MATERNAL OBESITY, GESTATIONAL WEIGHT GAIN, AND CHILD COGNITION, BEHAVIOR, AND ACADEMIC ACHIEVEMENT

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Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2015

UNIVERSITY OF PITTSBURGH

THE GRADUATE SCHOOL OF PUBLIC HEALTH

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ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is the most prevalent developmental disability in the United States and can compromise a child's behavioral and intellectual development. We used a longitudinal birth cohort from Pittsburgh, PA to study maternal pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) in relation to 1) offspring intelligence and executive function at age ten 2) offspring behavior and ADHD symptoms at age ten 3) offspring academic achievement at ages six, ten, and fourteen. Mother-child pairs (n=763) from the Maternal Health Practices and Child Development pregnancy cohort were followed from <21 weeks gestation to 14 years postpartum. Self-reported total GWG was classified using gestational-age standardized z-score charts and BMI was categorized in accordance with the World Health Organization (WHO) criteria. Validated assessment tools were used to measure child intelligence, executive function, and behaviors consistent with attention-deficit hyperactivity disorder (ADHD) as well as academic achievement. Compared with children of normal weight mothers, offspring of obese mothers had 3.2 lower IQ points (95% CI: -5.6, -0.8), were 12.7 seconds slower on the executive function scale (95% CI: 2.8, 22.7), and had increased problem behaviors consistent with ADHD including withdrawn or somatic complaints (adj β: 4.9 points, 95% CI: 1.7, 8.1), delinquent or aggressive behaviors (adj β: 4.2 points, 95% CI: 1.1, 7.3), and attention problems (adj β: 3.5 points, 95% CI: 1.2, 5.8) after adjusting for confounders. Academic achievement was also lower among children of obese mothers, compared with children of normal weight mothers. In generalized estimating equation models, high GWG was significantly associated with a 4 point decrease in reading (adjβ: -3.75, 95% CI: -7.1, -0.4) and spelling scores (adjβ: -3.90, 95% CI: -7.8, -0.2) at ages 6, 10, and 14. There was a non-significant trend towards lower offspring domain-specific cognition with high maternal GWG. This dissertation is important to public health because pre-pregnancy BMI and GWG are potentially modifiable factors and a reduction in obesity and excessive GWG could alleviate, although not eliminate, the burden of ADHD and related impairments in the population.

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PREFACE

I would like to acknowledge the many people that made this dissertation possible. I would like to thank my mentor and dissertation advisor, Lisa Bodnar, for the dedication she has shown to my education and completion of this degree. Lisa pushed me to constantly improve and spent countless hours critically evaluating my work, which has advanced my writing, critical thinking, and analytical skills. She has served as an exceptional role model and has imparted skills necessary for success. I would also like to thank my committee members who were each critically important to the completion of this degree. Their continued commitment to my growth and progress through guidance and shared knowledge made this possible.

I am also thankful for my friends and family for their support in my pursuit of this degree. To my best friends and roommates, Elizabeth and Dana: you have truly made this the best 4 years of my life. Your support, friendship, and comic relief made this an unforgettable experience that I will cherish dearly. To my love, Harry: you have constantly picked me up when I've been down and renewed my self-confidence; your patience, ability to make me laugh, and reminder to enjoy and balance life was necessary to my success. Most importantly to my parents and my sister: the high expectations you've held throughout my life have instilled a sense of passion, work ethic, and confidence that equipped me with the skills and drive necessary to pursue this degree. Above all, your unwavering love and support was critically important to my

completion of this degree. I would not have been able to do this without such a strong support system and for that I am truly thankful.

1.0 INTRODUCTION

1.1 BACKGROUND

In 2006-2008, developmental disabilities affected nearly 1 in 6 children aged 3 to 17 years in the United States(1), a 17% increase since 1998. The most prevalent developmental disability is attention deficit hyperactivity disorder (ADHD), a neurological disorder, reported at rates from 7% to 9% in 2006-2008(1). ADHD is caused by disrupted brain development and is diagnosed when a child presents at least 6 symptoms of inattention and hyperactivity/impulsivity in more than one setting (i.e. home, school, etc.)(2). Impaired executive function and intelligence often accompany the diagnostic criteria, though this is somewhat controversial(3-5). ADHD can compromise a child's behavioral and intellectual development, potentially limiting their social success and ability to achieve academically. There is no cure for ADHD, and treatments vary in effectiveness(6). Medications are costly and may have unfavorable side effects, while behavioral therapy and social skills training are not always fully effective without the addition of pharmacotherapy(7). The presence of ADHD results in a major mental and financial burden on the family, society, and the health care system. Given the high prevalence, the cost of treatment, the lifelong burden, and the lack of effectiveness of existing treatments, prevention of ADHD is a public health priority.

Maternal pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) are potentially modifiable factors that may be linked with ADHD through symptoms such as behavior problems, cognitive impairment, and academic underachievement(8). Intrauterine insults such as excessive inflammation, high circulating leptin levels, malnutrition, and ketonuria may accompany extremes of maternal weight and weight gain (9), and can permanently alter fetal cognitive function (10-14). A small body of evidence suggests that low and high maternal BMI are associated with lower offspring cognitive performance and increased behavior problems

in childhood and adulthood(15-18), but less research has explored GWG. Additionally, few studies have considered important confounders such as socioeconomic status and the amount of cognitive stimulation in the home environment (e.g. number of books in home, time spent with children, etc.). Understanding the impact of GWG and pre-pregnancy BMI on long-term cognitive, behavioral, and academic impairments may be an important step towards alleviating the familial and societal burden of ADHD.

1.2 SPECIFIC AIMS

The goal of the proposed project is to understand the independent association between gestational weight gain, pre-pregnancy BMI and areas of cognition, behavior, and academic achievement that are typically impaired in children with ADHD. To achieve this goal, we will use prenatal and postpartum data from the Maternal Health Practices and Child Development study (MHPCD) (n=829), a longitudinal birth cohort from Pittsburgh, PA, followed for 14 years. Our specific aims are to:

1. **Specific Aim 1:** Examine the association between maternal gestational weight gain, pre-pregnancy body mass index and offspring **intelligence and executive function** at 10 years of age. Determine whether pre-pregnancy body mass index modifies the association between gestational weight gain and child cognition.

2. **Specific Aim 2:** Examine the association between maternal gestational weight gain, pre-pregnancy body mass index and offspring **attention-deficit hyperactivity disorder (ADHD) symptoms and behavior** at 10 years of age. Determine whether pre-pregnancy body mass index modifies the association between gestational weight gain and child behavior.

3. **Specific Aim 3:** Examine the association between maternal gestational weight gain, pre-pregnancy body mass index and offspring **academic achievement** at 6, 10, and 14 years of

age. Determine whether pre-pregnancy body mass index modifies the association between gestational weight gain and child academic achievement.

Overall Hypotheses:

We hypothesize that excessive/inadequate GWG and high/low pre-pregnancy BMI will be associated with lower scores on the intelligence, executive function, and academic achievement assessments, and an increased number of ADHD symptoms and problem behaviors. We hypothesize that there will be significant effect modification by BMI: maternal overweight in the presence of excessive GWG will have a greater than additive effect on low intelligence scores, executive function, academic achievement assessments, and ADHD symptoms.

2.0 LITERATURE REVIEW

2.1 INTRODUCTION

2.1.1 Attention-deficit hyperactivity disorder is a public health problem

The prevalence of ADHD has reached epidemic proportions in the United States. ADHD is the most common developmental disability among children, affecting 7% to 9% of 5-17 year olds (19). It continues to affect children into adolescence (20) and oftentimes adulthood (21, 22). ADHD is a neurodevelopmental disability frequently associated with impairments in executive function, attention, intelligence, memory, reasoning, problem solving, and inhibition(19, 23, 24). The gold-standard for ADHD diagnosis includes a psychiatric, psychological, and neurologic evaluation consisting of in-person evaluations and observations by a health-professional (2). ADHD is diagnosed if a child presents at least 6 symptoms of inattention and hyperactivity/impulsivity listed in the DSM-V in more than one setting (e.g. school, home, etc.) before the age of 12(2). The previous version of the DSM (IV) had similar criteria for ADHD diagnosis but listed diagnosis as before the age of 7.

