification of the bias, it will be unclear how our results will be affected. Because most of the gestational weight gain measures we will use are based on prepregnancy BMI, the misreporting of prepregnancy weight and height may extend to impact our calculation of the exposure.

Prepregnancy BMI is a surrogate measure of preconception fat. Because BMI measures excess weight rather than excess fat, it cannot distinguish between anatomical components of body weight and cannot indicate fat distribution. Despite these limitations, BMI tends to correlate with direct measures of body fat and adverse perinatal outcomes, so it is an acceptable indicator of obesity.

(2.) Gestational age. There is a positive correlation between gestational age and gestational weight gain (2) where women stand to gain more weight over a longer pregnancy. For the fetus, a longer time spent in-utero is associated with a higher fat mass at birth (157).

In addition, gestational age influences postnatal growth. Gestational age may confound the GWG-child obesity relationship or the relationship may be more complicated, where

gestational age and child obesity may be common effects of gestational weight gain (**Figure 2**). Methodologic studies suggest that conditioning on a common effect (a collider) may induce an association that would not otherwise be observed (158). Thus, restriction to term births alone may be inappropriate. Because the role of gestational age in the GWG-child obesity relationship is unclear, we will run a sensitivity analysis to determine whether the inclusion of preterm infants (>37 weeks gestation) meaningfully changes estimates. If there are no meaningful differences, we will retain children of all gestational ages for maximal precision. In addition, since gestational age may be on the causal pathway to rapid infant weight gain or obesity, adjustment for the length of gestation may be inappropriate in our models (109).

Measurement: Ultrasound during the second trimester is considered the ideal method of gestational dating, but it was not widely available in the 1980s when our cohort was pregnant. The MHPCD obtained two measures of gestational age: 1) abstractions of gestational age from the medical records, and 2) the Ballard assessment (159) which is a modification of the Dubowitz scoring criteria (160). The Ballard score is based on a postnatal assessment of six physical and six neurological characteristics of the neonate. Among several neonatal assessments available at the time, the Ballard method was preferred because it was standardized and reliable. However, neonatal physical assessments tend to be less predictive of gestational age in the extremes of gestation (preterm or post-term) and in very sick infants (161). The Ballard score was shown to misclassify ultrasound-determined preterm and post-term infants by 2 weeks (162). Due to the expected misclassification of gestational age, women with excessive GWG will be misclassified as having gained adequate weight. In addition, birth weight for gestational age Z-score will also be underestimated. It is not clear how medical record-based gestational age was calculated in the MHPCD cohort. It is likely that gestational age for

pregnancies during the 1980s were calculated based on last menstrual period (LMP) dates. LMP is more reliable than neonatal estimates, but less reliable than ultrasound (163). Given the known limitations of neonatal estimates, we will use the abstracted medical record gestational age.

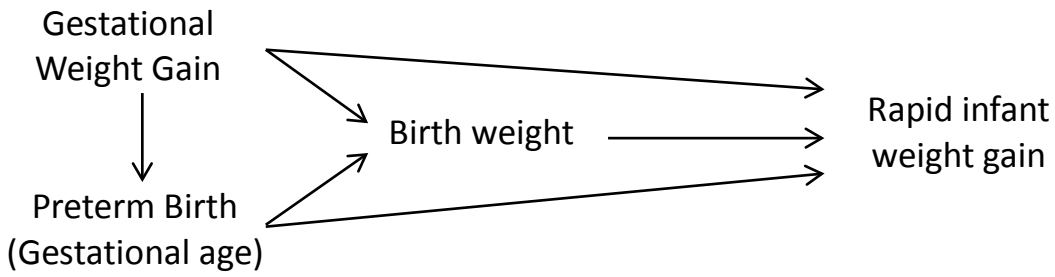


Figure 2. Directed acyclic graph (DAG) to demonstrate assumed causal model of gestational weight gain and rapid infant weight gain

(3.) Birth weight. It is not clear whether infancy is an extension of fetal growth or if early postnatal growth is a unique developmental period (23), making it unclear whether birth weight mediates associations between GWG and child weight. Complex modeling in a recent analysis suggested that birth weight mediates the association between GWG and early childhood BMI (104) but this may differ by prepregnancy body mass index (100). Since birth weight may be on the causal pathway between gestational weight gain and postnatal growth (**Figures 2, 3**), it is inappropriate to simply adjust for the mediating effect of birth weight in the model (109). Methodologists caution that adjusting for an intermediate variable does not provide a valid

estimate of the direct association (110). In the proposed study, our goal is to estimate the total effect of GWG on measures of childhood obesity (all pathways from GWG to childhood obesity, including through birth weight).

Measurement: We will use measured birth weight data abstracted from medical records and will calculate a Z-score adjusted for gestational age at birth and gender. Birth weight for gestational age Z-score is a widely accepted indicator of intrauterine growth for a given age. A series of means and standard deviations for both sexes over a range of gestational ages is necessary to calculate a continuous Z-score at birth. We will use a published reference based on a large Canadian population (n=676,605) born in the mid-1990's (164). This reference was chosen because it provides a mean and standard deviation over a range of gestational weeks, allowing the calculation of a continuous Z-score. Birth weight is positively related to lean and fat mass in childhood, but there is a stronger association with lean mass (36). Ideally, adjusting for neonatal fat mass would better indicate whether weight gain in pregnancy impacts postnatal fat mass, independent of intrauterine fat deposition. However, neonatal fat mass may mediate the association between GWG and child weight. Since our goal was to identify the total effect of GWG on postnatal weight, the adjustment of birth weight may attempt to partition the effect.

(4.) Pubertal status. Childhood fat and pubertal timing are correlated, however, it's unclear precisely how the two are related (165). To some extent, fat and the neuroendocrine system may dynamically signal to one another, thus blurring the direction of causality (166). A retrospective study using a subsample from the Nurses' Health Study II found that extremes of GWG are associated with an earlier age at menarche (167). Pubertal status may also be influenced by gestational age, low birth weight, and early growth pattern (168). Pubertal status may be on the causal pathway from GWG and adolescent weight **(Figure 3)**. Because we are interested in

estimating the total effect of GWG on childhood obesity (through all potential pathways, including pubertal status), it may be inappropriate for adjust for this factor in our models.

Measurement: In our data, pubertal development was measured at 16 years of age using the Petersen Pubertal Development scale (5-point Likert style ordinal scale) (169). The Petersen scale correlates well with Tanner stages of development, but tends to bias toward further development–especially among pre and early pubescent children (170). We do not see this as a major complication to our study as we are interested in child weight after puberty.

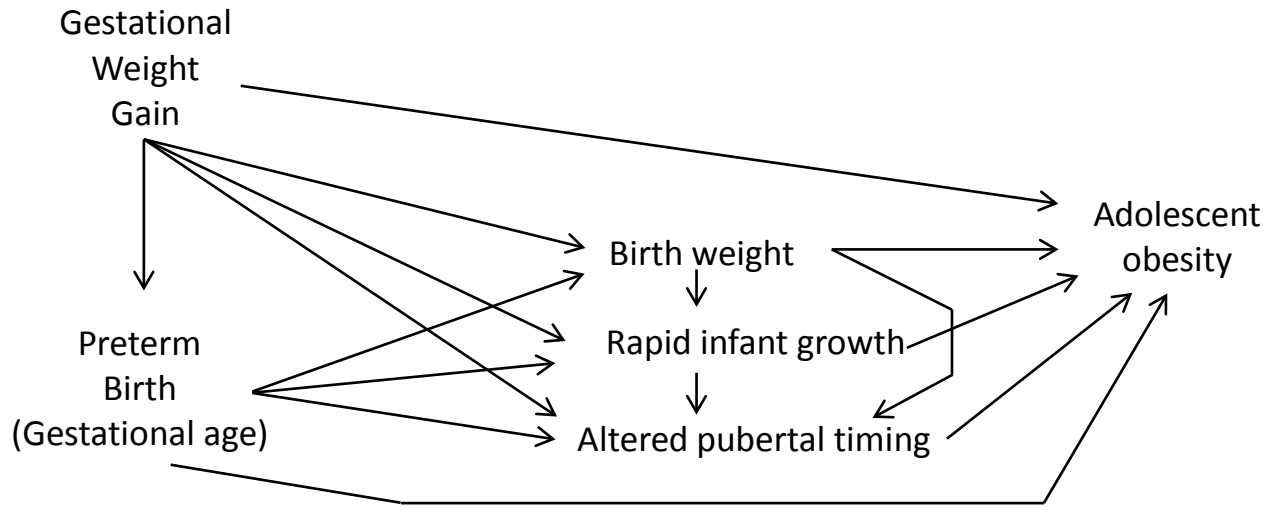


Figure 3. Directed acyclic graph (DAG) to demonstrate assumed causal model of gestational weight gain and adolescent obesity

(5.) Maternal postpartum weight. Postpartum maternal weight was assessed via self-report at 16 years and may serve as a marker for an obesogenic environment. Postpartum maternal weight

may confound the association between GWG and child weight (Figure 4). The association between maternal postpartum weight and child weight is unlikely to be causal, but associated due to common factors of an unhealthy lifestyle demonstrated by maternal postpartum characteristics. We will study maternal postpartum weight as a confounder, and will thus assume no causal association between GWG and postpartum characteristics. Evidence that excessive GWG is associated with higher maternal BMI, waist circumference, and systolic blood pressure 16 years postpartum (171) and that high (current) parental weight was associated with childhood obesity (6) support that postpartum weight is a confounder.

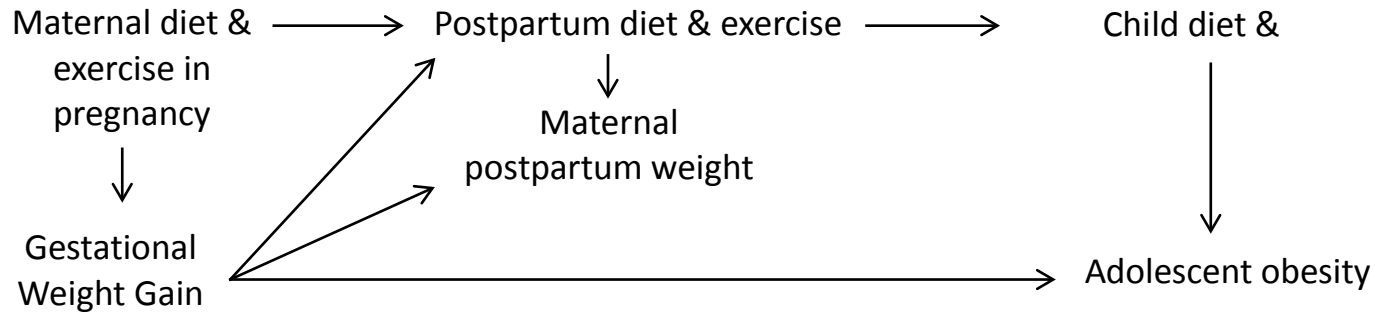


Figure 4. Directed acyclic graph (DAG) to demonstrate assumed causal model of gestational weight gain and adolescent obesity including postpartum maternal factors

(6.) Substance use. Use of tobacco, marijuana, alcohol and other illicit drugs are associated with weight (172-176), but the association with pregnancy weight gain is inconclusive since data are sparse (2). *Tobacco smoking* may be used as an appetite suppressant and it is thought to be associated with the risk of inadequate weight gain (177-179). Data suggest an association

between prenatal cigarette smoking and higher skinfold thickness (180) and childhood obesity (181). Prenatal tobacco use may partially explain the lower end of a U-shaped relation between GWG and child obesity. Prenatal *alcohol use* may also be negatively associated with high weight gain in pregnancy (182) but other data do not support an association (178, 183). In contrast to tobacco, prenatal alcohol has been associated with continued child growth deficits (180, 184-188). *Marijuana use* in pregnancy may be associated with a higher likelihood of excessive weight gain in pregnancy through appetite stimulation (189, 190). Though the association between prenatal marijuana and childhood growth is mixed (180, 187). Substance use was measured throughout pregnancy as well as at all follow up visits, so we will be able to adjust for potential confounding by maternal substance use. Since substance use is common in pregnancy (191) it is useful that our analysis can account for these factors. We will apply inverse probability sample weights (192) to reweight the sample to the original prenatal clinic sample from which the cohort was selected (193). This method will not eliminate the influence of substance use from the GWG-child weight estimates, but it will allow us to study the relationship among a weighted sample that reflects the original screening sample of 1,360 women.

(7.) Socioeconomic characteristics. Factors such as maternal education, current employment status, and family income will be used to assess socioeconomic status in this low-income population. Few studies have reported associations on GWG and SES, but SES has been related to infant outcomes closely related to GWG. These associations between SES and infant outcomes will loosely guide our hypotheses. Less education has been associated with low weight gain (194) and small infants (195). Exposure to a period of economic contraction (downturn) during the first trimester was associated with reduced fetal size and a 60% increase in

the odds for term SGA (195). Pregnant women reporting unemployment or being below the federal poverty level tended to have smaller infants for gestational age, as compared with employed women, but these associations did not reach significance (195). Women in the MHPCD reported socioeconomic characteristics at all pregnancy periods.

(8.) Other maternal characteristics. In addition to these, we will also adjust for several other factors which may imbalance comparison groups when studying the association between gestational weight gain and childhood obesity. These other factors include: maternal prenatal factors (age; marital status; prenatal mental health (depression (CES-D), anxiety (STAI: state & trait); social support). In addition, data suggest that GWG varies by racial status, where black women are more likely to gain less weight in pregnancy compared with white women (2, 194). We will consider additional adjustment for these characteristics in all models.

(9.) Postnatal lifestyle factors. As a child ages, he or she will be exposed to environmental factors known to impact obesity risk. Over time, prenatal exposures may be less important in the etiology of obesity, while postnatal factors become increasingly important. Thus, we must give thorough consideration to the role of postnatal factors pertinent to the age at obesity assessment. Such aspects that were measured in the MHPCD cohort include: childhood lifestyle factors (breastfeeding duration; diet; sedentary activity); behavioral aspects that may impact feeding (being a picky eater, having a fussy child (who is thus overfed), and maternal concerns that the child does not have adequate food). By adolescence, many environmental and biological factors impact obesity risk. Between early childhood and adolescence, offspring spend more time away from home, develop eating habits and food preferences, gain greater responsibility of food choices, and choose whether to engage in physical activities—each of which is affected by parental, peer, and societal influences. In addition, adolescents may develop medical conditions

affecting metabolism, a deficient sleep pattern, psychosocial vulnerabilities, or engage in substance use, all of which, will influence the likelihood of obesity. Because adolescence is the setting for these lifestyle changes, a weaker association between an early life exposure and an adolescent outcome is likely. Moreover, since the most strongly-related covariates of weight gain and obesity are unavailable in our data (i.e., current energy balance and sleep duration/quality), we are unable to measure the independent association between GWG and adolescent obesity. We will address this limitation by using maternal postpartum weight at 16 years as an indicator of offspring lifestyle.

3.4 STATISTICAL ANALYSIS AND POWER

Specific Aim 1: To determine the association between GWG and longitudinal growth over the first 36 months, as well as the risk of rapid infant weight gain from birth to 18 months. We will use age- and sex-adjusted weights to study weight gain over the first 36 months as well as the proportion of infants that grow rapidly from 0-18 months.

Specific Aim 2: To determine the association between total and pattern of GWG and the risk of childhood obesity at 36 months. We will study the proportion of children obese at 36 months, as well as the number of obesity cases at 36 months in which the child was not obese at 18 months. The proportion of obese 36 month-olds will be measured as the number obese at the 36-month follow-up study visit. We will measure the development of new cases of obesity at 36 months in a subgroup of children who were not obese at 18 months.

Specific Aim 3: To determine the association between total GWG and the risk of childhood obesity at 10 and 16 years. We will study the proportion of children obese at 16 years, as well as

the number of new obesity cases at 16 years among children who were not obese at 10 years. The proportion of obese 16 year-olds will be measured as the number obese at the 16-year follow-up study visit. We will measure the development of new cases of obesity at 16 years in a subgroup of children who were not considered obese at 10 years.