When diagnosis is not feasible due to the demanding protocol, symptoms of ADHD, including somatic complaints, anxious/depressed feelings, and deviant or aggressive behaviors, are often measured by parent and/or teacher assessments(25). These symptoms, though not required for diagnosis, are beyond what you would expect from an average child or adolescent; they limit a child's ability to learn and behave, resulting in lower academic achievement and fewer social relationships, often resulting in less future job and relationship success(26). Lower intelligence and executive function often co-occur with ADHD, but are not required for diagnosis(3, 27). Impairments to attention, hyperactivity/impulsivity, executive function, and

intelligence are commonly identified by teachers in an academic setting because children tend to disrupt class, have difficulty following directions, and become easily distracted, resulting in impaired academic achievement (19).

ADHD poses a significant lifelong burden on the individual and family. Compared with children who do not have ADHD, children with ADHD are more likely to have hospital inpatient, outpatient, and emergency department visits (28) (29). Children with ADHD receive less secondary education, are more likely to abuse substances, and have a significantly higher rate of arrest, conviction, and incarceration (30). An average ADHD child costs the health care system $1,500 versus $500 a year for an age-matched control(29). Annually, the United States spends in excess of $42 billion dollars on medical treatment as well as individual and parental lost wages (31) related to ADHD.

Prevention of ADHD is a public health priority. There is no cure for ADHD. Pharmacotherapy, behavioral therapy, and social skills training are treatment options available for children with ADHD. Pharmaceutical stimulants— methylphenidate and amphetamine – are the most effective treatment method, but may adversely affect sleep, mood, and appetite (32). Behavioral therapy provides valuable skills without any adverse side effects, but skills learned are not easily translated from one setting to the next (e.g. classroom to social settings) (33). A combination of pharmaceutical stimulants and behavioral therapy is most effective(34), but must be continued to have a lasting effect. Treatment by either means is expensive for families and the health care system (31, 34). Given the high prevalence, the cost of treatment, the lifelong burden, and the lack of effectiveness, prevention of ADHD is a public health priority.

2.1.2 Reducing extremes of maternal pre-pregnancy body mass index and gestational weight gain may be important in ADHD prevention

Extremes of maternal body mass index are common and associated with adverse child health outcomes. Body mass index (BMI) is a universal assessment method used to indicate body fatness and can inform a woman's nutritional status upon entering pregnancy(14, 35). Offspring of obese (BMI≥30) mothers are at an increased risk of congenital anomalies, preterm birth, fetal overgrowth, and infant mortality(36). Offspring of underweight (BMI<18.5) mothers

are at an increased risk of preterm birth, perinatal mortality, and birth defects (37). Recent data suggests that maternal underweight and obesity are both associated with lower intelligence in toddlers and adolescents (17, 18, 38), and increased inattention and hyperactivity/impulsivity symptoms in adolescents (15, 16, 39). **This is of concern because maternal overweight (BMI ≥25) and obesity (BMI≥30) affect nearly two-thirds of women of childbearing age (40).** Maternal underweight (BMI<18.5) is less common but still affects 2.6% of women of childbearing age (37). With nearly half of pregnancies unplanned, many women do not have the opportunity to optimize their pre-pregnancy weight (41).

Research has consistently shown that pre-pregnancy BMI modifies the effect of gestational weight gain (GWG) on adverse maternal and child outcomes(9). While for most outcomes, pre-pregnancy BMI has a stronger association than GWG(9), pre-pregnancy BMI cannot be altered once a woman is pregnant. GWG, on the other hand, is potentially modifiable, and research suggests that gaining the optimal amount of weight during pregnancy may attenuate some of the adverse maternal and infant risks associated with extremes of pre-pregnancy BMI(42).

The 2009 Institute of Medicine Committee stressed the importance of understanding how GWG affects child cognition. GWG reflects maternal physiologic changes that are necessary to support fetal growth and prepare the body for breastfeeding (9, 43). About 35% of GWG is comprised of products of conception including the placenta, fetus, and amniotic fluid (9, 44). The remainder of GWG consists of maternal fat and fat free mass (water and protein accumulation in maternal tissues such as the uterus and breasts) (44, 45). While GWG is necessary, too much or too little weight gain is associated with poor outcomes, but the amount needed to optimize the health of both mother and baby has been difficult to determine (46, 47). Excessive GWG is thought to increase the risk of postpartum weight retention, emergency caesarean delivery, large for gestational age birth (LGA), and offspring obesity, while inadequate GWG is associated with small for gestational age birth (SGA) and preterm delivery (48).

In 2009, the Institute of Medicine (IOM) published BMI-specific GWG recommendations, and for the first time attempted to balance risks of high and low GWG for both mother and child (9). Only 30% of women in the U.S. gain within the recommended ranges (49). Approximately half of overweight and obese women gain above the recommended weight gain guidelines during pregnancy, while 10% of overweight and 24% of obese women gain

below the recommended weight gain ranges and even lose weight. The IOM committee was interested in whether GWG, particularly low GWG, was associated with impaired offspring cognitive function. Weight loss is uncommon but increases with increasing BMI (9, 49, 50). The IOM report stated, "weight loss or failure to gain during pregnancy may in turn have subsequent consequences for the intellectual development of the child." (9) However, at the time of IOM review, no studies directly addressed the link between GWG and child neurocognitive development, precluding cognition from being included as an outcome in the assessment of optimal GWG (9). **The committee stressed the importance of directly examining GWG and offspring cognition.** Our project will explore the association between total GWG and cognitive dysfunction consistent with ADHD impairments and the potential joint association with BMI.

2.1.3 Biologically plausible links between extremes of maternal prepregnancy body mass index and gestational weight gain and offspring cognitive dysfunction

The mechanisms by which maternal weight and weight gain impact offspring cognition and behavior remain unclear(9); however, the mechanisms proposed are rooted in biologic plausibility. Rodent and nonhuman primate models provide evidence of implicated pathways. The current evidence suggests maternal obesity and a high fat diet impair offspring cognition and behavior through inflammation (pro-inflammatory cytokines) and hormones (leptin and insulin)(51, 52). However, a majority of rodent studies use a high fat diet to induce obesity, limiting the ability to differentiate the effect of a high fat diet (i.e. GWG) versus obesity. Maternal weight loss potentially impairs offspring cognition and behavior through malnutrition or ketosis. The negative impact of ketosis on fetal brain development is often inferred from human studies in diabetic women. However, diabetic women experience a number of metabolic abnormalities beyond ketosis. These mechanisms are discussed in detail below (**Figure 1**).

Inflammation. Obesity is a state of chronic inflammation associated with an increased blood concentration of circulating of pro-inflammatory cytokines (51, 53) (54). Cytokines can cause over- and under-activation of the following neurodevelopmental processes(55, 56): neuron proliferation and differentiation (57), neurotropic factors(15), apoptosis(58), neurogenesis(59), neurotransmitter levels(60), myelination, regulation of neurogenesis, axon growth, dendrite

proliferation, and synapse formation (57). Studies in nonhuman primates found increased circulating cytokines in the hypothalamus and hippocampus, where behavioral regulation systems (i.e. serotonergic and dopaminergic systems(61))(62) are located, in offspring of mothers consuming a high fat diet. Human studies confirmed this finding by reporting higher levels of circulating cytokines in the brains of children with ADHD compared to those without ADHD(63, 64). However, this study did not directly link maternal obesity to the increase in circulating cytokine levels.

Hormones. Obese women have higher levels of circulating glucose, which the body controls by increasing insulin production, a hormone that aids in glucose metabolism. Glucose can pass through the placental barrier, but insulin cannot[50]. Therefore, the fetus increases insulin production to regulate the increased transport of glucose [64]. The resulting increase in circulating insulin is hypothesized to induce cellular differentiation and alter signaling mechanisms in the hypothalamus, yet the exact mechanism between insulin and altered neural circuitry in the fetal brain remains unknown (65).

Leptin levels are proportional to adipose tissue and are therefore present in higher amounts in obese women. During pregnancy, the fetus and placenta also produce leptin, contributing to a higher total circulating concentration(57). While the traditional role of leptin is to inform feeding behavior and regulate energy expenditure (57, 66), recent evidence points to the importance of leptin in developing neural circuitry in the hypothalamus of the fetus(51) (67). A narrow range of leptin is required for brain development and excessive or inadequate levels of circulating leptin can impair neural circuits, as seen in rodent models(57). However, the exact mechanism of these pathways remains unclear(57, 65).

Ketosis. Maternal metabolism of carbohydrates and lipids is altered during pregnancy to allow a continuous supply of nutrients to the growing fetus, resulting in a state of “accelerated starvation” in the mother (9, 68). Prolonged periods of maternal fasting, such as between dinner and breakfast, lead to “accelerated starvation” and can create a ketogenic state(69)—the process of ketone production from the breakdown of lipids in the absence of glucose (70). As seen in studies on diabetic mothers(68, 71), excess use of ketones by the fetus for fuel can negatively affect fetal neurodevelopment by restraining growth of compounds necessary for cellular replication and tissue growth (70). Some studies reported a positive association between biomarkers of fasting in the blood (ketonemia) or urine (ketonuria) and child cognitive

development (70, 72-74), while some studies reported no association (12, 75). However, caution should be taken when attributing biological mechanisms reported in diabetic women as evidence for all women, since diabetics experience a number of metabolic abnormalities that could be implicated in fetal brain impairment. Additionally, no human studies have directly linked maternal ketosis due to weight loss with impaired offspring neurodevelopment.

Malnutrition. Weight loss during pregnancy is uncommon but increases with increasing BMI and can potentially result in malnourishment(9, 49, 50). Previous theories on malnutrition during pregnancy have suggested that fetal development, particularly of the brain, takes priority in receiving existing nutrient supplies at the expense of the mother's needs(76). However, non-human primate models suggest offspring of mothers with moderate nutrient reduction (30%) have impaired morphological brain development (76), although morphological changes were not linked to long-term impaired cognition or behavior. In contrast to the finding, a study in humans reported that offspring of mothers who were pregnant during the Dutch Famine (about 40% caloric reduction) had normal cognitive performance at 19-years old (77).

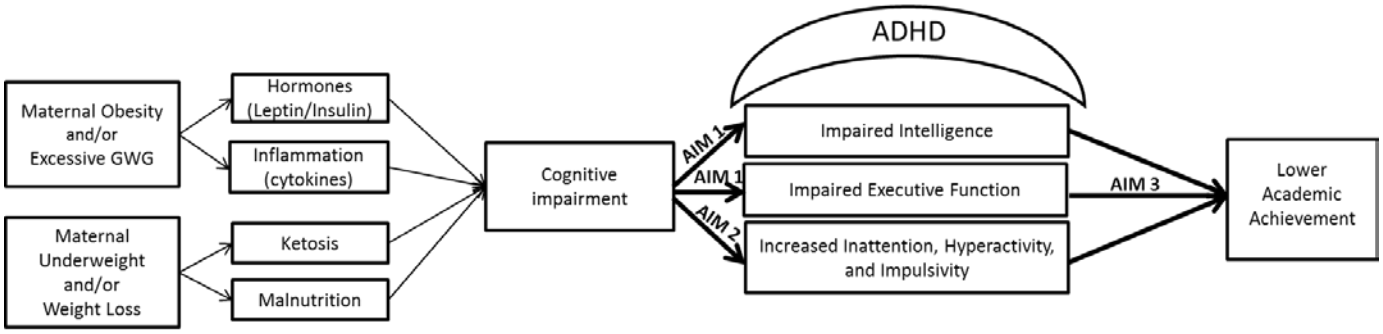

Figure 1: Proposed pathways of impaired offspring cognitive development and relation with academic achievement

Damage to brain subregions may result in cognitive dysfunction in three areas relevant to ADHD—intelligence, executive function, attention/hyperactivity/impulsivity- all of which may impede academic achievement(78). Recent brain-imaging studies in children with ADHD suggest a variety of brain subregions with impaired functionality or connectivity including the frontal cortex, parietal cortex, basal ganglia, cerebellum, hippocampus, and corpus callosum(79). Below, we discuss evidence linking maternal pre-pregnancy BMI and GWG to key ADHD symptoms (executive function; inattention, hyperactivity, impulsivity) as well as intelligence—a global measure of cognitive function—and academic achievement. Intelligence

and executive function are not universally considered to be components of ADHD; however, they form a complex relationship with ADHD and may provide further insight into general dysfunction children experience in everyday life such as academic underachievement.

2.2 REVIEW OF THE EVIDENCE

There are several methodological challenges to studying the relationship between maternal BMI, GWG, and child cognition. *First*, there is an inherent correlation between GWG and gestational age. Conventional measures of GWG—total GWG and rate of GWG—do not fully account for this correlation. This is a serious limitation when studying outcomes that are associated with prematurity, such as child brain development(80). *Second*, adjusting for factors on the causal pathway, such as gestational age or birthweight, can bias estimates(80) and obscure the total association between GWG and child cognition. *Third*, effect modification by BMI should be considered in studies assessing GWG and adverse outcomes. It has long been recognized that associations between GWG and adverse outcomes are modified by BMI. For example, low GWG is more strongly associated with small for gestational age among underweight women than heavier women(81). *Lastly*, parental cognition and the postnatal familial environment are important confounders, yet they are often not measured, leading to residual confounding. A lack of adjustment for these confounders may bias results away from the null. All of the literature reviewed below on the relationship between BMI or GWG and child cognitive measures is limited by at least one of these challenges, thereby limiting the inferences that can be drawn from current literature.

2.2.1 Intelligence

Intelligence (IQ) represents a general index of neuropsychological functioning, and is a valuable tool in research studies used to predict a child's academic potential(82) (27). *Intelligence* is not a cognitive process per se, but rather represents a general mental capability for a wide range of cognitive processes such as comprehension, vocabulary, and perceptual

organization. Measurement tools typically divide intelligence into *verbal IQ*—ability to analyze information and solve problems using acquired knowledge, and *performance IQ*—ability to think and solve problems independent from acquired knowledge(83). IQ tests involve the use of skills acquired with age; therefore, in infants or young children, general cognitive functioning tools can be used, although they may not be as predictive of adulthood intelligence compared with IQ assessments (84). Both cognitive functioning and intelligence tests aim to assess general intellectual functioning. In children with ADHD, intelligence ranges from low to high. Yet, low intelligence further inhibits a child's ability to learn, reason, conceptualize, and problem solve, skills important for achievement(85).

Evidence suggests an association exists between maternal BMI and offspring intelligence, although a number of studies only measured cognitive development in young children (Table 1). Cognitive development has been assessed in toddlers (ages 0-3) and pre-school children (ages 3-6) (86). Hinkle et al. (2012) examined data on 6,850 mothers and offspring from the Early Childhood Longitudinal Study Birth Cohort, a nationally representative cohort that oversampled select racial-ethnic groups. Cognitive functioning was assessed in 2–year-olds using the Bayley Scales of Infant Development (BSID), a commonly used and validated objective measure of cognitive development. This study reported a modest increased risk of cognitive scores < 40, representing mild cognitive delay, in 2 year old children of underweight (aRR: 1.36, 95% CI: 1.04, 1.8) and obese class 2+3 women (BMI≥35) (aRR: 1.38, 95% CI: 1.03-1.8) compared with children of normal weight mothers, adjusting for demographics, smoking, child sex, and poverty status (87). Two additional studies reported a modest negative association between maternal obesity and child cognitive performance on the BSID at ages 14 months and 2 years but not at 18 months (18, 35). Importantly, none of the aforementioned 3 studies(18, 35, 87) controlled for parental cognition or the postnatal home environment (e.g. number of books in home, time spent with children, etc.), so it is unclear whether the associations are due to maternal BMI or if mothers at unhealthy weights simply have lower intelligence or less enriching postnatal environments.