(1.) Statistical Analysis. A majority of analytic methods are similar across the specific aims. We will estimate the relative risks of child weight outcomes (rapid infant growth from 0-18 months; childhood obesity at 36 months, 10 and 16 years; newly developed childhood obesity at 36 months and 16 years) associated with excessive total gestational weight gain or the pattern of GWG using log-binomial models. In the event of difficulty in model convergence, we will attempt to fit modified Poisson models with a robust variance estimator to account for error overestimation known to occur (196) to estimate the relative risk. In addition to this simplified approach, we will study the change in weight over time, from birth to 3 years using longitudinal models. Weight from birth to 36 months will be measured as weight-for-age Z-scores (WAZ) at the four study visits in the first 36 months of life (at birth, approximately 8, 18, and 36 months). We will generalized linear latent and mixed models GLLAMM to model the predicted average WAZ and BMIZ over time by gestational weight gain category (197). These models are an appropriate choice for our data because they account for correlation within clusters of repeated outcomes and allow uneven spacing between the timing of the study measurements (198), as well as allowing for missing data for some of the outcomes. Adaptive quadrature will be used to achieve model convergence (199). We will analyze 743 mother-child pairs with complete data for total GWG, prepregnancy BMI, and one or more child weight measurements.

Directed acyclic graphs (200) will be used to determine potential confounders. To achieve a parsimonious fit, confounders meeting our *a priori* change-in-estimate criterion

(>10%) will remain in models. First, we will explore the unadjusted relative risk (RR) of rapid infant weight gain from 0 to 18 months and childhood obesity at 36 months, 10, and 16 years associated with total or pattern of gestational weight gain. Next, models will be adjusted for factors meeting our definition of confounding (change-in-estimate criterion >10%) that are not on the causal pathway from GWG to child weight; this allows us to consider confounders such as maternal race, employment, marital status, family income, and substance use. Models will be built under the assumption that covariates from the postnatal environment in infancy and early childhood (birth to 36 months), are largely determined by the mother and caretakers; at 16 years the postnatal environment is largely driven by lifestyle factors chosen by the adolescent, so potential covariates for adolescent models will reflect this.

We will study effect modification on the additive and multiplicative scales. We will test for effect modification on the multiplicative scale by conducting likelihood ratio tests between a model without the interaction term, and a model that includes the interaction term (product of the two terms). If effect modification is indicated ($p<0.10$), models will be stratified to examine the association at different levels of the modifier. Additionally, since epidemiologists argue studying the additive scale is more directly relevant to public health (201-204), we will also evaluate effect modification on the additive scale. We will calculate departures from the joint additive effect by calculating the synergy index (205, 206) and its confidence interval (207). The synergy index tested whether the joint effect is greater than the sum of the independent effects of the single factors exclusively. A synergy index value of 1 (perfect additivity) indicates that no interaction is present (206). Values greater than 1 indicate synergy, and values less than 1 indicate antagonism. The synergy index is not mis-specified in regression models adjusted for additional covariates, distinguishing it from other approaches (207). Effect modifiers in all

models include maternal prepregnancy BMI, race, maternal depression, anxiety, prenatal alcohol use, marijuana use, smoking, sex of the child, and the timing of maternal weight gain (early and late pregnancy). Due to the distribution of prenatal visits, we chose two periods to study pattern of GWG: early pregnancy (conception to 1st study visit <26 weeks) and later pregnancy (1st visit to delivery). In addition to these potential modifiers, interactions with offspring substance use will be considered in models of adolescent obesity.

Our goal is to estimate the total effect through all potential pathways that GWG may influence rapid weight gain and/or childhood obesity, including through preterm birth and previous growth periods. Thus, we will not explore whether the mechanism of the association is explained by mediators on the causal path. Factors such as gestational age at birth, short breastfeeding duration, caloric balance data (diet and activity), increased child appetite, pubertal status, and size at earlier periods may partially explain (attenuate) the main-effect association, thus explaining a portion of the effect of GWG on offspring weight. Since we will not conduct a mediation analysis to properly study these mediators, we may conclude that the data suggest an association between the total effect of GWG and early childhood obesity after adjustment for confounding factors.

(2.) Power and sample size calculations. Based on the 609 mother-infant pairs with complete total GWG and infant weight data at birth and 18 months, we will have 90% power to detect that a 1-SD increase in GWG is associated with a 36.7% *increase* in the odds for rapid infant weight gain, assuming a baseline probability of rapid weight gain at 5%, an R-squared of 1% between GWG and other independent (X) variables, and an alpha level of 5%. Assuming a two-sided Mantel-Haenszel test with an alpha of 0.025, we will have 90% power to detect an 0.1604

difference in the likelihood of rapid infant weight gain between excessive and adequate GWG groups and an 0.1973 difference between inadequate and adequate GWG.

At 36 months, 622 mother-child pairs have complete total GWG and early childhood BMI data. Assuming a baseline probability of obese BMI at 5%, an R-squared of 1% between GWG and other independent (X) variables, and an alpha level of 5%, we will have 90% power to detect that a 1-SD increase in GWG is associated with a 33.9% *increase* in the odds for obese BMI at 36 months. Assuming a two-sided Mantel-Haenszel test with an alpha of 0.025, we will have 90% power to detect an 0.1040 difference in the likelihood of obesity at 36 months between excessive and adequate GWG groups and an 0.1326 difference between inadequate and adequate GWG.

At 16 years, 566 mother-adolescent pairs have complete total GWG and adolescent BMI data. Assuming a baseline probability of obese skinfold at 5%, an R-squared of 1% between GWG and other independent variables, and an alpha level of 5%, we will have 90% power to detect that a 1-SD increase in GWG is associated with a 37.9% *increase* in the odds for obese BMI at 16 years. Assuming a two-sided Mantel-Haenszel test with an alpha of 0.025, we will have 90% power to detect an 0.1366 difference in the likelihood of obesity at 36 months between excessive and adequate GWG groups and an 0.1679 difference between inadequate and adequate GWG.

Table 8: Detectable odds ratio with a 1-SD increase in GWG above mean GWG, assuming 90% power

Odds Ratios	Probability of outcome at mean GWG adequacy			
R^2 of GWG & other X's	0.05	0.10	0.20	0.30
Infancy (to 18 months) n=609				
0.01	1.93	1.61	1.43	1.37
0.05	1.96	1.63	1.44	1.38
Early childhood (3 years) n=622				
0.01	1.85	1.56	1.40	1.40
0.05	1.87	1.58	1.41	1.35
Adolescence (16 years) n=566				
0.01	1.97	1.63	1.45	1.38
0.05	1.99	1.65	1.46	1.39

4.0 TOTAL GESTATIONAL WEIGHT GAIN AND RAPID INFANT WEIGHT GAIN, EARLY CHILDHOOD OBESITY, AND LONGITUDINAL GROWTH

4.1 ABSTRACT

Background: Excessive gestational weight gain (GWG) increases the risk of childhood obesity, but little is known about its association with infant growth patterns.

Aim: To examine the GWG-infant growth association.

Subjects and methods: Pregnant women (n=743) self-reported GWG at delivery, which we classified as inadequate, adequate, or excessive based on current guidelines. Offspring weight-for-age z-scores (WAZ) and body mass index z-scores (BMIZ) were calculated at birth, 8, 18, and 36 months based on the 2006 WHO growth standards for children <24 months and the 2000 CDC growth references for children ≥24 months. Linear mixed models were used to estimate the change in WAZ and BMIZ from birth to 36 months by GWG.

Results: The mean (SD) WAZ was -0.22 (1.20) at birth. Overall, WAZ and BMIZ increased from birth to approximately 24 months and decreased from 24 to 36 months. After adjusting for maternal prepregnancy BMI and education, child's diet and other confounders, excessive GWG was associated with higher offspring WAZ and BMIZ at birth, 8, and 36 months compared with adequate GWG. Compared with the same referent, inadequate GWG was associated with smaller WAZ and BMIZ at birth only.

Conclusion: Excessive GWG may predispose infants to obesogenic growth patterns.

4.2 INTRODUCTION

Childhood obesity affects one in ten infants and toddlers aged 6 to 23 months and one in six children and adolescents aged 2 to19 years in the U.S. (1). From a developmental perspective, it is thought that a path to obesity may be established in early life (208, 209), and that early-life obesity increases the likelihood of persistent obesity and related comorbidities over the life course (24-27). Infants who track along a path of faster growth may have increased risk for subsequent overweight and obesity (149, 210, 211).

Attained size is the primary outcome measure in many studies of child weight; consequently, we rely on a preponderance of cross-sectional assessments to understand a complex process beginning at conception (212). Growth velocity, on the other hand, precedes the attained size at a given assessment and includes multiple measurements, making growth a more informative measure (212). Literature suggests that infants who demonstrate catch-up growth (210) are more likely to be obese in later childhood, regardless of their size at birth (211). Furthermore, infants who grow rapidly in early life may be at greater metabolic and cardiovascular risk by early adulthood (150, 213).

Maternal weight gain in pregnancy may influence growth patterns in early childhood through the mechanism of fetal programming (214). Maternal overnutrition may irreversibly influence fetal organ and tissue development (215). Animal models suggest that these developmental changes may induce a persistent sensitivity to fat accrual (216-218).

The aim of our study was to evaluate the association between GWG and growth predictive of subsequent overweight and obesity risk in early childhood.

4.3 METHODS

The Maternal Health Practices and Child Development (MHPCD) study is a prospective birth cohort study designed to evaluate the long-term effects of prenatal substance use on child development (136, 187). We used these data for our secondary analysis because GWG and longitudinal measures of child growth were rigorously collected; substance use is common in pregnancy (191) and we controlled for its contribution in our analysis; and a low-income population has not been examined previously in the GWG and child growth literature. Pregnant women were recruited from 1982 to 1985 at a low-income prenatal clinic at Magee-Women's Hospital in Pittsburgh, PA. Women ≥18 years of age and in the fourth or fifth prenatal month were approached for the initial screening interview. A total of 1360 women agreed to screening (85% response rate). The study sample was selected based on first-trimester alcohol and marijuana use. All women who reported drinking three or more drinks per week in the first trimester of pregnancy and a random sample of those reporting less than this amount were selected for a study of the effects of prenatal alcohol exposure. Similarly, all women who reported using two or more joints per month in the first trimester of pregnancy and a random sample of those reporting less than this amount were selected for a study of prenatal marijuana exposure. The two cohorts were selected in parallel and with replacement, so that women could be in either or both cohorts (60% overlap). The combined MHPCD cohort (n=829) has been studied extensively (184, 186, 187).

Women were interviewed regarding lifestyle, sociodemographic characteristics, and substance use at the first study visit [mean: 18.8 (standard deviation (SD), 2.7) weeks gestation] and were followed to delivery. A total of 743 women had live, singleton births and had complete maternal weight and height data, and were therefore eligible for infant follow-up

evaluations. Our Institutional Review Boards approved the original study and written, informed consent was obtained at each phase. This secondary analysis used de-identified data and was granted exemption from ethics review.

Maternal prepregnancy BMI (weight (kg)/height(m)^2) was based on prepregnancy weight and height self-reported at the first prenatal visit. At delivery, women reported the total amount of weight that they gained since becoming pregnant. We classified women based on the adequacy of their GWG according to the 2009 Institute of Medicine (IOM) guidelines (2). Adequacy of GWG was defined as a ratio of observed GWG to expected GWG at delivery (219). Expected GWG was defined as 100% of the gestational age- and pregravid BMI-specific guidelines (2, 219). GWG within, less than, or greater than the recommended ranges was considered adequate, inadequate, and excessive, respectively. Because this measure of GWG may remain correlated with length of gestation (140), we performed a sensitivity analysis using GWG normalized z-scores (141).

Within 48 hours of delivery, trained study nurses measured infant crown to heel length. Gestational age at delivery and infant weight at birth were abstracted from medical records. We classified preterm birth as delivery of a live infant at <37 weeks. Birth weight for gestational age z-scores were based on weeks of gestational age and classified infants as <10th percentile; 10th to 90th percentile; >90th percentile (164). At 8, 18, and 36 months, trained study nurses measured the children's weight and length using standardized protocols. Children were measured on the same calibrated scale while wearing street clothing. We calculated weight-for-age z-scores (WAZ), weight-for-length z-scores (WLZ), and body-mass-index-for-age z-scores (BMIZ) at 0, 8, and 18 months using the 2006 World Health Organization (WHO) sex- and age-specific growth standards (143) for children <24 months. WAZ and BMIZ at 36 months were calculated

using the 2000 Centers for Disease Control (CDC) growth reference for children ≥24 months (144) in accordance with the American Academy of Pediatrics and CDC recommendations (145). We considered z-score measurements <-5 or >5 implausible and excluded them from analyses (WAZ, n=5; BMIZ, n=9). The 743 children contributed 2552 WAZ measurements and 2510 BMIZ measurements. Children had varying amounts of missing anthropometric data (missing WAZ score at one visit, n=259; two visits, n=108; three visits, n=53; missing BMIZ score at one visit, n=283; two visits, n=122; three visits, n=57). We classified rapid infant weight gain as a change in WAZ from birth to 18 months >0.67 SD units, corresponding to the crossing of one centile line on growth charts (i.e., 2^{nd}, 9^{th}, 25^{th}, 50^{th}, 75^{th}, 91^{st}, or 98^{th} percentile lines) (98, 150, 151). In sensitivity analysis, we tested the robustness of our findings by limiting models of rapid infant weight gain to those infants aged <20 months and <24 months at the 18-month assessment.

Self-reported data on race, marital status, employment, monthly household income, education, and parity were available. We categorized the frequency of first trimester substance use for tobacco, alcohol, and marijuana as well as the pattern of alcohol or marijuana use over the course of pregnancy and in the postpartum period. Elevated maternal depressive symptoms and trait anxiety were defined as scores ≥75^{th} percentile on the Center for Epidemiologic Studies Depression Scale (220) and on the State-Trait Personality Inventory (221), respectively, and low social support was a score <25^{th} percentile of a factor score measuring social support (222). The mother was asked to recall at 18 months if she ever breastfed her child and the age she introduced solid foods (<6 months; ≥6 months). At 36 months, the mother recalled the usual frequency with which her child ate fruit, vegetables, sugared drinks, and soda on a simple questionnaire designed for the study.

4.3.1 Statistical analysis

Bivariate associations between mother-child dyad characteristics and GWG were tested using Pearson chi-square tests, and their association with WAZ and BMIZ were tested using the nonparametric Kruskal-Wallis test. We used generalized linear latent and mixed models (GLLAMMs) to estimate associations between GWG and WAZ and BMIZ from birth to 36 months (197). These models account for within-child correlations across study visits and variation in the number of time intervals between repeated measurements within children (198). The underlying time variable was the child's age, which was specified as linear and quadratic terms to reflect the nonlinear relationship with WAZ and BMIZ. To achieve model convergence, we used adaptive quadrature (199). We calculated predicted WAZ and BMIZ by GWG adequacy using linear contrast statements at each growth measurement point. Next, we used multivariable log-binomial regression models to estimate the relative risks (RR) for the association between GWG and rapid infant weight gain.

Theory-based causal diagrams (200) were used to identify potential confounders (maternal sociodemographic variables, prepregnancy BMI, substance use, mental health, and breastfeeding and other child dietary variables). Our goal was to estimate the total effect of GWG on infant growth. Therefore, we did not adjust for gestational age at delivery and birth weight because they may be mediators on the causal path from GWG to child weight (158). In order to achieve parsimonious regression models, only variables that changed the main-effect estimate ≥10% were included in final models. Prepregnancy BMI and breastfeeding met our definition of confounding in log-binomial models of rapid infant weight gain. In linear mixed models, prepregnancy BMI, breastfeeding, and child's sugared drinks consumption met our definition of confounding, but we additionally included maternal education, pattern of prenatal

substance use, maternal smoking status, and child's intake of fruits and vegetables out of convention. We used a Wald test (α=0.05) in linear regression models and the synergy index (206) in log-binomial models to test for interaction by prepregnancy overweight (BMI $\geq$25.0 kg/m^2 vs. BMI<25.0 kg/m^2), race, maternal depression, anxiety, prenatal alcohol use, marijuana use, smoking, and child's sex.

We applied inverse probability sample weights (192) to reweight the study sample to resemble the original prenatal clinic sample from which the cohort was selected (193). Finally, we applied an analytic strategy (223) to determine whether our observed results were explained by regression to the mean.

4.4 RESULTS

Overall, the 743 women included in this sample were lean, young, high-school educated, unmarried, and low income (**Table 9**). Prenatal substance use reflected sampling for the cohort. Nearly half of the women were African-American. On average, infants were born small (mean (SD) birth weight for gestational age z-score: -0.38 (0.95)), and 10% were born at <37 weeks.

GWG was adequate, inadequate and excessive for 21%, 34%, and 45% of women, respectively. GWG varied by pregravid BMI, substance use, gestational age at delivery, and birth weight z-score (**Table 10**). Among the women who were obese prior to pregnancy, 73% had excessive GWG compared to 66%, 39%, and 28% of those who were overweight, normal weight, and underweight, respectively. Approximately half of those who abstained from prenatal alcohol or cigarettes gained excessive weight, while women who used either substance in the first trimester or during the second and/or third trimesters were less likely to gain excessive total

weight. There were no significant differences in GWG by maternal education, income, prenatal marijuana use, race, child sex, or mode of infant feeding.

Mean WAZ at 0, 8, 18, and 36 months were lower among children born to lean mothers, small-for-gestational age infants, and infants born <37 weeks (**Table 11**). Mothers who were African-American, smoked or used alcohol throughout pregnancy, and ever breastfed their infants had offspring with significantly lighter WAZ in early infancy than their counterparts, but differences diminished at later visits. Results were similar for BMIZ (data not shown). Rapid infant weight gain over the first 18 months was common (43%). Women who smoked during pregnancy, and infants born <37 weeks, small-for-gestational-age, and those who were not breastfed tended to exhibit rapid infant weight gain (**Appendix A**). Maternal race, income, parity, prenatal alcohol use, marijuana use, and infant sex were not associated with rapid infant weight gain.

Table 12 shows the beta coefficients from the final adjusted longitudinal multivariable models predicting WAZ and BMIZ, and **Figures 5 and 6** show the predicted values based on these models. The predicted values for WAZ and BMIZ show an overall pattern of increase from birth to approximately 24 months and decrease from 24 to 36 months in all GWG groups. The model coefficients indicate that the children of women who gained inadequate weight during pregnancy had smaller WAZ [adjusted beta coefficient (95% CI): -0.35 (-0.58, -0.11)] and BMIZ [-0.42 (-0.68, -0.16)] at birth than the children of women whose GWG was within recommended ranges, but there were no statistical differences thereafter. Women with excessive GWG had children with higher WAZ [0.34 (0.15, 0.54)] and BMIZ [0.27 (0.05, 0.48)] at birth compared with children of women with adequate gain. The children of women with excessive GWG remained heavier at 8 months and 36 months than the children of women who gained adequate

weight, but there was no difference at 18 months. When we excluded women who were heavy alcohol (≥1 drink per day in the first trimester) or marijuana users (≥1 joint per day in the first trimester), excessive GWG was associated with higher predicted WAZ and BMIZ over the entire study period (data not shown). For each category of GWG, the WAZ at 18 months was greater than the product of the initial WAZ at birth and the correlation between them, indicating that this change in WAZ was greater than the changes expected due to regression to the mean.

Women who gained inadequate weight were more likely to have an infant with rapid infant weight gain from birth to 18 months (**Table 13**). After adjustment for confounders, inadequate total GWG was associated with 33% higher risk of rapid infant weight gain compared with adequate GWG. Maternal excessive weight gain was not associated with the risk of rapid infant weight gain before or after confounder adjustment. Excluding heavy substance users did not meaningfully change these results.

None of our conclusions changed when we applied inverse probability sample weights; categorized GWG based on z-scores; used CDC-based WAZ for children <24 months and ≥24 months in longitudinal models; modeled the raw value of child's BMI; or constrained models of rapid infant weight gain using an upper age limit (data not shown). Use of weight-for-length z-scores (WLZ) resulted in similar associations as were noted for BMIZ (data not shown). Most past research relies on older references to define rapid infant weight gain, and when we defined rapid weight gain using the CDC-based z-scores, there was no significant association (data not shown). We did not find evidence of effect modification in any of the models by prepregnancy body mass index, maternal depression, anxiety, alcohol use, marijuana use, tobacco cigarette use, race, or child sex.

4.5 DISCUSSION

We found that the association between GWG and infant growth is dynamic over the first 36 months of infancy. Compared with women whose total weight gain was within the recommended ranges, women who gained excessive weight had children who were heavier at birth, 8, and 36 months, while women who had inadequate GWG had children that were lighter only at birth. The lack of a difference in WAZ from 8 to 36 months in these children of women who gained poorly is consistent with their increased risk of rapid weight gain from birth to 18 months. These associations were robust to adjustment for a number of potential confounders, including prepregnancy BMI, the infant ever having been breastfed, and child dietary factors.

Evidence suggests that excessive GWG is associated with greater adiposity (36, 82, 84-86) and higher weight (2) in infants at birth as well as an increased risk of obesity in early childhood (34). Yet we are aware of only two large rigorous studies of GWG in relation to infant growth—an informative measure of short- and long-term health (208, 224). Li et al., (92) examined GWG in relation to WHO-based WAZ and WLZ from birth to 12 months in 38 539 Chinese mothers delivering term infants, and Deierlein et al., (37) studied CDC-based WAZ and WLZ from birth to 36 months in 476 North Carolina mothers and their term infants. Our finding that infants of mothers who gained excessively were heavier but grew more slowly in the first year of life compared with infants of mothers who gained adequately were supported by Li et al. (92). Deierlein et al. in contrast, found that these infants were heavier and gained weight *faster* from birth to 36 months. The differences in growth over time may be explained by the high prevalence of prepregnancy obesity (15%) in the Deierlein cohort compared with our cohort (9%) and that of Li et al. (6%), which may alter infant growth trajectories (225). Additionally, Deierlein et al. compared infant weight to the CDC growth reference which describes a pattern of

infant growth distinct from the normative pattern of growth in the diverse longitudinal sample of breastfed infants that informed the WHO growth standard (146). In the first months of life, the CDC reference tends to grade weights as a higher z-score compared to z-score assigned by the WHO growth standard; from approximately 8 to 30 months, however, the CDC grades weights as lower z-scores as compared to the WHO growth standard. Consequently, the 2000 CDC growth standard sets a lower standard of weight gain in early infancy and a higher standard of weight gain in later months as compared to the WHO charts (147, 148). We used the 2006 WHO growth standard for infants <24 months as this represents ideal growth (143) and addresses several limitations of the CDC growth charts. Thus, it is logical that Deierlein and colleagues (37) described a shape of infant growth inconsistent to our study.

In our study, inadequate GWG was associated with smaller infant WAZ only at birth and rapid weight gain from 0 to 18 months compared with adequate GWG. In contrast, Li et al. reported that inadequate GWG was associated with WAZ scores that were consistently lower from 0 to 12 months, faster changes in WAZ and WLZ from 0 to 12 months, and Deierlein et al. found no difference in WAZ from birth to 36 months between GWG groups. GWG was unassociated with the crude risk of rapid infant weight gain from birth to 24 months based on UK standards, though their objective was to generate a predictive model for rapid infant weight gain rather than assess the independent association between GWG and RWG (98). We hypothesize that in our sample of children born to predominantly lean, low-income mothers, these infants experienced catch-up growth (98). For growth restricted infants, a period of postnatal catch-up growth may confer a number of advantages, such as overcoming neurological deficit (226). Yet, catch-up growth continues to be associated with the risk of childhood obesity (210, 227). Children in our sample with rapid weight gain were more likely than their

counterparts to be obese on CDC growth charts at 6, 10, 14, 16, and 22 years of age, but not at 3 years (data available upon request). Ongoing analyses will enhance our understanding of long-term child growth in this cohort.

Our results should be considered in light of several limitations. Self-reported maternal weight and height may lead to misclassification. However women in our study recalled their prepregnancy weight early in pregnancy and reported their GWG within 48 hours after delivery, and shorter intervals between measurement and recall are associated with greater accuracy in self-report (228). WAZ and BMIZ can only estimate adiposity (229), and it is thus unclear whether the differences we observed by GWG were due to fat or fat-free mass. While WAZ is a standardized measure of weight relative to age and sex that does not account for length, our findings for WAZ, BMIZ, and WLZ were consistent.

We cannot conclude whether GWG is causally associated with infant growth or due to common factors related to maternal weight gain and child growth that we could not measure, including shared maternal-child genetic traits. While we adjusted for the child ever having been breastfed and dietary intake, we had no information on breastfeeding intensity or duration and our measure of dietary intake was not validated. Residual confounding, therefore, may exist. Additionally, it is unclear whether these findings can be generalized to contemporary populations without a large proportion of substance users. Notably, our results were either consistent or were strengthened when we excluded heavy users from the analysis. Current US data confirm that prenatal substance use is widespread (191) thus, controlling for this confounding using a detailed, validated assessment (230) was a strength of our study. Major strengths of our study also include the use of an economically disadvantaged population of African-American and white mother-child dyads that are at high risk for childhood obesity; measured weight and height

performed using a standardized protocol at four study visits; classification of WAZ and BMIZ using the recommended WHO standards; and control for a wide range of confounders.

Our results suggest that GWG may impact infant growth and the propensity for fat accrual. Whether this relationship reflects causality will be clarified by the results of ongoing randomized clinical trials to optimize GWG. Trials employing rigorous longitudinal anthropometric assessments of the offspring will best elucidate the link between maternal BMI-specific GWG and growth trajectory of the offspring.

4.6 FIGURES AND TABLES

Table 9. Characteristics of the study sample, n=743

	%
Prepregnancy body mass index (kg/m^2)	
Underweight (<18.5)	12
Normal weight (18.5-24.9)	62
Overweight (25.9-29.9)	17
Obese (≥30.0)	9
Maternal race/ethnicity	
Caucasian	49
African-American	51
Maternal age (years)	
<20	19
20-24	51
25-29	24
≥30	6
Maternal education (years)	
<12	26
=12	60
>12	14
Marital status	
Unmarried	67
Married	33
Employment	
Working or in school	26
Not working or in school	74
Income Level ($/month)	
<400	61
≥400	39
Parity	
Nulliparous	45
Multiparous	55
Prenatal smoking	
None	46
<0.5 packs/day	20
0.5 to <1 packs/day	19
≥1 packs/day	15
Prenatal alcohol use	
None	36
>0 to <1.5 drinks/week	21

Table 9 continued.

1.5 drink/week to <1 drinks/day	24
≥1 drinks/day	20
Prenatal marijuana use	
None	59
>0 to <0.5 joint/day	21
0.5 to <1 joints/day	7
≥1 joints/day	13
Prenatal smoking pattern	
Never used in pregnancy	42
First trimester use only	5
Second and/or third trimester use	53
Prenatal alcohol use pattern	
Never used in pregnancy	30
First trimester use only	38
Second and/or third trimester use	32
Prenatal marijuana use pattern	
Never used in pregnancy	58
First trimester use only	24
Second and/or third trimester use	18
Gestational age at delivery (weeks)	
<37 weeks	10
≥37 weeks	90
Birth weight for gestational age z-score *	
Small for age (<10^{th} percentile)	17
Appropriate for age (10^{th} to 90^{th} percentile)	79
Large for age (>90^{th} percentile)	4
Infant sex	
Female	50
Male	50
Ever breastfed infant	
Yes	21
No	79

* Birth weight for gestational age z-score reference (164)

Table 10. Adequacy of gestational weight gain (GWG) by characteristics of the sample

	Inadequate GWG	Adequate GWG	Excessive GWG
Prepregnancy body mass index (kg/m^2), n (row %'s) *			
Underweight (<18.5)	17 (19)	49 (54)	25 (28)
Normal weight (18.5-24.9)	110 (24)	169 (37)	177 (39)
Overweight (25.9-29.9)	16 (13)	27 (21)	84 (66)
Obese (≥30.0)	11 (16)	8 (12)	50 (72)
Maternal race/ethnicity, n (%)			
Caucasian	69 (19)	135 (37)	159 (44)
African-American	85 (22)	118 (31)	177 (47)
Maternal education (years), n (%)			
<12	44 (23)	74 (38)	75 (39)
=12	95 (21)	147 (33)	207 (46)
≥12	15 (15)	32 (32)	54 (54)
Income level ($/month), n (%)			
<400	90 (21)	160 (36)	189 (43)
≥400	57 (21)	83 (30)	137 (49)
Pattern of prenatal alcohol use, n (%) *			
Never used in pregnancy	53 (23)	59 (26)	114 (50)
First trimester use only	49 (18)	109 (39)	122 (44)
Second and/or third trimester use	52 (22)	85 (36)	100 (42)
Pattern of prenatal marijuana use, n (%)			
Never used in pregnancy	92 (21)	153 (35)	188 (43)
First trimester use only	32 (18)	55 (31)	91 (51)
Second and/or third trimester use	30 (23)	45 (34)	57 (43)
Pattern of prenatal cigarette use, n (%) *			
Never used in pregnancy	60 (19)	92 (29)	162 (52)
First trimester use only	6 (16)	14 (37)	18 (47)
Second and/or third trimester use	88 (23)	147 (38)	156 (40)
Gestational age at delivery (weeks), n (%) *			
<37 weeks	23 (32)	29 (41)	19 (27)
≥37 weeks	131 (20)	224 (33)	317 (47)
Birth weight for gestational age z-score, n (%) *			
Small for age (<10^{th} percentile)	43 (35)	37 (30)	44 (36)
Appropriate for age (10^{th} to 90^{th} percentile)	107 (18)	209 (35)	275 (47)
Large for age (>90^{th} percentile)	4 (14)	7 (25)	17 (61)
Infant sex, n (%)			
Female	79 (22)	127 (35)	162 (44)
Male	75 (20)	126 (34)	174 (47)

Table 10 continued.

Ever breastfed infant, n (%)			
Yes	25 (19)	45 (34)	63 (47)
No	105 (21)	173 (35)	218 (44)

* Pearson chi-square test $p<0.05$

Table 11. Weight-for-age z-score (WAZ) by maternal and infant characteristics

	WAZ 0 mo. Mean (SD)	WAZ 8 mo. Mean (SD)	WAZ 18 mo. Mean (SD)	WAZ 36 mo. Mean (SD)
Prepregnancy body mass index (kg/m^2)				
Underweight (<18.5)	-0.50 (1.15) **	-0.16 (1.11) ***	0.10 (1.10) ***	-0.18 (1.02) ***
Normal weight (18.5-24.9)	-0.26 (1.15)	0.13 (1.01)	0.30 (0.99)	0.08 (1.02)
Overweight (25.9-29.9)	-0.02 (1.32)	0.35 (1.11)	0.57 (1.10)	0.26 (1.14)
Obese (≥30.0)	0.02 (1.25)	0.16 (1.20)	0.45 (1.29)	0.25 (1.18)
Maternal race/ethnicity				
Caucasian	0.04 (1.08) *	0.20 (1.02)	0.47 (1.08)	0.16 (1.04)
African-American	-0.47 (1.24)	0.07 (1.10)	0.22 (1.03)	0.04 (1.08)
Pattern of prenatal smoking				
Never used in pregnancy	-0.01 (1.19) *	0.17 (1.07)	0.33 (1.07)	0.09 (1.06)
First trimester use only	-0.06 (1.24)	0.33 (0.96)	0.54 (1.05)	0.21 (1.15)
Second and/or third trimester use	-0.41 (1.17)	0.09 (1.07)	0.33 (1.06)	0.09 (1.06)
Pattern of prenatal alcohol use				
Abstained entire pregnancy	-0.29 (1.22)	0.24 (1.09) ***	0.35 (1.11)	0.17 (1.11)***
Abstained after 1st trimester	-0.17 (1.24)	0.17 (1.04)	0.43 (1.01)	0.16 (1.04)
Did not abstain after 1st trimester	-0.22 (1.11)	0.001 (1.07)	0.22 (1.07)	-0.05 (1.04)
GWG category				
Inadequate	-0.77 (1.35) *	-0.12 (1.05) *	0.11 (1.00) **	-0.16 (1.13) *
Adequate	-0.29 (1.09)	0.03 (1.03)	0.30 (1.06)	-0.08 (0.97)
Excessive	0.08 (1.10)	0.33 (1.07)	0.47 (1.07)	0.35 (1.06)
Gestational age at delivery (weeks)				
<37 weeks	-2.28 (1.18) *	-0.45 (1.36) **	-0.19 (1.16) *	-0.50 (1.28) *
≥37 weeks	-0.02 (0.99)	0.19 (1.01)	0.39 (1.04)	0.16 (1.02)

Table 11 continued.