In pre-school aged children, two studies reported a small decrease in cognitive development scores using the Differential Abilities Scale (DAS) and British Abilities scale (BAS), nationally standardized assessment tools for the United States and the United Kingdom, respectively. In a homogenous cohort of low income African American women enrolled in a zinc

supplementation trial, Neggers et al. (2003), reported children of obese women (BMI>29) had IQ scores, on average, 4.7 points lower than children of normal weight women (aβ=-4.7, p=0.001) at the age of 5 years old. Bastemur et al. (2013) analyzed data on nearly 20,000 women from the Millennium Cohort, a nationally representative cohort in the United Kingdom and reported a significant inverse association between maternal BMI and cognitive development in 5 year olds measured by the BAS. Bliddal et al. (2014) reported a 0.3 point decrease in 5 year old offspring IQ score for every 1 kg/m^2 increase in maternal BMI in a cohort of 1,783 Danish mothers and children. This study also assessed the relation between paternal BMI and offspring IQ as a way to determine whether any associations with maternal BMI were actually due to social and environmental factors influencing child cognitive development. The estimated coefficient for paternal BMI was similar to mothers, but not significant (aβ= -0.3, p-value= 0.12). All of these studies were further limited by the adjustment for factors on the causal pathway such as gestational age, GWG, birthweight or maternal diabetes; neither Bastemur et al. (2013) nor Neggers et al. (2003) controlled for parental ADHD. Bastemur et al. (2013) also did not control for the home environment.

Several studies examined intelligence in older, primary-school children ages 6-13. Huang et al. (2014) used mothers and children from the Collaborative Perinatal Project (CPP), a United States prospective study begun in the 1960s, to examine the combined association of maternal BMI and GWG with offspring intelligence using the Wechsler Intelligence Scale at age 7. This study used a conventional analysis including all children and compared the findings to a sibling analysis, a quasi-experimental method that controls for unmeasured confounding (e.g. parenting and the environment) by examining outcomes among siblings with different exposures (maternal GWG). All models adjusted for maternal age, education, race, marital status, socioeconomic status, parity, prenatal smoking, and hospital visits. GWG, grouped into deciles, significantly modified the relationship between maternal BMI and offspring intelligence. Among obese women, GWG >41 lbs was associated with a nearly 7 point decrease (95% CI: -2.0, -11.0) in offspring IQ compared to children of normal weight mothers with average weight gain (21-25 lbs)(88). This relationship was attenuated but remained in both conventional and sibling analyses, indicating that the adverse effect of obesity remained despite accounting for familial and environmental factors(88). Gage et al. (2013) used 12,500 participants from the AVON longitudinal study of parents and children, a prospective population based birth cohort from the

United Kingdom. Intelligence in 8 year old children was assessed using the Wechsler Intelligence Scale (WISC), a traditional psychologist administered test to measure intelligence. This study reported that for every 1 kg increase in maternal pre-pregnancy weight, there was a very modest decrease in offspring IQ levels (mean SD difference: -0.004, 95% CI: -0.006, -0.002), controlling for maternal and prenatal factors such as smoking, education, and GWG. A study using the AVON cohort confirmed the above findings in 8 year old children, and reported lower offspring IQ scores, measured using the WISC, in children of overweight women (BMI≥25) (aOR: 0.84, 95% CI: 0.73-0.98) compared with children of normal weight women(17). Three additional studies reported a significant association between maternal obesity and lower child intelligence in 6-8 year olds, measured by the WISC, or similarly valid scale (i.e. PIAT) (89), in diverse populations(8, 35, 38). However, none of these studies controlled for parental IQ or the postnatal environment.

The evidence examining GWG and child intelligence remains unclear due to methodological limitations, although the majority of studies report no association (**Table 1).** Keim et al. (2012) used the CPP to examine self-reported total GWG categorized by IOM ranges (i.e. above or below the 2009 IOM guidelines) and child performance on the Stanford Binet Scale at age 4 and the Wechsler Intelligence Scale at age 7, both validated and commonly used measurements of intelligence. This study also used a conventional analysis and compared the results to a sibling analysis. Effect modification by BMI was assessed but it was not significant. In the conventional analysis, low and high GWG were significantly associated with lower child IQ, compared with average GWG. However, the sibling analysis found no association between GWG above or below the IOM guidelines and child IQ at ages 4 or 7. Both the conventional and sibling analysis controlled for maternal age, race, parity, smoking, SES, and child sex(90). Three additional studies support the conclusion by Keim et al. (2012) and reported no association between maternal GWG—measured as total GWG (continuous or categorized by IOM) and rate of total GWG— and offspring cognitive development at 8 months and 4 years old (12) or offspring intelligence at age 5(91). In contrast to these null findings, two studies reported a significant association between GWG and cognitive function or intelligence(14, 92). Tavris et al. (1986) reported total maternal GWG >30 pounds or <5 pounds was significantly associated with lower cognitive performance in offspring at age 5 compared with maternal GWG between 5 and 29 pounds, in women from the Kaiser Health Plan in California. Gage et al. (2013) assessed

GWG in two ways, GWG above or below the IOM guidelines and GWG from 0-18, 18-28, >28 weeks gestation. Total GWG above or below the guidelines was not associated with child IQ but increasing GWG in each of the gestational age ranges was positively associated with child IQ(14).

Overall, there is a trend towards a significant association between increased maternal BMI and worse offspring cognitive development and intelligence with limited evidence in underweight women due to sample size limitations or exclusion. The majority of studies found no association between maternal GWG and offspring intelligence. Intelligence at older ages may be a better predictor of adult intelligence, yet no study examined GWG and intelligence in children over the age of 8(84). All of these studies were limited by at least one or more of the "important challenges" discussed previously (i.e. GWG and GA correlation; unmeasured confounding; controlling for factors on the causal pathway), which may obscure the total association between BMI or GWG and offspring IQ. These data highlight the need to study intelligence in older children, use a GWG measure independent of gestational age, and take into account appropriate covariates as well as environmental and parental factors.

Table 1: Summary of the findings on the association between pre-pregnancy body mass index, gestational weight gain, and offspring intelligence

Author, year	Age	BMI Measure	BMI Results	GWG Measure	GWG Results	Assessment Tool
Basatemur, 2013	5-7 years	Continuous- nonlinear	(-)			British Abilities Scale
Bliddal, 2014	5 years	Continuous	(-) maternal & paternal			WPPSI-R
Brion, 2010	3-4 years	Categorical	(-) OV+OB[1]			WISC-II
Casas, 2013	11-22 mo	Categorical	(-) OB[1]			BSID
Craig, 2013	2 years 8 years	Categorical	(-) OB[1]			BSID (age 2) WISC-III (age 8)
Gage, 2013	8 years	Continuous	(-)	Continuous IOM Categories	(+) GWG Null	WISC
Hinkle, 2012	2 years	Categorical	(-) UW, OB2+3[1]			Mental Development Index
Huang, 2014	7 years	Continuous-nonlinear	(-)	Deciles	Effect Modification	WISC
Keim, 2013	4, 7 years			Total GWG IOM Categories	Null Null	Stanford Binet (age 4) WISC (age 7)
Naeye, 1980	5 years			Total GWG	Null	Stanford Binet
Neggers, 2002*	5 years	Categorical	(-) OB[1]	Total GWG	Null	Differential Abilities Scale
Tavris, 1981	5 years			Total GWG	(-) GWG 5-29 lbs	Raven Coloured Matrices Test

Abbreviations: **WPPSI-R**- Wechsler Preschool and Primary Scale of Intelligence-Revised; **WISC**- Wechsler Intelligence Scale for Children; **BSID**- Bayley Scales of Infant Development; **BMI-** pre-pregnancy body mass index; **GWG**- gestational weight gain; **UW**- underweight (BMI <18.5 kg/m^2); **OV**- overweight (BMI 25-29.9 kg/m^2); **OB**-Obese (BMI 30-34.9 kg/m^2); **OB2**- obese class 2 (BMI 35-39.9 kg/m^2); **OB3**- obese class 3 (≥40 kg/m^2)