Birth weight for gestational age z-score				
Small for age (<10th percentile)	-1.49 (0.80) *	-0.29 (1.04) *	-0.10 (0.95) *	-0.19 (1.09) *
Appropriate for age (10th to 90th percentile)	-0.05 (1.05)	0.19 (1.05)	0.40 (1.05)	0.13 (1.06)
Large for age (>90th percentile)	1.66 (0.73)	0.94 (0.85)	1.02 (1.14)	0.77 (0.77)
Ever breastfed infant				
Yes	-0.002 (1.07) ***	0.15 (1.04)	0.30 (1.01)	0.10 (1.06)
No	-0.25 (1.22)	0.15 (1.08)	0.35 (1.07)	0.10 (1.07)

* Statistical significance level for Kruskall-Wallis equality of populations test, *p<0.001, **p<0.01, ***p<0.05

Table 12. Beta coefficients for weight-for-age z-scores (WAZ) and body mass index z-score (BMIZ) by gestational weight gain (GWG)

	WAZ Beta coefficient (95% CI)	BMIZ Beta coefficient (95% CI)
Intercept	-0.35 (-0.71, -0.002)	-0.29 (-0.65, 0.06)
Child's age (months)	0.05 (0.04, 0.06)	0.07 (0.06, 0.09)
Inadequate vs. adequate	-0.35 (-0.58, -0.11)	-0.48 (-0.74, -0.22)
Inadequate x child's age	0.02 (0.002, 0.05)	0.05 (0.02, 0.08)
Inadequate x child's age squared	-0.0004 (-0.001, 0.0001)	-0.001 (-0.002, -0.002)
Excessive vs. adequate	0.34 (0.15, 0.54)	0.27 (0.05, 0.49)
Excessive x child's age squared	0.001 (0.00004, 0.001)	0.0003 (-0.0002, 0.001)

* Multivariable linear model adjusted for prepregnancy body mass index, child's age squared, inadequate x child's age squared, excessive x child's age squared, maternal education, pattern of prenatal alcohol, marijuana, cigarette smoking, ever breastfed infant, solid foods introduced ≥6 months, and frequency of sugared drinks, and fruits and vegetables.

Table 13. Association between gestational weight gain (GWG) and rapid infant weight gain from 0 to 18 months (n=609)

	Rapid infant weight gain from 0 to18 months		Unadjusted RR (95% CI)	Adjusted† RR (95% CI)
	No	Yes		
GWG category, n (%) *				
Inadequate	55 (44)	69 (56)	1.32 (1.05, 1.64)	1.31 (1.05, 1.64)
Adequate	123 (58)	90 (42)	1.0 (ref)	1.0 (ref)
Excessive	167 (61)	105 (39)	0.91 (0.74, 1.14)	0.90 (0.72, 1.13)

* Pearson chi-square test $p<0.05$

† Adjusted for prepregnancy body mass index and infant ever breastfed.

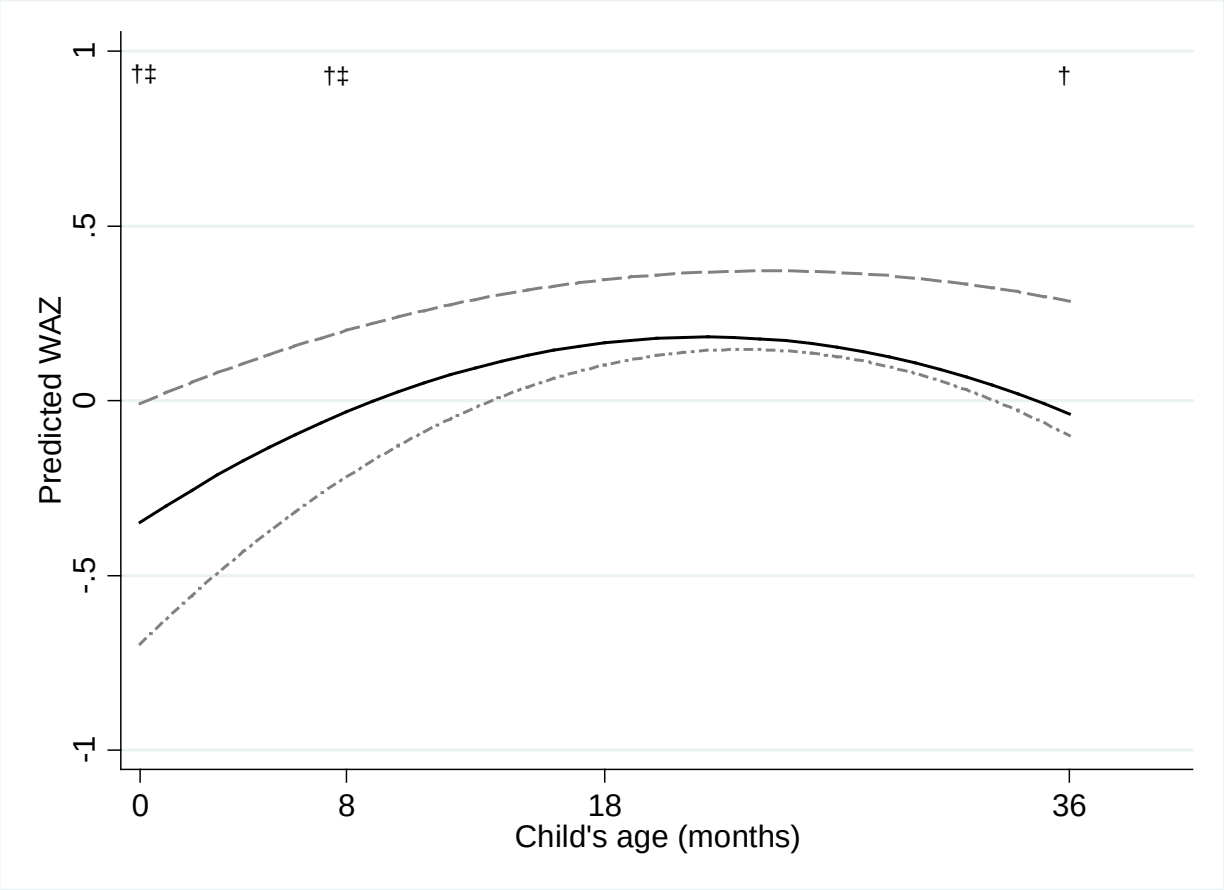


Figure 5. Predicted weight-for-age z-score (WAZ) from 0-36 months by gestational weight gain (GWG; excessive GWG, solid; adequate GWG, dashed; inadequate GWG, dotted)

* Predictions based on a multivariable linear model assuming prepregnancy normal weight, high school education, used alcohol in the 1st, abstained from marijuana, smoked tobacco throughout pregnancy, did not breastfeed infant, introduced solid foods ≥6 months, and children who consumed sugared drinks twice per day, and fruits and vegetables twice per day.

† $p<0.05$ for excessive compared to adequate

‡ $p<0.05$ for inadequate compared to adequate

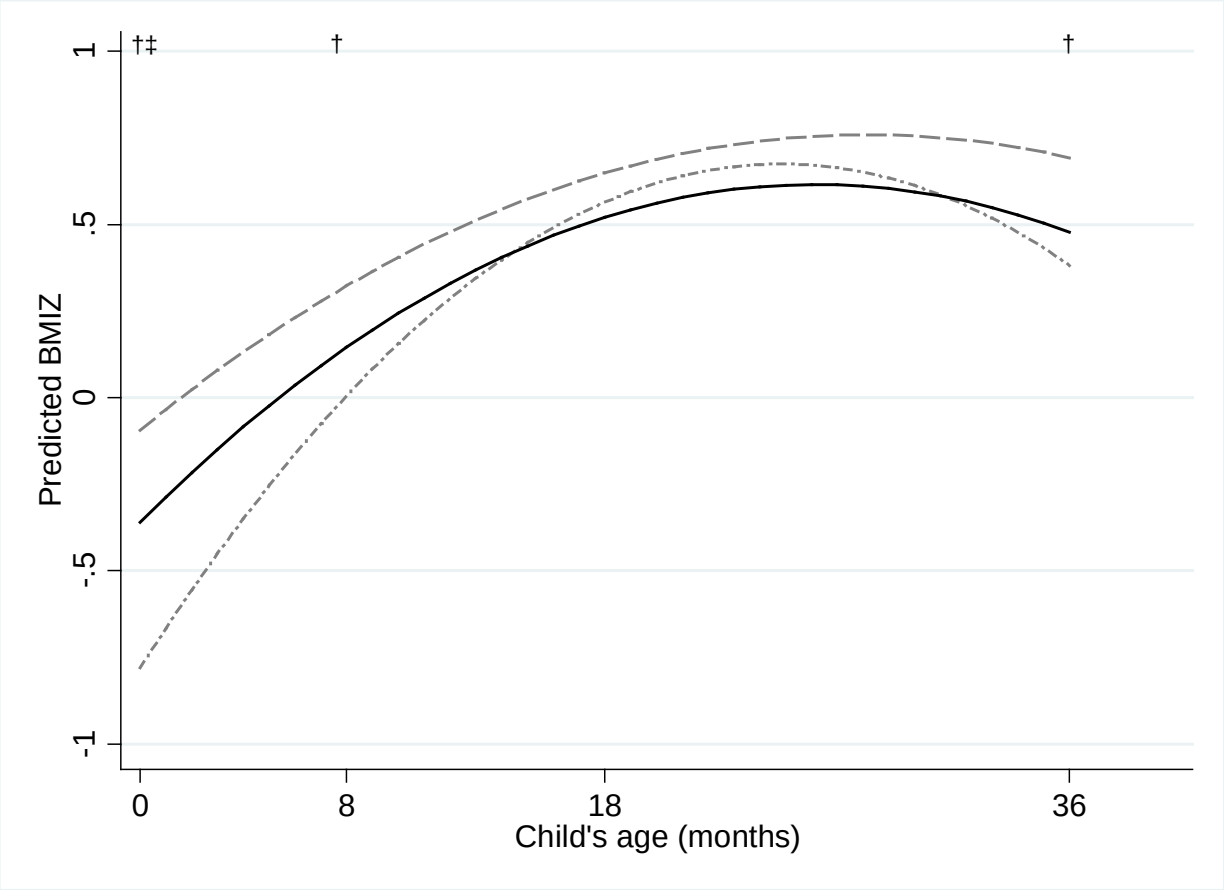


Figure 6. Predicted body mass index z-score (BMIZ) from 0-36 months by gestational weight gain (GWG; excessive GWG, solid; adequate GWG, dashed; inadequate GWG, dotted)

* Predictions based on a multivariable linear model assuming prepregnancy normal weight, high school education, used alcohol in the 1st trimester, abstained from marijuana, smoked tobacco throughout pregnancy, did not breastfeed infant, introduced solid foods ≥6 months, and children who consumed sugared drinks twice per day, and fruits and vegetables twice per day.

† $p<0.05$ for excessive compared to adequate

‡ $p<0.05$ for inadequate compared to adequate

5.0 IS GESTATIONAL WEIGHT GAIN ASSOCIATED WITH OFFSPRING OBESITY AT 36 MONTHS?

5.1 ABSTRACT

Objective: We examined the association between gestational weight gain (GWG) and offspring obesity at age 36 months.

Methods: Mother-infant dyads (n=609) were followed from <26 weeks of pregnancy to 36 months postpartum. Total GWG over the entire pregnancy was defined as excessive or non-excessive according to the 2009 Institute of Medicine guidelines. GWG pattern was defined as four mutually exclusive categories of excessive or non-excessive across early (0 to 26 weeks) and late (26 weeks to delivery) pregnancy. Offspring obesity at 36 months was defined as a body mass index (BMI) z-score ≥95th percentile of the 2000 CDC references. Multivariable log-binomial models adjusted for prepregnancy BMI and breastfeeding were used to estimate the association between GWG and childhood obesity risk.

Results: Nearly half of the women had total excessive GWG. Of these, 46% gained excessively during both early and late pregnancy while 22% gained excessively early and non-excessively late, and the remaining 32% gained non-excess weight early and excessively later. Thirteen percent of all children were obese at 36 months. Excessive total GWG was associated with more than twice the risk of child obesity [adjusted risk ratio (95% CI): 2.20 (1.35, 3.61)] compared

with overall non-excessive GWG. Compared with a pattern of non-excessive GWG in both early and late pregnancy, excessive GWG in both periods was associated with an increased risk of obesity [2.39 (1.13, 5.08)].

Conclusions: Excessive GWG is a potentially modifiable factor that may influence obesity development in early childhood..

5.2 INTRODUCTION

Pediatric obesity is one of the most important public health concerns in the United States. From 1971 to 2000, obesity prevalence rates more than doubled for preschoolers and adolescents, more than tripled for children 6 to 11 years (3), and have since plateaued for all age groups (1), except among 2 to 5 year-olds, for whom obesity rates have declined by 43% in the last 10 years (231). Childhood obesity has been associated with a variety of immediate and long-term comorbidities, such as insulin resistance, diabetes mellitus, hypertension, asthma, altered pubertal timing, depression, unhealthy eating behaviors, and substance use (4). Moreover, obese children are also more likely to be obese adults (22, 23). Given that obesity is resistant to treatment, research efforts focused on modifiable factors to prevent obesity are essential.

Gestational weight gain (GWG) may influence offspring obesity risk in early life. In normal pregnancy, maternal insulin resistance is one of several physiologic adaptations that sustains a constant supply of glucose to the growing fetus (73). Excessive GWG may lead to an over-abundant glucose supply, potentially resulting in fetal fat accumulation and altered programming of the pancreas (215). A recent meta-analysis suggested that excessive total GWG

may be associated with offspring weight in early childhood (87), though studies among young children have been inconsistent (34, 36, 105, 112). Moreover, evidence suggests that fetal programming may be time-sensitive. Thus, the timing of maternal weight gain may be linked to offspring body size and fat mass, with early GWG exerting greater influence than later gain (38, 84, 116). Use of an overall measure of GWG across the entirety of pregnancy may contribute to inconsistent results because it is a heterogeneous measure, mixing periods of excessive gain which may or may not result in a total excessive weight gain.

Our objective was to estimate the risk of obesity in early childhood in relation to total GWG as well as patterns of early and late GWG.

5.3 METHODS

The study sample included mother and child pairs participating in the Maternal Health Practices and Child Development project. Comprehensive descriptions of study design and methods are available elsewhere (136). Briefly, from 1982 to 1985, women <26 weeks pregnant and attending a prenatal clinic at Magee-Womens Hospital in Pittsburgh, PA were recruited for a study of the effects of prenatal substance use. Two cohorts were selected: (1) the alcohol cohort consisted of women who drank three or more alcoholic drinks per week in the first trimester and a random sample women who drank less often and (2) the marijuana cohort consisted of women who used two or more joints per month in the first trimester and a random sample of those who reported using less often. Women could be in either or both cohorts; we studied the combined cohort (n=829). The Institutional Review Boards of Magee-Womens Hospital and University of

Pittsburgh approved the original study and written, informed consent was obtained at each study phase.

There were 763 women with live, singleton births that were eligible for follow-up evaluations at 8, 18, and 36 postnatal months. At the 36 month follow-up visit, 95% of the eligible cohort was interviewed (n=672). The 91 ineligible dyads included 56 for whom a child had died, was adopted, or moved more than 150 miles away, and an additional 35 dyads who refused or were lost to follow-up. We further excluded dyads for whom maternal prepregnancy BMI or GWG data were missing (n=24), those with missing child weight or height data at 36 months (n=31), those where the mother's first prenatal visit was ≥26 weeks (n=6), and those with implausible child weight-for-age or BMI-for-age z-scores (n=2), resulting in a total of 609 mother-child dyads for analysis.

Our primary exposure was GWG based on self-reported total amount of weight gain at the first prenatal visit [mean: 18.8 (standard deviation (SD), 2.7) weeks gestation] and at delivery. We studied GWG in two ways. First, total GWG (0 weeks to delivery) was categorized as excessive versus non-excessive based on the 2009 Institute of Medicine recommendations. Observed weight gain was divided by recommended weight gain (2) based on the gestational age at assessment and prepregnancy BMI (self-reported pregravid weight (kilograms) divided by height (meters) squared). Second, we studied four mutually exclusive patterns of GWG adequacy based on excessive and non-excessive gain during early (0 to 26 weeks) and late (26 weeks to delivery) pregnancy. To determine the sensitivity of our findings to residual confounding by gestational age, we additionally calculated GWG z-scores for total GWG (141).

Our primary outcome was offspring obesity at 36 months, defined as a BMI z-score ≥95th percentile on sex and age-adjusted CDC growth charts (144). Child's weight and length at 36 months were measured using a calibrated scale operated by trained pediatric study nurses.

Covariates including race, marital status, employment status, monthly household income, education level, parity, mental health, and substance use were ascertained via maternal interview. The frequency of tobacco, alcohol, and marijuana use during the first trimester (188, 232) as well as patterns over the course of pregnancy (abstained throughout pregnancy; abstained after first trimester; did not abstain after first trimester) and the postpartum period (≥1 packs/day at 8, 18, or 36 months; ≥1 drinks/day at 8, 18, or 36 months; ≥1 joint/day at 8, 18, or 36 months) was calculated based on interview data. Elevated maternal depressive symptoms and trait anxiety were defined as scores ≥75th percentile on the Center for Epidemiologic Studies Depression Scale (220) and on the State-Trait Personality Inventory (221), respectively, and low social support was a score <25th percentile of a factor score (222). Gestational age at delivery and infant weight at birth were abstracted from medical records. Preterm birth was classified as the delivery of a liveborn infant at <37 weeks. Babies were classified as small- or large-for-gestational age (<10th percentile, >90th percentile, respectively) based on birth weight for gestational age z-scores (164). At 18 months, mothers reported having ever breastfed the child and the age at which solid foods were introduced to her child's diet (<6 months; ≥6 months). At 36 months, mothers recalled the usual frequency of child's fruit, vegetable, sugared drink, and soda consumption using a simple questionnaire designed for the study.

5.3.1 Statistical analysis

Pearson chi-square tests were used to study the bivariate associations between maternal characteristics at <26 weeks and category of total and pattern GWG, and with childhood obesity. Characteristics measured at <26 weeks may potentially confound associations of interest and were thus preferred to characteristics measured at later assessments. Multivariable log-binomial regression models were used to estimate the relative risks (RR) of childhood obesity at 36 months by categories of total and pattern GWG after adjusting for confounders. We also ran these models among a subset of children who were not obese at the previous study visit at 18 months (BMI at 18 months <95th percentile on age and sex-adjusted WHO growth charts (2006)) to estimate whether associations were observed after the critical period of infant growth. In the interest of parsimony, we classified GWG as excessive or non-excessive, grouping women who gained inadequately and adequately together because of the similarity in their adjusted risk ratio.

Theory-based causal diagrams (200) were used to select potential confounders (maternal prepregnancy BMI, age, race, parity, first trimester income, education, substance use, child's sex, and dietary characteristics). Parsimonious models were generated by removing potential confounders from the full model based on a change-in-estimate strategy (change in the main-effect estimate by ≥10%). Only prepregnancy BMI and ever-breastfed met our definition of confounding and were retained in our final models. Gestational age at delivery and birth weight were considered potential mediators on the causal path from GWG to child weight and were not included in models (158). Effect modification on the additive scale was evaluated by prepregnancy overweight, race, maternal depression, anxiety, prenatal substance use, and child's sex using the synergy index (206). Finally, we applied inverse probability sample weights (192)

to reweight the study sample to reflect the original prenatal clinic sample from which the cohort was selected. Stata Software, version 11 (College Station, TX) was used for analysis.

5.4 RESULTS

Most women (62%) in the study had a normal prepregnancy BMI (**Table 14**). Women tended to be young (mean 23.1 years of age), unmarried (67%), have at least a high-school education (86%), and have a monthly household income <$400 (62%). A majority of women drank alcohol in the first trimester (65%), half smoked tobacco (53%), and two in five women used marijuana. Black mothers and nulliparous mothers made up approximately half of the sample. Children were light at birth [mean (SD) birth weight for gestational age z-score -0.36 (0.94)] and born at term [39.1 (2.18)].

A majority of women had total non-excessive GWG (55%), of which, 36% had total inadequate GWG and 64% had total adequate GWG. For the 45% of women with total excessive GWG, half had excessive GWG in both early and late pregnancy, while the remainder gained excessively in only one of these periods (**Table 15**). Mothers who had a higher prepregnancy BMI and more years of education tended to gain excessive weight during both early and late pregnancy as compared to lean women and women who were less educated, respectively (**Appendix B**). There were no significant differences in pattern of GWG by maternal race/ethnicity, income, prenatal substance use, sex, or infant ever breastfed status.

Thirteen percent of children were obese at 36 months. Of these, approximately half were already obese prior to their 18-month study visit, while the remainder developed obesity between

18 and 36 months of age. Women who were heavier at the start of pregnancy were more likely to have an obese child at 36 months, but there were no differences in other maternal or child characteristics by child obesity status at 36 months (**Table 16**).

Women who had total excessive GWG were more likely than women with total non–excessive GWG to have an obese child at 36 months (**Table 17**). In models adjusted for prepregnancy BMI and ever breastfed status, total excessive GWG was associated with a higher risk of childhood obesity at 36 months. Similarly, among the subset of children who were not obese at 18 months (n=392), total excessive GWG remained associated with increased obesity risk at 36 months (adjusted RR (95% CI): 2.51 (1.23, 5.11)).

Compared with women whose GWG pattern was non-excessive in both early and late pregnancy, women who had excess GWG in both periods were more than twice as likely to have an obese child at 36 months after adjustment (**Table 17**). Compared with the same referent, a pattern of early excessive gain and late non-excessive gain was associated with a higher risk of child obesity in crude models, but the effect was attenuated after adjustment. In contrast, a gain pattern of early non-excessive and late excessive was unassociated with obesity risk in crude or adjusted models. There was no interaction between early and late GWG for the risk of child obesity.

In a series of sensitivity analyses, none of the results changed meaningfully when we applied inverse probability sample weights; excluded heavy alcohol or marijuana users (≥1 drink or ≥1 joint per day in the first trimester) or those who continued prenatal use of alcohol or marijuana; or used GWG z-scores to classify GWG. We did not find evidence of effect modification on the additive scale by prepregnancy BMI, maternal depression, anxiety, alcohol use, marijuana use, tobacco cigarette use, race, or child sex in any of the models.

5.5 DISCUSSION

In a sample of predominantly low-income mothers, women who gained more weight during pregnancy than is recommended by the 2009 IOM Committee (2) had children with an increased risk of obesity at 36 months as compared with women with non-excessive gain. This link between excessive GWG and childhood obesity appeared to be limited to women who gained excessively during both early and late periods of their pregnancy and was not evident in women with excessive gain only in either early or late pregnancy. This association remained after adjustment for confounders.

There are many studies on total GWG and BMI in children aged approximately 2 to 5 years, with some (34, 100-103) reporting a positive association and others (105, 111-114) reporting no association. Our findings are consistent with four (34, 100, 102, 103) of the six studies that classified total GWG according to guidelines that account for strong confounding by prepregnancy BMI (2). Although we lacked child anthropometric indicators of body composition other than child BMI, others have found that total excessive GWG is associated with offspring higher summed triceps and subscapular skinfold thickness at 36 months (34), waist circumference, and DEXA-measured fat mass at 4 and 5 years (36, 103).

There are fewer studies of the relationship between pattern of GWG and childhood obesity. Most of the previous work has shown that higher GWG in early pregnancy has a stronger influence on childhood anthropometric indicators of body composition than later-pregnancy weight gain (38, 104, 116, 130). For instance, in a large cohort of U.S. births from 1959 to 1967, researchers found that each 1-kg increase in GWG in the first trimester was associated with a 5% increase in the adjusted odds of child overweight (BMI$\geq 85^{th}$ percentile) at

5 years (odds ratio (95% CI): 1.05 (1.02, 1.09)), but there was no relationship with GWG in the second and third trimesters (116). We found that the increased risk of childhood obesity was statistically significant only among women who gained excessively in both early and late pregnancy. There was a crude positive association among women with early excessive GWG and risk of child obesity, but this relation was null after confounder adjustment. Unlike our study, von Kries and colleagues found that GWG specific to late pregnancy may contribute to the risk of childhood obesity (117). Using data from a large Bavarian retrospective cohort, they found that only third-trimester excessive GWG was associated with childhood overweight at a mean of 5.8 years, regardless of the gain at <14 weeks or 14 to <26 weeks. In both our study and von Kries' study, GWG at <26 weeks was the earliest period of pregnancy studied, yet gain in earlier periods may be more relevant to fetal programming. Data suggest that higher early maternal weight gain may reflect an increase in maternal fat (2), which may influence biological processes that promote offspring fat accrual. Fetal organogenesis occurs at specific times during pregnancy, and development may be influenced by maternal factors. Fetal pancreatic beta cells differentiate and are functional as early as 13 weeks gestation (233), and adipose tissue appears as early as 14 weeks (234). Neural networks responsible for regulating appetite (235) and energy balance (236) are developed by mid-pregnancy. Early pregnancy overnutrition may program these tissues and networks to function suboptimally, which could impact feeding behavior, energy balance, and ultimately body composition. We may have failed to find an effect limited to early pregnancy weight gain because excessive first-trimester weight gain may be most relevant, and we did not have the data to isolate weight gain in this period. In later pregnancy, maternal weight gain is primarily attributed to rapid fetal growth (2). Overnourishment in late gestation may occur outside of the fetal programming period, yet still influence overall body

composition. Thus, children of women with excess weight gain throughout pregnancy may indeed have an elevated risk for later obesity.

The Maternal Health Practices and Child Development Project was not undertaken with this research question in mind, so our analysis has several limitations. This cohort had a high proportion of women using substances during pregnancy, which may limit generalizability. Nevertheless, our results were similar when we eliminated heavy substance users from our analysis, so it is likely that our findings extend to samples with lower levels of substance use. Misclassification of GWG was possible, as it was based on self-report at each study visit. However, the reporting of weight occurred shortly after the patient was weighed at a prenatal visit or delivery, which may reduce the likelihood of major bias. Our study used GWG as a crude measure of maternal nutritional status and child BMI as a proxy for excess body fat adjusted for height (229). Studies of direct measures of body composition or body fat distribution in mothers or children are needed. Like several previous reports (34, 36, 38, 104, 117), we did not find evidence that the effect of total GWG on childhood obesity varied by prepregnancy BMI, or that the effect of excessive GWG at <26 weeks was modified by GWG at ≥26 weeks, but our sample size may have been too small to detect these effects.

In our study and all observational studies of GWG and child outcomes, there is a concern regarding unmeasured confounding by shared family characteristics of mothers and children. We tested a number of child dietary characteristics, such as ever breastfed and regular intake of sugared drinks and fruits and vegetables as confounders in our model, and the results did not change. However, these factors were not measured with validated instruments and residual confounding may exist. Branum et al. conducted a study of GWG across two pregnancies in the same mother. They found that a positive association between GWG and childhood obesity was

eliminated after accounting for shared factors in the sibling analysis (105). More research is needed to evaluate the causality of these associations.

Excessive GWG is common in U.S. mothers (2), and our study adds to the growing body of evidence linking excessive weight gain during pregnancy to offspring obesity. If randomized trials prove that this is a casual relationship, then interventions to reduce excessive GWG may serve not only to improve the health of mothers but to break the intergenerational link between excess adiposity in mothers and their children.

5.6 FIGURES AND TABLES

Table 14. Characteristics of the study sample, n=609

	%
Prepregnancy body mass index (kg/m^2)	
Underweight (<18.5)	12
Normal weight (18.5-24.9)	60
Overweight (25.9-29.9)	18
Obese (≥30.0)	10
Maternal race/ethnicity	
White	48
Black	52
Maternal age (years)	
<20	18
20-24	51
25-29	25
≥30	6
Maternal education (years)	
<12	27
=12	60
>12	13
Marital status	
Unmarried	68
Married	32
Employment	
Working or in school	25
Not working or in school	75
Income Level ($/month)	
<400	62
≥400	38
Parity	
Nulliparous	45
Multiparous	55
Prenatal smoking	
None	47
<0.5 packs/day	22
0.5 to <1 packs/day	18
≥1 packs/day	14

Table 14 continued.

Prenatal alcohol use	
None	35
>0 to <1.5 drinks/week	21
1.5 drink/week to <1 drinks/day	25
≥1 drinks/day	19
Prenatal marijuana use	
None	58
>0 to <0.5 joint/day	21
0.5 to <1 joints/day	7
≥1 joints/day	13
Prenatal smoking pattern	
Never used in pregnancy	43
First trimester use only	5
Second and/or third trimester use	52
Prenatal alcohol use pattern	
Never used in pregnancy	30
First trimester use only	38
Second and/or third trimester use	32
Prenatal marijuana use pattern	
Never used in pregnancy	58
First trimester use only	24
Second and/or third trimester use	18
Gestational age at delivery (weeks)	
<37 weeks	9
≥37 weeks	91
Birth weight for gestational age z-score [1]	
Small for age (<10^{th} percentile)	16
Appropriate for age (10^{th} to 90^{th} percentile)	80
Large for age (>90^{th} percentile)	4
Infant sex	
Female	50
Male	50
Ever breastfed infant	
Yes	22
No	78

[1] Reference for birth weight for gestational age z-score (164)

Table 15. Gestational weight gain (GWG) pattern by overall GWG

GWG Pattern [1]	Overall sample	2009 IOM Overall GWG Category	
		Not Excessive	Excessive
	n (%)	n (%)	n (%)
Early non-excessive; late non-excessive	148 (24)	148 (44)	0 (0)
Early non-excessive; late excessive	166 (27)	79 (24)	87 (32)
Early excessive; late non-excessive	170 (28)	109 (32)	61 (22)
Early excessive; late excessive	125 (21)	0 (0)	125 (46)

[1] Pearson chi-square test $p<0.001$

Table 16. Childhood obesity at 36 months by characteristics of the sample

	Obesity at 36 months (N=609)	
	Not Obese	Obese
Prepregnancy body mass index (kg/m^2), % [1]		
Underweight (<18.5)	96	4
Normal weight (18.5-24.9)	88	12
Overweight (25.9-29.9)	81	19
Obese (≥30.0)	82	18
Maternal race/ethnicity, %		
White	85	15
Black	90	10
Income level ($/month), %		
<400	88	12
≥400	86	14
Parity, %		
Nulliparous	85	15
Multiparous	89	11
Prenatal smoking, %		
None	88	12
<0.5 packs/day	86	13
0.5 to <1 packs/day	95	5
≥1 packs/day	82	19
Prenatal alcohol use, %		
None	85	15
>0 to <1.5 drinks/week	92	8
1.5 drink/week to <1 drinks/day	90	10
≥1 drinks/day	8	17
Prenatal marijuana use, %		
None	88	12
>0 to <0.5 joint/day	89	11
0.5 to <1 joints/day	85	15
≥1 joints/day	85	15
Gestational age at delivery (weeks), %		
<37 weeks	93	7
≥37 weeks	87	13
Birth weight for gestational age z-score, % *		
Small for age (<10th percentile)	90	10
Appropriate for age (10th to 90th percentile)	87	13
Large for age (>90th percentile)	82	18
Infant sex, %		
Female	89	11
Male	86	14

Table 16 continued.