*Calculated BMI: <19.8 kg/m^2 (underweight), 19.8-16 kg/m^2 (reference), 26.1 to 29 kg/m^2 (overweight), >29 kg/m^2 (obese)

[1]Normal weight Reference (BMI: 18.5-24.9 kg/m^2)

(-) indicates a significant negative association; (+) indicates a significant positive association; Null indicates no association

2.2.2 Executive function

Executive dysfunction results in an inability to plan, organize, develop timelines, adjust to novel situations, or complete tasks in a timely manner—skills critical for a child's academic success(5). Executive function is a term that describes a complex set of cognitive processes used to self-regulate behavior and manage internal resources used to achieve a goal (78, 93). In children with ADHD, executive dysfunction typically corresponds to impairments in cognitive processes such as r*esponse inhibition*— self-restraint; *working memory*— temporary storage of new information and simultaneous processing to perform tasks such as reading, problem solving, and learning(94); and *attention*— the ability to selectively concentrate on one aspect of the environment while ignoring others (4, 95) (5). Executive dysfunction alone is insufficient for ADHD diagnosis, but assessments of executive function and related processes (i.e. inhibition, attention, working memory) are often used during ADHD testing (96). While not all children with ADHD have executive dysfunction, it may be an important indicator of impairment. In fact, some studies show that children with ADHD but high executive functioning can overcome some of their everyday difficulties associated with the disorder (78).

A single study assessed the association between maternal BMI, GWG and child executive function (Table 2) (15). Buss et al. (2012) followed a small diverse cohort of <50% Caucasians from Cedars Sinai medical center in California. A small sample size limited the number of women in each BMI group, particularly obese (n=28), and underweight women were excluded. Executive function was measured in children 7 years old using the Go/No Go Task, an objective, commonly used, and validated measure. This study reported significantly lower executive function performance in children of obese mothers compared with children of normal and overweight mothers, adjusting for maternal demographics, intelligence, obstetric risk conditions, parity and three measures potentially on the causal pathway— gestational age at birth, birthweight, and child BMI. Total GWG was estimated at 37 weeks based on GWG measurements throughout pregnancy. There was no association between total gestational weight gain and child executive function ($F_{(1,157)} = 0.27$, $p=0.61$). Future studies need to use a larger cohort of women to examine executive function in children of obese mothers. Additionally,

studies should use a measure of GWG that is not correlated with length of pregnancy and adjust for appropriate confounders.

Table 2: Summary of the findings on the association between gestational weight gain and offspring executive function

Author, year	Age (mean)	BMI Measure	BMI Results	GWG Measure	GWG Results	Assessment Tool
Buss, 2012	7.3 years	Categorical	(-) OB[1]	Total GWG	Null	Go/No-Go Task

Abbreviations: **BMI-** pre-pregnancy body mass index; **GWG-** gestational weight gain; **OB-** Obese (BMI 30-34.9 kg/m^2)
[1] Normal weight as the reference (BMI 18.5-24.9 kg/m^2)
(-) indicates a negative association; Null indicates no association

2.2.3 Attention-deficit hyperactivity disorder

Inattention, hyperactivity, and impulsivity— behaviors symptomatic of ADHD— inhibit a child's ability to learn and socially interact. The Diagnostic Statistical Manual for Psychological Disorders (DSM-V) set the gold-standard criteria for ADHD diagnosis, which in short requires at least 6 symptoms of inattention and hyperactivity/impulsivity and in more than one setting before the age of 12(97). Symptoms of *inattention* include becoming easily distracted, daydreaming, and having difficulty completing homework or tasks. Symptoms of *hyperactivity* include talking nonstop, fidgeting, and moving around at inappropriate times. Symptoms of *impulsivity* include acting out, interrupting conversations, and having difficulty waiting turns(97). While these three processes are thought to be controlled and regulated by executive function(5), executive dysfunction is not required for ADHD diagnosis. Measures of executive function indicate dysfunction in a cognitive process; measures of behavior indicate how dysfunction is apparent in a child's life and affects their ability to learn and interact (98).

The evidence suggests an association between maternal BMI, but not GWG, and child inattention, hyperactivity, impulsivity (ADHD symptoms). Rodriguez et al. (2008) evaluated ADHD symptoms in 7-12 year old children from a healthy Nordic cohort of over 14,000 mothers and children using teacher-rated symptoms on the Strengths and Difficulties Questionnaire (SDQ) or a similarly valid subjective scale (99). This study reported that there

were more ADHD symptoms in children of overweight mothers (BMI ≥25) compared with children of normal weight mothers (Finish sample: OR: 1.5, 95% CI: 1.1, 1.9) (Danish sample: OR: 1.6, 95% CI: 0.9-2.4) adjusting for maternal smoking, GWG, gestational age, birthweight, infant sex, maternal age, education, and family structure (16). Rodriguez et al. (2010) replicated their 2008 study in a similar Nordic cohort and also reported higher teacher rated ADHD symptoms in children of overweight (BMI 25- <30) (aOR: 2.0, 95% CI: 1.2-3.4) and obese mothers (BMI≥30) (aOR: 2.1, 95% CI: 1.2-4.8) after controlling for parental ADHD and the same factors listed above. Additional studies reported a positive association between maternal BMI and ADHD diagnosis (100) or ADHD symptoms in children aged 2-7 using the Child Behavior Check List (CBCL)(15, 17, 101, 102), a reliable subjective screening instrument for ADHD filled out by parents. However, it remains unclear if low BMI is associated with child ADHD symptoms since underweight women were either excluded(15) or were too few in number to detect a difference (16, 39). Additionally, these studies may be limited by their lack of adjustment for postnatal environmental influences and parental cognition, and adjustment for GWG, a factor potentially on the causal pathway.

Chen et al. (2014) conducted a sibling analysis on over 600,000 Swedish women from 9 national and regional linked registries(103). Maternal BMI was based on self-reported weight and height at 10 weeks gestation. ADHD status in the child was determined based on ICD-9 and ICD-10 codes, DSM-IV diagnosis, or treatment with ADHD medication after age 3, which is strictly prescribed in Sweden and reduces the potential for overprescribing to unaffected children. There was a significant association between increased maternal BMI and higher ADHD diagnosis in children after age 3 in the conventional analysis, which included all children. But, there was no association between maternal BMI and ADHD diagnosis in offspring in the sibling analysis. This is an important analysis that provides insight into the impact of unmeasured confounding by the postnatal environment and inherited ADHD, on the reported association.

Only one study examined the independent association between maternal GWG and ADHD symptoms (15). Buss et al. (2012) reported no association between total GWG, calculated as the difference between GWG at 37 weeks and pre-pregnancy weight, and child ADHD symptoms at 7 years as measured by the CBCL in a small cohort from California, comprised of 48% White women, controlling for maternal and prenatal characteristics, and gestational age. This study did not control for the home environment and there was adjustment of

factors on the causal pathway such gestational age, birthweight, and obstetric complications. No overall conclusion can be drawn since this is the only study that examined the relation between GWG and ADHD symptoms in offspring and the methods used may obscure the total effect of GWG.

In general, the majority of findings support the conclusion that inattention, hyperactivity, and impulsivity between the ages of 7 and 12 are more common among children of obese and sometimes overweight women (**Table 3)**. No conclusion can be drawn about GWG and child ADHD symptoms since only one study examined this relationship. The contribution by Chen et al. (2013) raises a concern about the bias associated with unmeasured confounding in existing studies. Additional gaps in the literature exist including: the use of mostly subjective assessment tools, unmeasured confounding, controlling for factors on the causal pathway, and a significant amount of missing data that may differ by exposure or outcome status. Future studies need to address these limitations.