Ever breastfed infant, %		
Yes	85	15
No	88	12

[1] Pearson chi-square test $p<0.05$

[*] Reference for birth weight for gestational age z-score (164)

Table 17. Association between measures of gestational weight gain (GWG) and childhood obesity at 36 months (n=609)

	Obesity Status at 36 months		Unadjusted RR	Adjusted RR†
	Not Obese	Obese	(95% CI)	(95% CI)
Overall GWG, n (%) [1]				
overall non-excessive	313 (93)	23 (7)	1.0 (ref)	1.0 (ref)
overall excessive	219 (80)	54 (20)	2.89 (1.82, 4.58)	2.20 (1.35, 3.61)
GWG Pattern, n (%) [1]				
early non-excessive; late non-excessive	139 (94)	9 (6)	1.0 (ref)	1.0 (ref)
early non-excessive; late excessive	148 (89)	18 (11)	1.78 (0.83, 3.85)	1.35 (0.62, 2.97)
early excessive; late non-excessive	148 (87)	22 (13)	2.13 (1.01, 4.45)	1.86 (0.88, 3.93)
early excessive; late excessive	97 (78)	28 (22)	3.68 (1.81, 7.51)	2.39 (1.13, 5.08)

[1] Pearson chi-square test $p<0.05$

†Adjusted for prepregnancy body mass index and ever breastfed infant

6.0 GESTATIONAL WEIGHT GAIN AND THE RISK OF OFFSPRING OBESITY AT 10 AND 16 YEARS

6.1 ABSTRACT

Data from a prospective birth cohort (n=660) were used to study the association between gestational weight gain (GWG) and offspring obesity risk at ages chosen to approximate pre-puberty (10 years) and post-puberty (16 years). BMI z-scores were calculated using measured height and weight, and obesity was defined as z-score ≥95th percentile of the 2000 CDC references. GWG was classified based on maternal GWG-for-gestational-age z-score charts and was modeled using flexible spline terms in modified Poisson regression models. The prevalence of offspring obesity was 20% at 10 years and 21% at 16 years. The association between GWG and offspring obesity varied by prepregnancy BMI. Among mothers who had a pregravid BMI<25, the risk of offspring obesity at 16 years was flat until a GWG z-score of 0 SD (16.4 kg at 40 weeks gestation), after which it increased. Adjusted obesity risk ratios at 16 years (95% confidence interval) for GWG z-scores of +0.5 SD (19.5 kg), +1.0 SD (23.0 kg), and +1.5 SD (26.8 kg) were 1.22 (1.06, 1.41), 1.60 (1.15, 2.24), and 2.13 (1.25, 3.65) , respectively, compared with women with a GWG z-score of 0 SD. Results were similar at 10 years. Among overweight women, the risk of offspring obesity increased to a z-score of 0 SD and plateaued. Low GWG was protective against obesity at 10 years but did not reach statistical significance at 16 years.

Prenatal overnutrition differs by prepregnancy BMI and may have lasting effects on offspring obesity risk.

6.2 INTRODUCTION

Nearly one in five U.S. adolescents aged 12 to 19 years is obese (body mass index $\geq 95^{th}$ percentile of the CDC 2000 growth reference) (1). These adolescents are more likely to adopt unhealthy weight control behaviors, such as using laxatives, diet pills, vomiting (237) and skipping breakfast (238), and less often practice affirmative health behaviors such as physical activity or healthy eating (237); these behaviors may persist and contribute to additional weight gain into young adulthood (239). As well, obese adolescents may be more likely to have depression (240) and use substances (241), and are more likely to be obese in adulthood and suffer from obesity-related comorbidities (8-10).

Children are expected to gain weight and fat during puberty (22, 23, 69) so as to provide a reserve of energy for upcoming periods of physiologic and evolutionary importance (54, 55). Yet, puberty also may be a high-risk period for obesity development, especially among children whose mothers gained an excessive amount of weight during their pregnancy. GWG may program fetal metabolism and pancreatic beta cell number and function (216, 242). The resulting impact on offspring fat storage and fat metabolism may be more evident after a period of fat promotion such as puberty. GWG has been associated with child obesity risk over a range of ages (87), but relatively few studies have addressed offspring obesity beyond puberty. Our

objective was to estimate the association between GWG and the risk of offspring obesity at ages that approximate pre-puberty (10 years) and post-puberty (16 years).

6.3 METHODS

We used secondary data from a prospective birth cohort of pregnant women and their children designed to investigate the influence of prenatal substance use on child growth and development (187). At an urban prenatal clinic at Magee-Women's Hospital (Pittsburgh, Pennsylvania; 1982-85), 1,600 women ≥18 years old and <26 weeks pregnant were selected at random from an appointment book and 85% agreed to screening for prenatal substance use. From this sample, women were selected into one of two cohorts based on first trimester alcohol or marijuana use. Each cohort included women using alcohol or marijuana at light to moderate levels as well as women who refrained from use. The cohorts were combined (n=829) for this analysis (184, 186, 187). Women were interviewed at initial screening [mean: 18.8 weeks gestation (standard deviation (SD), 2.7)], and with their offspring at delivery and 10 and 16 postnatal years. Further details of the core study design and methodology are available elsewhere (136). The original study was approved by the Institutional Review Boards of Magee-Womens Hospital and University of Pittsburgh. Written, informed consent was obtained at each study phase.

At birth, 763 women and their liveborn singleton infants were eligible for follow-up assessment. Of these, 90% and 85% were interviewed at the 10- and 16-year follow-up visits, respectively. We excluded mother-child pairs with missing maternal data for prepregnancy BMI or GWG (n=20), implausible GWG z-scores (<-5 SD, n=2), and those for whom the child's

weight and height were unavailable at both the 10 and 16 year assessment (n=81). A total of 660 mother-child pairs were analyzed. As compared with the excluded group, the final analytic sample had a higher proportion of women who were underweight before becoming pregnant (13% vs. 4%). There were no differences by other variables including sociodemographic characteristics, substance use, mental health, or measures of adolescent (data not shown).

Maternal prepregnancy body mass index (BMI, weight (kg)/height(m)^2) was based on prepregnancy weight and height self-reported at the first study visit. The total amount of weight gained since becoming pregnant was self-reported at delivery. GWG was assessed using gestational age-standardized maternal weight gain z-score charts (141). Percentile charts have not yet been published for underweight women, so we applied those for normal weight women to this group.

At the 10- and 16-year postnatal assessments, trained study nurses measured the adolescent's weight and height using a calibrated scale. We calculated age- and sex-adjusted BMI z-scores based on the CDC growth charts to define obesity at 10 and 16 years (144). All z-score calculations fell within a predetermined plausible range (>-5 to <5).

Maternal race, age, marital status, employment status, monthly household income, education level, parity, and substance use, as well as psychological, social, and environmental factors were self-reported at each visit. Maternal first-trimester use of tobacco, alcohol, and marijuana was categorized using published classifications (184). We also studied the pattern of alcohol or marijuana use over the course of pregnancy (abstained throughout pregnancy; abstained after first trimester; did not abstain after first trimester). Scores $\geq 75^{th}$ percentile on the Center for Epidemiologic Studies Depression Scale (220) and the State-Trait Personality Inventory (221) were considered elevated levels of maternal depression and anxiety,

respectively, during pregnancy. A social support factor score <25th percentile defined low maternal social support (222). We additionally used measures of postpartum depression, anxiety, substance use, maternal obesity, and maternal weight change from prepregnancy to 10 or 16 years postpartum.

We classified adolescents as having early pubertal development at 10 and 16 years if they answered 'much earlier' or 'somewhat earlier' to one item from the Petersen Development Scale (169): 'Do you think your development is any earlier or later than most other boys/girls your age?' All other responses were classified as 'same or later.' Also at 16 years, adolescents self-reported their pubertal status using the full Petersen Development Scale (169) and were classified as 'advanced puberty/post-pubertal' or 'pre-pubescent/early puberty'. Diagnosis of major depression in the adolescent was assessed using the Diagnostic Interview Schedule (DIS-IV) (243) and anxiety was measured using the Children's Manifest Anxiety Scale (CMAS) (244). Adolescents' involvement in sports, hobbies, responsibility for chores, and number of close friends was assessed by maternal report using the Child Behavior Checklist (CBCL) (245). Validated measures of adolescent alcohol, marijuana, and tobacco use (246) were classified as abstained or ever used.

6.3.1 Statistical analysis

Differences between categorical maternal characteristics at <26 weeks gestation and adolescent obesity were tested with Pearson chi-square tests. The relative risks (RR) and 95% confidence intervals (CI) for the association between GWG z-score and adolescent obesity at 10 and 16 years were estimated using multivariable modified Poisson regression with a robust variance

estimator (196). There was a non-linear relation between GWG and the log of obesity at 16 years. We therefore modeled GWG using restricted cubic splines with three knots (247). We also categorized GWG z-scores into three groups based on thirds of the distribution.

Potential confounders (maternal: prepregnancy BMI, age, race, parity, first-trimester income, education, mental health, substance use, and the pattern of prenatal substance use; and adolescent offspring: sex, substance use, mental health, involvement in sports, hobbies, or chores) were selected using theory-based causal diagrams (200). Birth weight, gestational age, maternal postpartum obesity, change in postpartum weight, and pubertal status of the adolescent may lie on the causal path and thus were not potential confounders (158). Parsimonious models were built by including only potential confounders that met a change-in-estimate criterion (≥10% for the main effect). To balance limited degrees of freedom and a wide array of covariates, we considered potential confounders in groups. Maternal prepregnancy BMI, first trimester cigarettes, and whether the adolescent had tried alcohol met our definition of confounding. A likelihood ratio test (α=0.10) was used to test for effect modification on the multiplicative scale by race, prepregnancy overweight, postpartum obesity, change in postpartum BMI, maternal depression, anxiety, substance use, and offspring sex. In sensitivity analyses, we used inverse probability sample weights to account for the sampling scheme (192, 193). All analyses were conducted using Stata Software, version 11 (College Station, TX).

6.4 RESULTS

At study enrollment, women were an average of 23 (SD, 3.9) years old, and most were unmarried (68%), and reported a household income of <$400 per month (62%). Approximately 60% of women had a normal prepregnancy BMI and 18% and 9% were overweight or obese, respectively (**Table 18**). Slightly more than half the sample included black mothers and parous women, and only 13% had more than 12 years of education. Alcohol or marijuana use was common in the first trimester. On average, women in our sample gained 14.4 (SD: 5.87) kilograms at delivery. For the offspring at age 10, 79% reported developing at a stage similar to their peers, while the remainder reported earlier development. At 16 years, 89% of adolescents reported an advanced or post-pubertal stage.

At 10 years and 16 years, 20% and 21% of adolescents were obese, respectively. Approximately 69% of those who were obese at 10 years remained obese at 16 years. Women with a heavier prepregnancy BMI were more likely to have an obese adolescent compared with leaner women. As compared with their counterparts, white women and women who reported more frequent smoking and marijuana in the first trimester were more likely to have an obese 16 year-old. Adolescents who had tried alcohol use were less likely to be obese than those who abstained, while no differences in the likelihood of obesity were observed by adolescent pubertal status. Mothers with obesity at 16 years postpartum, as well as mothers with 10 to <30 lb. of postpartum weight gain were more likely to have an obese 16 year-old.

In bivariate analyses, adolescent obesity at 10 years varied significantly by GWG z-scores tertile (lowest tertile 17%, middle tertile 16%, highest tertile 28%, $p<0.01$), but at 16 years the difference was not statistically significant (18%, 20%, 25%, respectively). After adjusting

for prepregnancy BMI, first-trimester smoking status and adolescent experimental alcohol use, risk curves for the association between GWG z-score and child obesity at 10 and 16 years were flat for GWG z-scores increasing from -2 SD to 0 SD, but for GWG z-scores increasing from 0 SD to +2 SD, the risk curves increased (**Figure 7, Panel A, Panel D, respectively**).

The association between GWG and adolescent obesity risk was modified by prepregnancy BMI. Among mothers who were lean before pregnancy (BMI <25), the risk curves for offspring obesity at 10 years (**Figure 7, Panel B**) and 16 years (**Figure 7, Panel E**) rose starting at GWG z-scores of 0 SD (16.4 kg at 40 weeks gestation). After adjusting for confounders, women with GWG z-scores of +0.5 SD (19.5 kg at 40 weeks), +1.0 SD (23.0 kg), and +1.5 SD (26.8 kg) had 27%, 76%, and 146% increases in the risk of having a child with obesity at 16 years, respectively, compared with women with GWG z-scores of 0 SD (**Table 19**). The association between very low GWG and risk of offspring obesity at 16 years was not statistically significant. Results were similar for offspring obesity at 10 years.

In contrast, among women who were overweight before pregnancy (BMI ≥25), the adjusted risk of offspring obesity at 10 years and 16 years tended to increase as GWG z-score rose to 0 SD (15.8 kg at 40 weeks) and leveled off thereafter (**Figure 7, Panel C; Figure 7, Panel F**). GWG z-scores of -2.0 SD (4.8 kg at 40 weeks), -1.5 SD (6.9 kg), -1.0 SD (9.4 kg), and -0.5 SD (12.4 kg) were associated with 85%, 73%, 57%, and 25% decreases in the risk of obesity at 10 years, respectively, compared with GWG z-score of 0 SD after adjustment for confounders. Similar decreases in risk were observed at 16 years, with 73%, 61%, 43%, and 21% lower likelihoods of obesity respective to the same z-scores, but statistical significance was reached only at a z-score of -0.5 SD.

Results did not additionally vary by race, postpartum obesity, a change in postpartum weight or BMI, maternal depression, anxiety, alcohol, marijuana, or tobacco smoking, or sex of the offspring. When we limited models to women who stopped using of alcohol or marijuana after the first trimester, similar results were found (data not shown). Results were also similar after adjusting for additional confounders and after applying inverse probability sample weights.

6.5 DISCUSSION

Research suggests that puberty may be a period of greater sensitivity to weight gain and that gain in this period increases the risk of obesity in later life. Simultaneously, obesity may begin in early life and excess GWG is a potential prenatal factor. We previously reported using data from the current study sample that higher GWG was associated with higher weight at birth, slower growth over infancy (ref paper 1) and a greater likelihood of obesity at age 3 (ref paper 2). This report extends the analysis to adolescents to reveal that the positive association remains at 10 and 16 years. After adjusting for prenatal and postnatal factors, we found that as GWG z-scores increased from 0 SD (approximately 16 kg at 40 weeks gestation) to 1.5 SD (approximately 28 kg), there was an increased risk of obesity at ages 10 and 16 years. Among lean mothers, we found that as GWG z-scores increased in the higher end of the spectrum, there was an increase in the risk for obesity; yet among overweight women, an increase in GWG at a lower range was associated with a distinct increase in obesity risk.

We know of only one study that followed children throughout adolescents and reported findings at ages likely to represent pre- and post-puberty (111). Rooney and colleagues studied

GWG in 532 U.S. women and, like our study, found significant increases in the odds of offspring overweight (BMI $\geq 85^{th}$ percentile of the CDC growth curves) at 9-14 years and obesity (BMI ≥ 30.0 kg/m^2) at 18-20 years among women who gained in excess of the 1990 Institute of Medicine (IOM) GWG guidelines compared with those gaining within the recommended ranges though these estimates were not adjusted for prepregnancy BMI which is known to be a strong confounder.

Studies of young adolescents tend to support a positive association between GWG and offspring weight or fat mass (33, 38, 123). Oken and colleagues studied 11,994 US 9-14 year-old offspring and their mothers. Pubertal development varied across the sample, with 47% pre- or early puberty (Tanner Stage I or II). Every 5-pound increase in GWG was associated with a 9% increase in the odds of child obesity (95% CI: 1.06, 1.13) after adjusting for prepregnancy BMI, smoking in pregnancy, Tanner stage of pubertal development and other confounders. Unlike our study, adolescents self-reported their weight and height, which may be prone to misreporting during growth spurts (118, 119). In two studies of British 9 year-olds with measured anthropometric data, one found a positive association with BMI, waist circumference, and fat mass (38), while fat mass was unassociated in a smaller sample (123). Among older adolescents, positive associations between GWG and BMI (106) as well as waist circumference (130) were reported in two Nordic samples, though once adjusted for shared maternal factors the association remained among overweight but not lean women (106). In contrast, the U-shaped association reported by Stuebe and colleagues (28) is inconsistent with the findings presented here as well as a number of other studies in adolescents (33, 111, 130) in which low GWG and offspring obesity were unassociated, and others that suggest a protective effect (38, 87, 112).