Table 3: Summary of the findings on the association between pre-pregnancy body mass index, gestational weight gain and offspring attention-deficit hyperactivity symptoms or behavior

Author, year	Age (mean)	BMI Measure	BMI Results	GWG measure	GWG Result	Assessment Tool
ADHD Symptoms						
Antoniou, 2014	2-5 years	Categorical Continuous	Null (+) Externalizing			Child Behavior Checklist (Internalizing, Externalizing, Total)
Brion, 2010	3-4 years	Categorical	(+) OV[1] externalizing,			Strength and Difficulties Questionnaire (Maternal Report) Child Behavior Checklist (Internalizing, Externalizing, Attention, Total)
Buss, 2012	7.3 years	Categorical	(+) OB[1]	Total GWG	Null	Child Behavior Checklist (Problem Behavior)
Rodriguez, 2008	7-12 years	Categorical	(+) OV, OB[1]			Strength and Difficulties Questionnaire (Teacher Report)
Rodriguez, 2010	5 years	Categorical	(+) OV, OB[1] inattention only			Strength and Difficulties Questionnaire (Teacher & Maternal Report)
Van Lieshout, 2013	1-2 years	Continuous	(+) Externalizing			Child Behavior Checklist (Internalizing, Externalizing)
Van Lieshout, 2013	5,8,10,14, 17 years	Continuous	(+)			Child Behavior Checklist (Internalizing, Externalizing)
ADHD Diagnosis						
Chen, 2014	≥3 years	Categorical	Null			ICD-9 and ICD-10 codes, DSM-IV diagnosis, ADHD medication
Hinkle, 2013	2 years	Categorical	(+) OB2+OB3			Parent-report of doctor's diagnosis

Abbreviations: **BMI-** pre-pregnancy body mass index; **GWG**- gestational weight gain; **OV**- overweight (BMI 25-29.9 kg/m^2); **OB**- Obese (BMI 30-34.9 kg/m^2); **OB2**- obese class 2 (BMI 35-39.9 kg/m^2); **OB3**- obese class 3 (≥40 kg/m^2)
[1] Normal weight as the reference (BMI 18.5-24.9 kg/m^2)
(+) indicates a significant positive association; Null indicates no association

2.2.4 Academic achievement

Academic underachievement is often an initial sign that a child is suffering from ADHD or related cognitive deficits. Academic achievement is necessary for job attainment and future success. In order for a child to achieve academically, behaviors and skills such as studying, avoiding counterproductive behaviors, effective communication, and managing conflicting goals must be employed(104, 105). Children with ADHD often struggle to engage these skills due to symptoms that interfere with their ability to focus and manage behaviors(106). This often results in lower academic performance, which can limit future work success (107). Basic skills including math, reading, and spelling skills are a good indicator of a child's overall academic ability(108).

The evidence is sparse but suggests an association between maternal obesity, but not GWG, and lower offspring academic achievement (Table 4). Hinkle et al. (2013) assessed the association between pre-pregnancy BMI and offspring reading and math skills in 5200 children between 5 and 6 years of age participating in the Early Childhood Longitudinal Study Birth Cohort in the United States(100). Lower reading, but not math, z-scores were reported in children of overweight (adjβ: -0.11 standard deviations, 95% CI: -0.19, -0.03) and obese class 1 mothers (adjβ: -0.14 standard deviations, 95% CI: -0.27, -0.01) after adjusting for child's sex, age at assessment, year of kindergarten entry, TV hours, number of children's books, maternal age, race, parity, schooling, poverty, child's weight, and smoking during pregnancy. Data from the National Longitudinal Study of Youth (NLSY) (1986-2008, n=3,412) found that 5-7 year old children of obese mothers scored 2-3 points lower on math and reading portions of the Peabody Individual Achievement Test compared with children of normal weight mothers(8). These studies may be limited by a single measure of academic achievement since academics may vary over time(109) (110).

Three studies examined the association between GWG and offspring academic achievement. In the following studies GWG was classified according the 2009 Institute of Medicine guidelines: below, within, or above the guidelines range for pre-pregnancy BMI. In a

study of 8,704 seven-year old siblings in the Collaborative Perinatal Project (1959-1973), GWG above the guidelines was not associated with offspring math or reading scores (as assessed using the same tool we used) compared with GWG within the guidelines, after controlling for shared factors among siblings such as maternal intelligence and whether the home environment promotes cognitive development(111). In nearly 6,000 four-year old children from the AVON longitudinal study in the United Kingdom (1991-1997), GWG below the guidelines was associated with clinically insignificant decrease (<0.1 point) in offspring composite academic scores(14). A third study in the NLSY reported a non-significant trend towards lower reading and math scores among children of mothers with GWG above the guidelines(8). The findings from all 3 studies are limited by the use of a measure of GWG that is correlated with length of pregnancy, as well as adjustment for factors on the causal pathway including birthweight and gestational age.

Overall, the evidence suggests maternal obesity is associated with lower offspring academic performance, but GWG is not associated with academic performance in children 4-7 years. However, the methodologic gaps and limited number of studies on this topic make it difficult to draw substantial conclusions. Several knowledge gaps should be addressed in future studies including a single time-point of academic achievement, which does not capture the potential variation over time, adjustment for factors on the causal pathway, and the use of a measure of GWG correlated with gestational age.

Table 4: Summary of the findings on the association between pre-pregnancy body mass index, gestational weight gain, and offspring academic achievement

Author, year	Age (mean)	BMI Measure	BMI Results	GWG measure	GWG Results	Assessment Tool
Gage, 2013	4 years			IOM Categories	Null	School Entry Assessment (Composite of language, reading, writing, and math)
Hinkle, 2013	5-6 years	Categorical	(-) OV, OB2[1] with reading			Unspecified tool specific to study (Reading and math)
Keim, 2013	7 years			IOM Categories	Null	Wide Range Achievement Test (Reading, spelling, math)
Tanda, 2013	5-7 years	Categorical	(-) OB[1]	IOM Categories	Null	Peabody Individual Achievement Test (Reading and math)

Abbreviations: **BMI-** pre-pregnancy body mass index; **GWG-** gestational weight gain; **OV-** overweight (BMI 25-29.9 kg/m^2); **OB-** Obese (BMI 30-34.9 kg/m^2); **OB2-** obese class 2 (BMI 35-39.9 kg/m^2)

[1] Normal weight as the reference (BMI 18.5-24.9 kg/m^2)

(+) indicates a significant positive association; (-) indicates a significant negative association; Null indicates no association

2.3 MAJOR GAPS IN THE LITERATURE

Major gaps exist in our understanding of child cognition in relation to pre-pregnancy BMI and GWG.

First, while executive function has been identified as a key component of ADHD and has a biologically plausible association with maternal adiposity, only one study examined maternal weight in relation to executive function. Understanding this association is important because it may provide insight into a modifiable risk factor for executive dysfunction. The Maternal Health Practices and Child Development (MHPCD) project measured child executive function at age 10 using 2 assessment tools, the Trail Making Test and the Wisconsin Card Sorting Test, which will address this gap.

Second, the age at child assessment in a large portion of the literature is in ages 7 and under, which may be too early to detect cognitive dysfunction. Evidence suggests 95% of children with ADHD are identified before age 12 versus only 50% before age 7(112). Studies examining cognitive function in young children may misclassify cognitive status because dysfunction is not fully developed or apparent at younger ages. This may explain the reason behind the null or conflicting findings between BMI and ADHD in infants or toddlers. We will address this gap by using assessments of offspring cognition at age 10.

Third, ADHD symptoms have been assessed using only subjective assessments, which may be biased. Mothers may intentionally or unintentionally rate their children as having fewer symptoms for several reasons: they do not want their child to have a disorder or they are not around their child in constrained environments—school or organized groups—where behavior is taxed and ADHD symptoms are more apparent(113). A combination of objective and subjective assessments is likely to yield more valid results. The MHPCD project includes assessments of ADHD symptoms using the Child Behavior Checklist and Teachers Report Form, both subjective tests, and the Connors Continuous Performance Task, an objective test. We will use all 3 tools to address this gap.