GWG may directly impact offspring adiposity through a number of developmental programming mechanisms (248) which may function jointly or independently. Offspring may be predisposed to fat accrual via the fetal pancreas (216, 242) or may impact neural circuitry (235), leading to a failure to limit energy reserves through altered appetite regulation (218). In later life, offspring who were conditioned in-utero may have an intrinsic hypervigilance or 'overprotection' against weight loss during biologically important growth periods such as puberty. Interestingly, we did not observe a major difference in the relationship between GWG and offspring weight between the pre- and postpubertal periods in children of lean or overweight mothers. This may be due to most of the obese children in our cohort who were obese at 10 years were also obese at 16 years. This lack of a difference at 10 and 16 year findings may also be due to our use of BMI to measure adiposity rather than a direct measure which may capture key differences in body composition and fat distribution across these two periods.

We found that the risk of adolescent obesity rose as GWG increased to approximately 16 kg and then leveled off among overweight women, but among lean women the risk curve was flat until about 16 kg and then rose. We are not aware of previous studies that examined nonlinear relationships between GWG and adolescent obesity risk separately by maternal BMI. However, several research groups have reported that excessive GWG increases the risk of adolescent obesity for children of lean and overweight women to a similar extent (33, 106). Previous investigations have lacked adequate sample size to evaluate the optimal range of GWG for prevention of adolescent obesity among obese or severely obese mothers, and this remains a research priority (2).

The GWG-child obesity association that we and others noted may not be causal, but due to shared familial or environmental characteristics in adolescence such as an obesogenic environment. In an effort to control for shared factors, Lawlor and colleagues compared the association between GWG and offspring weight within siblings, and also ran models between nonsiblings similar to conventional analyses. Using a sample of 146,894 Swedish 18 year-old men (born 1973 to 1988) from 136,050 families, the study found that among overweight women, every 1-kilogram increase in GWG was associated with an increase in offspring BMI within siblings (accounting for shared factors), an effect that was stronger than the positive relation between nonsiblings. For lean women, there was an association between nonsiblings only but not within siblings. These results suggest that for lean women, an association may be largely driven by genetic and environmental factors; for overweight women the association may be driven by both shared familial as well as intrauterine mechanisms. We lacked sibling data and instead used maternal postpartum BMI and weight change as a proxy for an obesogenic environment. However, we did not find evidence that the GWG-adolescent obesity relationship varied by levels of maternal postpartum weight or weight change.

Our prospective cohort study was not originally designed to evaluate research on GWG and childhood obesity, so this study has several limitations. Our findings in this low-income sample of women pregnant in the 1980s, a majority of whom used substances early in pregnancy, may not generalize to other populations. However, it is notable that our findings were consistent when we excluded heavy users. Substance use in pregnancy remains common in the United States today (191), and we feel that our ability to adjust for substance use is a strength. The parent study evaluated children at 10 and 16 years and did not collect data on the age of pubertal onset. Although most children at age 16 were post-puberty, we ideally would have studied the

association between GWG and adolescent obesity in a group of children both before and after confirmed puberty. Although we considered breastfeeding, pre- and postnatal substance use and mental health status, socioeconomic factors, and social support as confounders in our analysis, unmeasured variables such as child's diet and physical activity may have biased our results. Maternal weight data was recalled, but its collection proximal to the time period of interest lessens the likelihood of bias.

Our results support the growing body of evidence suggesting that GWG is positively associated with adolescent obesity risk. However, in light of the increased risks of preterm birth and fetal growth restriction associated with low GWG, more research is needed to determine the optimal range of GWG to balance risks for the offspring, as well as the mother.

6.6 FIGURES AND TABLES

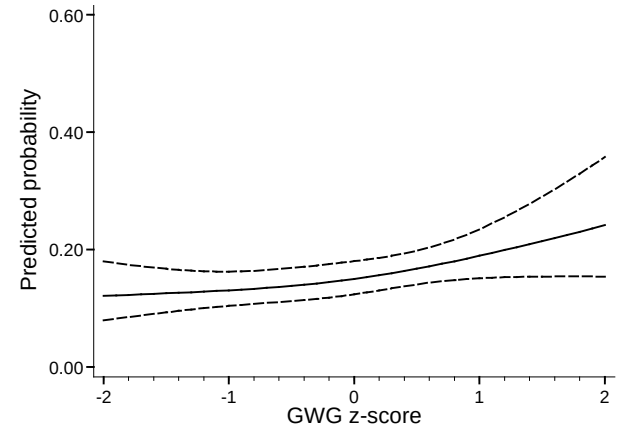
Table 18. Characteristics of the study sample overall and by adolescent obesity at 16 years

	Overall	Obesity at 16 years	
		Not Obese	Obese
	n=564	n=445	n=119
Perinatal characteristics			
Prepregnancy BMI (kg/m^2), n (%)			
Underweight (<18.5)	72 (13)	67 (93)	5 (7) [1]
Normal weight (18.5-24.9)	334 (59)	273 (82)	61 (18)
Overweight (25.9-29.9)	104 (18)	72 (69)	32 (31)
Obese (≥30.0)	54 (10)	33 (61)	21 (39)
Maternal race/ethnicity, n (%)			
White	259 (46)	217 (84)	42 (16) [1]
Black	305 (54)	228 (75)	77 (25)
Maternal education (years), n (%)			
<12	152 (27)	114 (75)	38 (25)
=12	338 (60)	266 (79)	72 (21)
>12	74 (13)	65 (88)	9 (12)
Infant sex, n (%)			
Female	289 (51)	228 (79)	61 (21)
Male	275 (49)	217 (79)	58 (21)
Gestational age (weeks), n (%)			
<37	54 (10)	399 (78)	111 (22)
≥37	510 (90)	46 (85)	8 (15)
Birth weight for gestational age z-score, n (%)			
Small for age (<10th percentile)	98 (17)	79 (81)	19 (19)
Appropriate for age (10th to 90th percentile)	446 (79)	352 (79)	94 (21)
Large for age (>90th percentile)	20 (4)	14 (70)	6 (30)
Prenatal smoking in the first trimester, n (%)			
None	266 (48)	209 (79)	57 (21) [1]
<0.5 packs/day	114 (20)	99 (87)	15 (13)
0.5 to <1 packs/day	100 (18)	71 (71)	29 (29)
≥1 packs/day	84 (15)	66 (79)	18 (21)

Table 18 continued.

Prenatal alcohol use in the first trimester, n (%)			
None	201 (36)	148 (74)	53 (26)
>0 to <1.5 drinks/week	120 (21)	97 (81)	23 (19)
1.5 drink/week to <1 drinks/day	137 (24)	113 (82)	24 (18)
≥1 drinks/day	106 (19)	87 (82)	19 (18)
Prenatal marijuana use in the first trimester, n (%)			
None	328 (59)	270 (82)	58 (18) [1]
>0 to <0.5 joint/day	119 (21)	93 (78)	26 (22)
0.5 to <1 joints/day	41 (7)	30 (73)	11 (27)
≥1 joints/day	76 (14)	52 (68)	24 (32)
Characteristics at 16 years			
Adolescent pubertal status, n (%)			
Advanced puberty/Post-pubertal (≥4)	459 (89)	360 (78)	99 (22)
Pre-pubescent/Early puberty (<4)	58 (11)	49 (84)	9 (16)
Adolescent tried alcohol, n (%)			
Yes	308 (55)	255 (83)	53 (17) [1]
No	255 (45)	190 (75)	65 (26)
Maternal postpartum obesity (kg/m^2), n (%)			
Not obese (<30.0)	319 (59)	278 (87)	41 (13) [1]
Obese (≥30.0)	220 (41)	145 (66)	75 (34)
Maternal weight increase from prepregnancy to 16 years postpartum, n (%)			
<10 lb	96 (18)	77 (80)	19 (20) [1]
10 - <20 lb	82 (15)	70 (85)	12 (15)
20 - <30 lb	81 (15)	71 (88)	10 (12)
≥30 lb	280 (52)	205 (73)	75 (27)

[1] Pearson chi-square test $p<0.05$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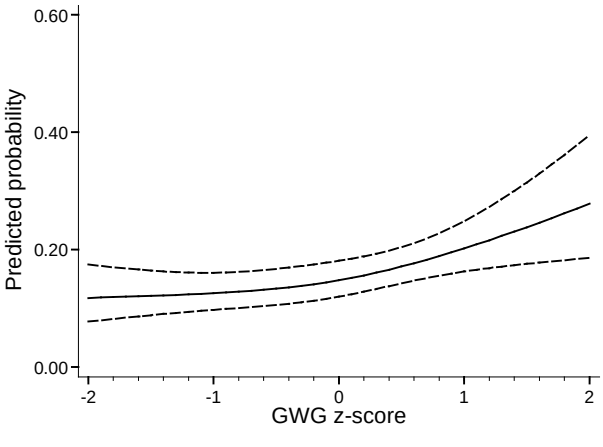
0.00
0.20
0.40
0.60
-2
-1
0
1
2
GWG z-score

A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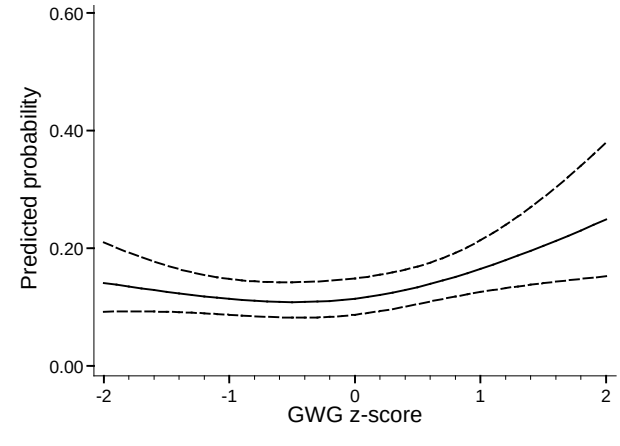
0.20
0.40
0.60
-2
-1
0
1
2
GWG z-score

D


Predicted probability
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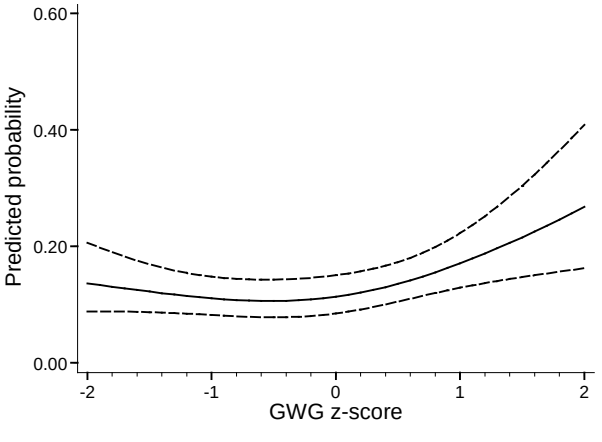
0.20
0.40
0.60
-2
-1
0
1
2
GWG z-score

B


Predicted probability
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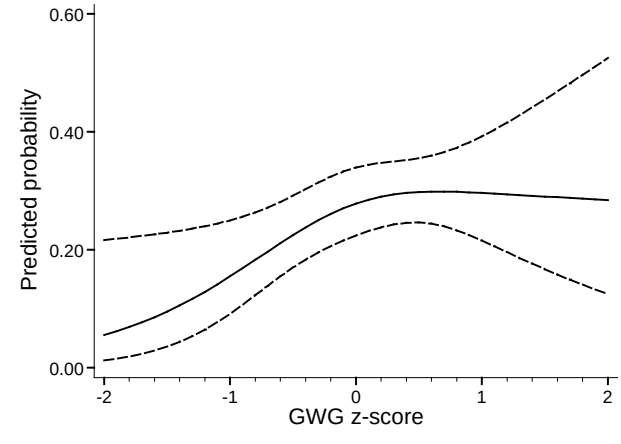
0.20
0.40
0.60
-2
-1
0
1
2
GWG z-score

E


Predicted probability
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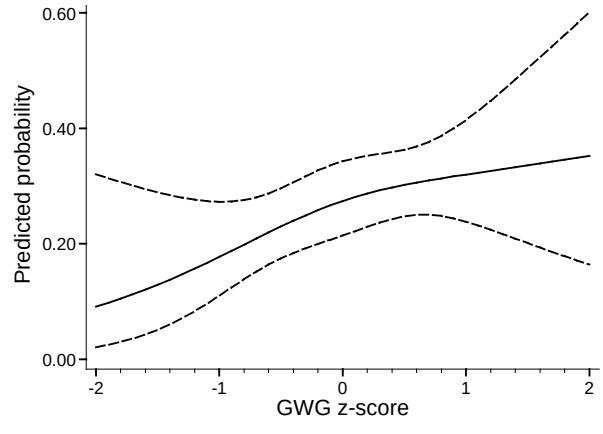
0.20
0.40
0.60
-2
-1
0
1
2
GWG z-score

C


Predicted probability
0.00
0.20
0.40
0.60
-2
-1
0
1
2
GWG z-score

F

Figure 7. Adjusted predicted probability of offspring obesity by GWG z-score using restricted cubic splines with knots at -1.60, -0.20, and 1.10

Panel A. Obesity at 10 years, overall (n=564).†

Panel B. Obesity at 10 years, among mothers who were lean (BMI <25 kg/m^2) before pregnancy (n=414).†

Panel C. Obesity at 10 years, among mothers who were overweight (BMI ≥25 kg/m^2) before pregnancy (n=150).†

Panel D. Obesity at 16 years, overall (n=477).†‡

Panel E. Obesity at 16 years, among mothers who were lean (BMI <25 kg/m^2) before pregnancy (n=347).††

Panel F. Obesity at 16 years, among mothers who were overweight (BMI ≥25 kg/m^2) before pregnancy (n=130).†‡

†Adjusted for smoking in the first trimester (none; <0.5 packs/day; 0.5 to <1 packs/day; >1 packs/day), and whether the child had tried alcohol at 10 years (yes; no).

‡Additionally adjusted for whether the child had tried alcohol at 16 years (yes; no).

Table 19. Association between gestational weight gain z-score and risk of offspring obesity at 10 and 16 years, overall and stratified by maternal prepregnancy overweight

	Obesity at 10 years		Obesity at 16 years	
GWG Z-score	Unadjusted RR (95% CI)	Adjusted RR † (95% CI)	Unadjusted RR (95% CI)	Adjusted RR †‡ (95% CI)
Overall				
-2.0	0.76 (0.48, 1.21)	0.79 (0.48, 1.30)	0.89 (0.58, 1.38)	0.77 (0.48, 1.22)
-1.5	0.80 (0.59, 1.10)	0.82 (0.58, 1.15)	0.89 (0.67, 1.20)	0.80 (0.58, 1.09)
-1.0	0.85 (0.71, 1.02)	0.85 (0.71, 1.04)	0.90 (0.76, 1.06)	0.83 (0.69, 1.00)
-0.5	0.91 (0.85, 0.99)	0.91 (0.83, 0.99)	0.93 (0.86, 1.00)	0.89 (0.82, 0.97)
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.5	1.12 (1.01, 1.25)	1.14 (1.01, 1.29)	1.13 (1.01, 1.26)	1.19 (1.05, 1.34)
1.0	1.27 (0.99, 1.63)	1.33 (1.00, 1.76)	1.31 (1.02, 1.68)	1.45 (1.10, 1.90)
1.5	1.44 (0.97, 2.15)	1.55 (0.98, 2.44)	1.52 (1.02, 2.28)	1.78 (1.15, 2.76)
Lean (prepregnancy BMI <25 kg/m^2)				
-2.0	1.22 (0.73, 2.05)	1.28 (0.73, 2.23)	1.39 (0.85, 2.27)	1.23 (0.71, 2.14)
-1.5	1.09 (0.77, 1.55)	1.12 (0.77, 1.63)	1.18 (0.85, 1.65)	1.08 (0.75, 1.57)
-1.0	0.99 (0.81, 1.21)	1.00 (0.81, 1.23)	1.03 (0.85, 1.24)	0.97 (0.79, 1.20)
-0.5	0.95 (0.87, 1.04)	0.94 (0.86, 1.04)	0.95 (0.87, 1.04)	0.93 (0.84, 1.02)
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.5	1.17 (1.02, 1.34)	1.19 (1.04, 1.37)	1.19 (1.04, 1.37)	1.22 (1.06, 1.41)
1.0	1.46 (1.06, 2.00)	1.52 (1.11, 2.10)	1.53 (1.12, 2.10)	1.60 (1.15, 2.24)
1.5	1.83 (1.10, 3.05)	1.98 (1.18, 3.30)	2.00 (1.20, 3.33)	2.13 (1.25, 3.65)
Overweight (prepregnancy BMI ≥25 kg/m^2)				
-2.0	0.37 (0.12, 1.12)	0.15 (0.03, 0.77)	0.50 (0.19, 1.29)	0.27 (0.05, 1.43)
-1.5	0.50 (0.24, 1.06)	0.27 (0.09, 0.81)	0.62 (0.33, 1.17)	0.39 (0.13, 1.21)
-1.0	0.67 (0.45, 1.02)	0.47 (0.26, 0.87)	0.77 (0.54, 1.09)	0.57 (0.31, 1.05)
-0.5	0.86 (0.73, 1.01)	0.75 (0.60, 0.94)	0.91 (0.79, 1.05)	0.79 (0.64, 0.98)
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.5	1.05 (0.87, 1.26)	1.11 (0.89, 1.38)	1.02 (0.84, 1.22)	1.14 (0.92, 1.40)
1.0	1.03 (0.67, 1.60)	1.10 (0.66, 1.84)	0.99 (0.63, 1.53)	1.23 (0.73, 2.06)
1.5	1.00 (0.49, 2.04)	1.07 (0.47, 2.47)	0.95 (0.46, 1.94)	1.30 (0.55, 3.08)

† Adjusted for prepregnancy BMI, smoking in the first trimester (none; <0.5 packs/day; 0.5 to <1 packs/day; >1 packs/day), and whether the child had tried alcohol at 10 years (yes; no)

‡ Additionally adjusted for whether the child had tried alcohol at 16 years (yes; no)

7.0 SYNTHESIS

7.1 OVERVIEW OF RESEARCH FINDINGS

This dissertation used data from a pregnancy cohort of low-income women to study the relationship between GWG and child growth and obesity risk across the three critical growth periods of childhood that are thought to be predictive of obesity in later life. We found that women who gained more weight had children who were persistently heavier and were more likely to be obese in early childhood and adolescence. Lower GWG was associated with lighter weights at birth, and faster infant growth, but not later obesity. However, rapid infant weight gain was associated with adolescent obesity at 10 and 16 years, suggesting a separate, unique path to obesity. Here we outline the findings presented in this dissertation.

1.) Determine the association between GWG and longitudinal growth over the first 36 months, as well as the risk of rapid infant weight gain from birth to 18 months.

Prepregnancy BMI and gestational age-adjusted measures of GWG were used to assess the longitudinal association between GWG and infant weight gain. We studied infant weight-for-age and body mass index-for-age z-scores based on the 2006 WHO growth standards for children <24 months and the 2000 CDC growth reference for children ≥24 months, in accordance with the current recommendations. GWG in excess of the 2009 IOM recommendations was associated with higher infant weight at birth, slower growth from birth to

36 months, and higher weights at 36 months as compared with gain that met the guidelines, after adjustment for confounders, including prepregnancy BMI, first trimester alcohol use, and aspects of the child's diet. Our findings were consistent with a cross-sectional analysis of GWG and changes in infant WHO-based WAZ and BMIZ over shorter growth periods, but were in the opposite direction of findings which had used CDC-based measures of child growth. The WHO growth standard sets a lower standard of weight gain from approximately 8 to 30 months than the CDC reference, perhaps explaining the inconsistent growth curves reported in our study using WHO-based child growth and a previous longitudinal study of GWG and CDC-based child growth. Our results may also differ from previous findings since we studied a cohort of women who tended to use substances in pregnancy and tended to be leaner than others.

We also found that inadequate GWG was associated with lower weights at birth as compared to children of women who gained adequate weight, but there were no differences in child weight thereafter. Inadequate GWG was associated with a dichotomous measure of faster infant weight gain from birth to 18 months as compared to adequate, suggesting that these children may have demonstrated catch-up growth. We reported an association on GWG and rapid infant weight gain as defined according to the WHO growth standard, unlike other studies based on CDC or UK-based definitions, each of which reported null findings.

2.) Determine the association between total and pattern of GWG and the risk of childhood obesity at 36 months.

We studied total as well as pattern of excessive GWG by using four mutually exclusive categories based on early (<26 weeks) and late (≥26 weeks) gestation to study the relationship with the risk of childhood obesity at 36 months. We defined childhood obesity using age- and sex-adjusted BMI z-scores according to the 2000 CDC growth reference. Nearly half of the

women with total excessive GWG also had excessive gain during both early and late pregnancy, while the remainder had excessive gain in only one period. Compared with total non-excessive GWG, excessive total GWG was associated with a greater risk for childhood obesity at 36 months, after confounder adjustment. Similarly, women with excessive GWG in both early and late pregnancy were more likely to have obese children as compared with women with non-excess GWG in both periods. There was an increase in the risk of obesity among the children of women who gained excess weight in early pregnancy and non-excess weight in late pregnancy, but the relationship was attenuated after confounder adjustment. Our results differed from several studies which had suggested early, rather than late gain, may more greatly influence offspring obesity risk, though our measure of early gain is later than other studies and thus may capture a different biological state.

3.) Determine the association between total GWG and the risk of offspring obesity at 10 and 16 years.

We studied GWG z-scores, a measure of GWG that is based on prepregnancy BMI and is uncorrelated with gestational length, in relation to the risk for obesity among 10 and 16 year-old offspring. We found that higher GWG was related to a greater risk for adolescent obesity at 10 and 16 years and that the relationship was not stronger after puberty. The relationship between GWG and child obesity varied by maternal prepregnancy overweight, yet among both lean and overweight women the results suggested a positive relationship. Among lean women, there was no relationship between GWG and obesity risk at 10 or 16 years as GWG z-scores increased from -2 SD to 0 SD, but for z-scores increasing at and above 0 SD to +2 SD, there was an increase in the risk curve for adolescent obesity at 10 and 16 years. These estimates remained after adjustment for prenatal and postnatal confounders. As GWG increased from -2 SD to 0 SD

among overweight women, there was an increase in the risk curve for offspring obesity at 10 years and not 16 years; and with an increase in GWG from 0 to +2 SD the risk curve was flat indicating no further increase in the risk for obesity. Our findings suggest that lean women should avoid excess gain and that the current 2009 IOM recommendations may be too high for overweight women, and that lowered gain may prevent later obesity, similar to two previous studies.

7.2 STRENGTHS AND LIMITATIONS OF THIS RESEARCH

Our findings should be considered in the context of a number of limitations. First and foremost, our observational study data cannot determine causality, so we may be describing a relationship due to shared factors. We did not have measures of offspring adiposity, so it is unclear whether the observed changes reflect fat or fat-free mass. Similarly, we lacked data across critical periods of development, so the variation in developmental stages in our sample is unknown. However, we purposely selected ages near to critical periods when confounding by growth spurt would be unlikely. We had pubertal development data at age 16 years, and 89% of the sample reported advanced or post-puberty. Our findings may be affected by unmeasured confounding, though we were able to consider aspects of the child's diet, and adolescent factors such as mental health and substance use. Further, our results may not be generalizable to the general obstetric population; this cohort was enrolled in the early 1980's and had a higher prevalence of substance use in the first trimester. Though, even when we excluded heavy substance users or applied

inverse probability sample weights, our results were not meaningfully different. Maternal pregnancy weight and GWG were self-reported. However, women were interviewed within 48 hours of delivery, minimizing the likelihood of recall bias. Our measure of early GWG is likely too late to capture the biological state of early pregnancy that we are interested in. We did not detect effect modification by prepregnancy BMI for obesity at 36 months, though our power may have been limited. Indeed, when we tested for effect modification for obesity at 10 and 16 years, when obesity was more common, we did detect an interaction.

Major strengths of our study should be noted. We conducted a longitudinal analysis allowing us to examine growth over time for the first 36 months, so we were able to study a developmental pathway to obesity. Child weight was measured by trained study personnel, making it more likely that these measures were reproducible and valid. We had access to a number of confounders and were able to consider factors relevant to pre- and post-natal life. We studied a sample of low-income black and white American women and their children, which importantly adds to the vast literature on predominantly white, middle-income, and European samples. In addition, we contributed to the limited literature on GWG pattern. Finally, substance use is common in pregnancy and we were able to adjust for prenatal substance use by using well-measured substance use variables.

7.3 PUBLIC HEALTH SIGNIFICANCE

This dissertation makes a significant contribution to public health. GWG is a modifiable and early-life risk factor for pediatric obesity. If our findings are supported by randomized clinical trials, avoiding excess GWG may be an important means of preventing child obesity. Since these findings suggest an association in infancy, early childhood, and adolescence, it suggests that the effect of high GWG follows children over time, making it more likely that affected offspring will be obese as adults. Obese and overweight daughters are more likely to gain excess weight, which has negative health consequences for their own long-term health, as well as negative health consequences for the long-term health of their infant.

We identified a pathway to obesity where heavier infants exhibited slower weight gain; pediatricians may use our finding as justification to monitor slowed weight gain, in addition to rapid infant weight gain. Finally, our findings suggest that the IOM GWG recommendations for overweight and obese women may need to be lowered to impact obesity risk.

7.4 DIRECTIONS FOR FUTURE RESEARCH

Randomized clinical trials are needed to determine causality. Randomized nutritional interventions have shown that GWG is modifiable and that dietary interventions may be more effective than interventions focused on physical activity alone. However, no trials have data to determine whether interventions are effective in preventing child obesity development or the associated comorbidities we are ultimately interested in. Longitudinal adiposity data will help to

determine the developmental path to obesity, as well as incident obesity at one or several critical periods. Finally, randomized trials may be most effective if they target a woman's lifestyle rather than counseling women on weight gain alone. Trials with a comprehensive approach may be best-suited to modify GWG and impact a woman and her child's long-term health.

Additional studies should also focus on aspects of maternal weight to determine whether an association is driven by increases in maternal fat or fat-free mass. Repeated measures of maternal body composition and body fat distribution will help to determine whether particular aspects of maternal fat affect child obesity. In addition, future studies should capture early pregnancy weight gain to determine periods of potential intervention and to determine specific weight gain advice to women over time.

There is limited data on severe obesity and gestational weight loss, as these groups have been historically excluded from studies. The current GWG guidelines are already contentious as some experts believe that obese women should gain less weight, no weight, or perhaps even lose weight, and rely on reserves to fuel maternal and fetal tissue growth. However, this remains a major concern as restricted gain may negatively influence child cognition. Thus, research in this area is greatly needed.

These findings will need to be weighed against a number of other maternal and child risks associated with high and low gain, the results of which may influence future revisions of the GWG guidelines. Racially-diverse US samples should be studied to determine whether and how to prevent excessive GWG and child obesity in American women and children.

APPENDIX A

SUPPLEMENTARY TABLE FOR MANUSCRIPT 1

Table 20. Characteristics by rapid infant weight gain from 0 to 18 months

	Rapid infant weight gain from 0 to 18 months (N=609)	
	Not Rapid	Rapid
Prepregnancy body mass index (kg/m^2), %		
Underweight (<18.5)	55	45
Normal weight (18.5-24.9)	57	43
Overweight (25.9-29.9)	55	45
Obese (≥30.0)	60	40
Maternal race/ethnicity, %		
White	60	40
Black	53	47
Income level ($/month), %		
<400	57	43
≥400	57	43
Parity		
Nulliparous	55	45
Multiparous	58	42
Pattern of prenatal smoking, % *		
Never used in pregnancy	65	35
First trimester use only	51	49
Second and/or third trimester use	51	49
Pattern of prenatal alcohol use, %		
Never used in pregnancy	52	48
First trimester use only	56	44
Second and/or third trimester use	62	38

Table 20 continued.

Pattern of prenatal marijuana use, %		
Never used in pregnancy	59	41
First trimester use only	57	43
Second and/or third trimester use	48	52
Gestational age at delivery (weeks), (%) *		
<37 weeks	6	94
≥37 weeks	61	39
Birth weight for gestational age z-score, % *		
Small for age (<10th percentile)	26	74
Appropriate for age (10th to 90th percentile)	62	38
Large for age (>90th percentile)	91	9
Infant sex, %		
Female	56	44
Male	58	42
Ever breastfed infant, % *		
Yes	65	35
No	55	45

* Pearson chi-square test $p<0.05$

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APPENDIX B

SUPPLEMENTARY TABLE FOR MANUSCRIPT 2

Table 21. Frequency of gestational weight gain (GWG) pattern by characteristics of the sample (n=609)

N (%)	Early non-excessive; Late non-excessive	Early non-excessive; Late excessive	Early excessive; Late non-excessive	Early excessive; Late excessive
Prepregnancy body mass index (kg/m^2), n (%) [1]				
Underweight (<18.5)	25 (33)	13 (17)	28 (37)	9 (12)
Normal weight (18.5-24.9)	104 (29)	109 (30)	96 (26)	56 (15)
Overweight (25.9-29.9)	13 (12)	26 (24)	33 (30)	37 (34)
Obese (≥30.0)	6 (10)	18 (30)	13 (22)	23 (38)
Maternal race/ethnicity, n (%)				
White	78 (27)	81 (28)	77 (26)	58 (20)
Black	70 (22)	85 (27)	93 (30)	67 (21)
Maternal education (years), n (%) [1]				
<12	42 (25)	59 (36)	41 (25)	23 (14)
=12	92 (25)	85 (23)	106 (29)	81 (22)
≥12	14 (18)	22 (28)	23 (29)	21 (26)
Income level ($/month), n (%)				
<400	87 (24)	103 (28)	105 (29)	67 (19)
≥400	58 (26)	56 (25)	57 (25)	54 (24)
Prenatal smoking, n (%)				
None	58 (21)	82 (29)	76 (27)	67 (24)
<0.5 packs/day	35 (27)	31 (24)	34 (26)	31 (24)
0.5 to <1 packs/day	34 (31)	31 (28)	32 (29)	12 (11)
≥1 packs/day	21 (24)	22 (26)	28 (33)	15 (17)

Table 21 continued.

Prenatal alcohol use, n (%)				
None	47 (22)	56 (26)	57 (27)	52 (25)
>0 to <1.5 drinks/week	35 (28)	41 (33)	28 (22)	22 (18)
1.5 drink/week to <1 drinks/day	34 (22)	45 (29)	43 (28)	32 (21)
≥1 drinks/day	32 (27)	24 (21)	42 (36)	19 (16)
Prenatal marijuana use, n (%)				
None	92 (26)	90 (25)	94 (27)	79 (22)
>0 to <0.5 joint/day	29 (23)	46 (36)	33 (26)	21 (16)
0.5 to <1 joints/day	10 (23)	9 (20)	14 (32)	11 (25)
≥1 joints/day	17 (21)	21 (26)	29 (36)	14 (17)
Gestational age at delivery, n (%)				
<37 weeks	17 (30)	16 (29)	18 (32)	5 (9)
≥37 weeks	131 (24)	150 (27)	152 (28)	120 (22)
Birth weight for gestational age z-score, n (%) *				
Small for age (<10th percentile)	33 (33)	23 (23)	27 (27)	16 (16)
Appropriate for age (10th to 90th percentile)	112 (23)	136 (28)	138 (28)	102 (21)
Large for age (>90th percentile)	3 (14)	7 (32)	5 (23)	7 (32)
Infant sex, n (%)				
Female	77 (25)	82 (27)	82 (27)	62 (21)
Male	71 (23)	84 (28)	88 (29)	63 (21)
Ever breastfed infant, n (%)				
Yes	26 (21)	30 (24)	39 (31)	30 (24)
No	108 (25)	123 (28)	118 (27)	87 (20)

[1] Pearson chi-square test $p<0.05$

[*] Reference for birth weight for gestational age z-score (164)

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