Fourth, academic achievement is a measurable end-result for how ADHD and cognitive deficits may impact a child's real-life functioning, yet the evidence relating academic achievement to pre-pregnancy BMI and GWG is limited. Additionally, multiple assessments of academic performance are important to account for the potential variation in performance over time (109, 110). The MHPCD project measured child academic achievement at ages 6 and 10 years using the Wide Range Achievement Test and at 14 years using the Wechsler Individual Achievement Test.

Fifth, unmeasured confounding is a major concern in published research, with few studies adjusting for critical variables including maternal intelligence, substance use during pregnancy, neighborhood characteristics, and postnatal factors like child stimulation in the home, which may bias the association in an unknown direction. Additionally, covariates that should not be included in adjustment since they may lie on the causal pathway include offspring birthweight, gestational diabetes, and offspring BMI. We will address this gap by controlling for the appropriate aforementioned unmeasured confounders.

Lastly, all published research has used GWG measures (total, rate, and adequacy of GWG) that are correlated with gestational age; this may introduce bias in studies examining the association between GWG and child cognition by creating a spurious association based on the amount of time available to gain weight (i.e. gestational age) (114). Studies examining GWG and child cognition typically control for gestational age to account for this correlation, yet this may not appropriately reduce the bias since gestational age is associated with child cognition. For example, a woman delivering at 36 weeks is categorized as gaining too little weight based on a 40-week scale (IOM recommendation), therefore, adjusting for gestational age does not change her categorization and she remains inappropriately categorized. A GWG method independent of gestational age is necessary. We will address this gap by using standardized GWG z-scores, which by design are uncorrelated with gestational age(115).

2.4 INNOVATION

This work will contribute to public health by directly addressing the Institute of Medicine (IOM) call for studies to assess maternal GWG and child neurodevelopment. The aim of this study is to evaluate the total association between GWG, pre-pregnancy BMI and offspring intelligence, executive function, and attention, hyperactivity/impulsivity at age 10 and academic achievement at ages 6, 10, and 14. An additional aim is to investigate potential effect modification by maternal pre-pregnancy BMI on the relation between GWG and outcomes.

The Maternal Health Practices and Child Development project will be used to address the aims of this study. This cohort is a longitudinal study with robust information on both mothers and offspring. Mothers were enrolled in the study during gestation and followed along with their children for 14 years. Maternal prenatal, demographic, and environmental characteristics were collected at enrollment and 10 years postpartum and offspring cognition and environmental characteristics were collected at 6, 10 and 14 years of age (114).

Although the existing evidence in humans is somewhat equivocal, there is a trend towards an association between high maternal BMI and impaired child executive function, intelligence, attention, hyperactivity/impulsivity, and academic achievement. Fewer studies examined GWG, yet GWG is an important component since women are more apt to change their diet and exercise patterns when it comes to the health of their baby(42, 116). There are biologically plausible pathways to suggest in utero exposures negatively affect child brain development, which in turn can have damaging effects on social and academic growth, resulting in a lifelong and costly burden to the individual and society. Our study aims to contribute to public health, and determine whether potentially modifiable maternal exposures, such as GWG, are associated with impaired neurodevelopment.

3.0 METHODS

3.1 OVERVIEW OF THE PROJECT PLAN

We have the opportunity to inform the Institute of Medicine (IOM) gestational weight gain guidelines using data from the Maternal Health Practices and Child Development Study (MHPCD) (N=829), a longitudinal birth cohort followed 14 years postpartum in Pittsburgh, PA. Maternal self-reported pre-pregnancy height and weight at enrollment will be used to calculate pre-pregnancy BMI and categorized based on the World Health Organization criteria(117). We will assess the relation between BMI and long-term offspring cognitive development, specifically intelligence, executive function, and ADHD symptoms (i.e. attention, hyperactivity, and impulsivity) at 10 years and academic achievement at 6, 10, and 14 years. We will conduct similar analyses with maternal self-reported total GWG at delivery, calculated as gestational age standardized z-scores. Additionally, we will examine whether these relations vary by maternal prepregnancy BMI.

3.2 DESCRIPTION OF THE POPULATION

The aim of the MHPCD project was to understand the effects of prenatal substance use on long-term offspring outcomes such as deviant behavior, substance use, and academic achievement. Recruitment for the MHPCD cohort took place between 1983 and 1986 at a prenatal clinic in Magee-Women's Hospital in Pittsburgh, Pennsylvania. Women ≥18 years and less than 21 weeks gestation were approached and interviewed in a private setting. Among the women

approached, 15% refused and a total of 1,360 women agreed to be screened. Two cohorts were selected from the screening process based on their first trimester use of alcohol and marijuana.

Table 5: Population characteristics (N=763)

Enrollment or Delivery	N(%)
Maternal Age, Mean(SD)	23.0 (4.0)
Maternal Race	
White	370 (48.5)
Black	393 (51.5)
Marital Status	
Never Married	513 (67.2)
Married	250 (32.8)
Maternal Education(yrs), Mean(SD)	11.8 (1.4)
Maternal Employment[1]	
No	559 (73.3)
Yes	204 (26.7)
Income ($ per month)	
<500*	454 (61.7)
≥500	282 (38.3)
Parity	
0 live births	341 (44.7)
1 or 2 live births	254 (33.3)
3 or more live births	168 (22.0)
Body Mass Index	
Underweight	91 (12.0)
Normal Weight	461 (60.9)
Overweight	130 (17.2)
Obese	75 (9.9)
GWG z-Score	
<-1 SD	190 (25.4)
-1 to +1 SD	487 (65.3)
>+1 SD	69 (9.3)
1st trimester marijuana use <2 joints/month	516 (67.6)
1st trimester alcohol use <3 drinks/week	508 (66.6)
No prenatal Illicit Drug Use	673 (88.2)
No prenatal cigarette use	292 (38.3)

*corresponds to <$1400 per month in 2014
[1] includes school

The alcohol cohort was comprised of all women who drank an average of 3 or more drinks per week and an equal sample of women who drank <3 drinks per week. The marijuana cohort included all women who had an average of two or more joints per month and an equal sample of women who smoked <2 joints per month. The two cohorts were combined for analyses (n=829 combined). There was a 48% overlap between cohorts, but majority of the women used <2 joints per month or <3 drinks per week**.** Mothers were assessed a second time during pregnancy (median of 31.3 weeks (IQR: 29.4, 33.1)) and both mother and offspring were assessed by separate interviewers at delivery, 8 months, 18 months, and 3, 6, 10, and 14 years of age. At each phase, a trained interviewer assessed demographic characteristics, psychological status, social characteristics (e.g. number of friends, amount of support), household environment (e.g. number of people living in the home, number of books, time spent with children, etc.), and maternal substance use. Our analyses used offspring cognitive and behavioral development measured at 10 years of age and academic achievement measured at 6, 10, and 14 years. Data collection for this cohort is complete.

Of the 829 eligible women interviewed at the first prenatal visit, 66 were later deemed ineligible and excluded due to fetal or perinatal deaths (n=18), refusal (n=8), missed visit (n=16), twins (n=2), adoption (n=1), or relocation (n=21). There were 763 eligible women at delivery and 88%, 83%, and 76% of the cohort remained at 6, 10, and 14 years, respectively (**Figure 2**).

The sample of women at enrollment included 51.5% African Americans and 48.5% Caucasians (**Table 5**). The mean (SD) age of mothers in the first trimester was 23 (4.0). The women in this study represent a lower socioeconomic status where 73% were unemployed, more than 60% had an income of less than $500 a month (<$1400 per month in 2014(118)), and the mean (SD) length of education was 11.8 (1.4) years. Thirty-two percent of women were married at the first interview and 44% of women were nulliparous. Substance use in this cohort was light to moderate in general(119) and majority of the cohort drank <3 drinks per week (n=508) or used less 2 joints per month (n=516) during the first trimester.

The generalizability of this population may be limited due to the presence of substance use, yet prenatal substance use in the general population is not absent. Additionally, these women were not substance abusers, and higher substance use reported was during the first trimester, when many women do not know they are pregnant. To minimize confounding by prenatal substance use, we will adjust for frequency, amount, and duration of use in all models.

Sensitivity analyses excluding heavy substance users will also be conducted to determine whether the relationship between maternal GWG and offspring cognition differs by heavy versus non/light prenatal substance users.

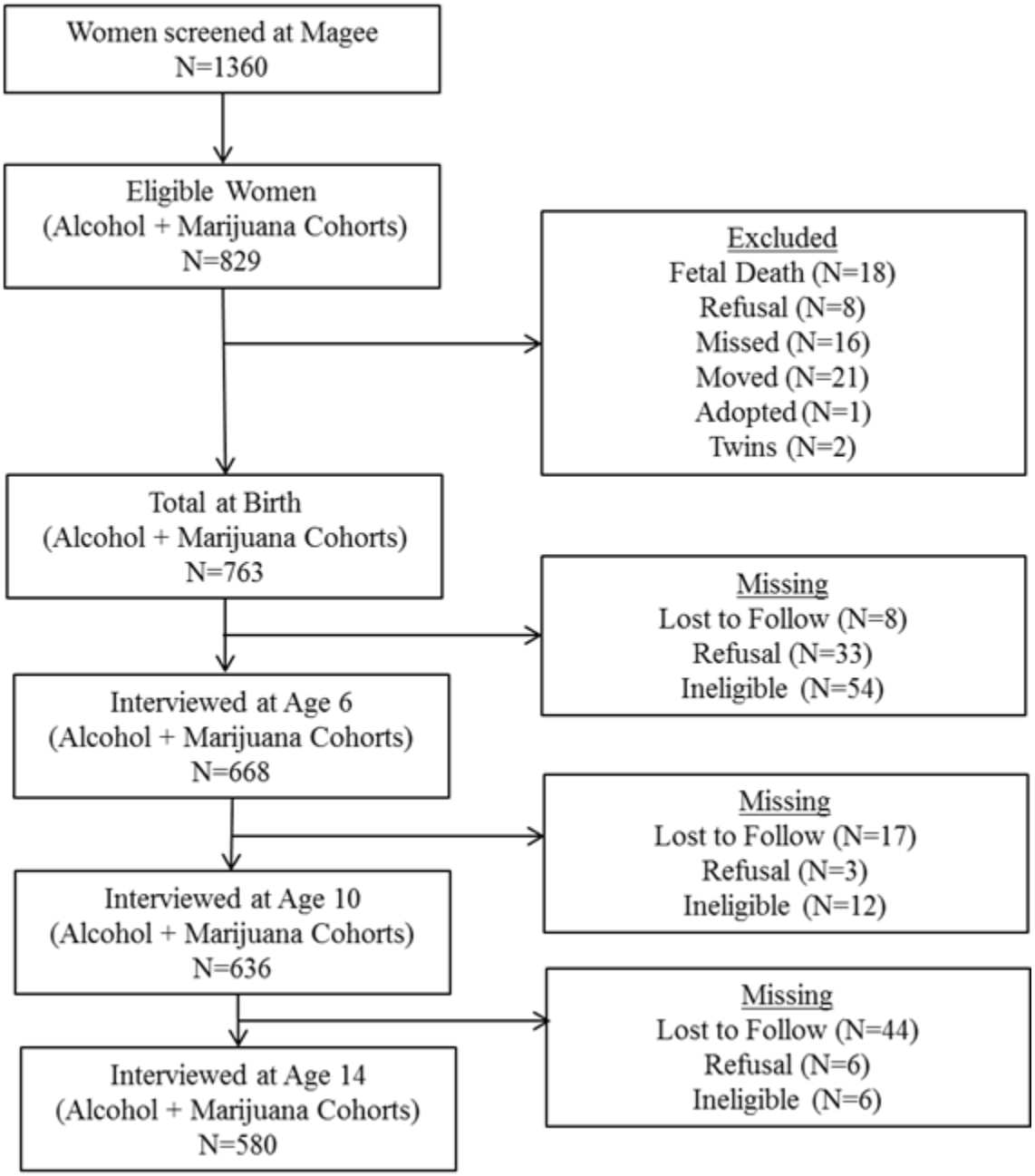

Figure 2: Participant Flow Diagram for the Maternal Health Practices and Child Development Cohort, Pittsburgh, PA (1983-1986)

3.3 MEASURES

3.3.1 Exposure measurements

Pre-pregnancy BMI: Pre-pregnancy weight and height were self-reported at the first study visit (median 18.7 weeks (IQR: 17.1, 20.7)). BMI will be calculated using the formula [weight (kg)/ height (m^2). BMI will be categorized using the World Health Organization (WHO) criteria(117): BMI <18.5 as underweight, BMI 18.5-24.9 as normal weight, BMI 25-29.9 as overweight, and BMI ≥30 as obese. Although BMI is not an actual measure of body fat, it is a feasible assessment tool routinely used in clinical settings to monitor health. BMI is limited in that it may overestimate body fat in individuals with above average muscle mass(120), but we do not expect this to impact our results. BMI is highly correlated with more invasive and direct measures of body fat such as underwater weighing(120) and continues to be a universal assessment method to monitor population obesity trends.

Gestational weight gain (GWG): Total weight gained (in pounds) during pregnancy was self-reported at delivery. Total GWG will be classified according to gestational age-standardized z-scores, a measure of total GWG that by design is uncorrelated with gestational age(115). Z-score charts were developed from serial prenatal weight measurements in a random sample of normal weight term pregnancies without complications from Magee-Womens Hospital in Pittsburgh, PA (1998-2008)(115). Conventional measures of GWG, such as total GWG or rate of GWG (kg/wk), have a built-in correlation with gestational age, which can bias studies examining outcomes correlated with gestational age, such as cognitive function(121), birthweight, and stillbirth(114). Z-score charts describe the mean and standard deviation of GWG where a z-score of -1 indicates a weight gain that is 1 SD below the mean value of GWG. Normal weight z-score charts will be applied to all BMI categories to allow us to evaluate whether the association between GWG and outcomes varies by pre-pregnancy BMI. We will analyze z-scores continuously and categorized as <-1SD, -1 to +1SD, and >+1SD from the mean.

The reliance on self-reported total weight gain poses the potential for misclassification of GWG, which may depend on pre-pregnancy BMI(122). Most normal weight women with

appropriate weight gain accurately report their total GWG (80%)(123). Accuracy of GWG recall decreases with increasing pre-pregnancy BMI and among women with excessive or inadequate GWG(123). Self-reported weight and height may lead to misclassification of pre-pregnancy BMI. On average, women under-report their pre-pregnancy weight by 1-4kg(124-126) (127) and overestimate their height by 0.6-3cm(125), but larger deviations exist. Some data suggest that BMI is correctly classified in 85% of women(126). Yet, studies have shown that the accuracy of self-reported weight, height, and BMI may vary by maternal weight, race/ethnicity, or other factors (126), which makes it difficult to predict the direction and magnitude of the bias this may cause(128). We do not have information on the validity of self-reported weight and weight gain in this population or access to data on other pregnant cohorts in the 1980's to assess the validity. Therefore, maternal BMI and GWG misclassification remain a potential bias of this study's findings.

3.3.2 Outcome measurements

All neuropsychological assessments were administered by trained interviewers blinded to maternal prenatal and current substance use (**Table 6 and Table 7**).

Intelligence. *The Stanford Binet Intelligence Scale-4th edition* (SBIS) was administered to children at age 10. The SBIS is a commonly used intelligence battery that is highly correlated (r=0.84) with the gold standard intelligence test: the Wechsler Intelligence Scale for Children (WISC) (129). The SBIS takes 60 minutes to complete and is comprised of one standardized composite score and 4 subtests: verbal reasoning, visual reasoning, quantitative reasoning, and short term memory. The verbal and quantitative reasoning subtests comprise crystallized intelligence(129) while visual reasoning comprises fluid intelligence(130). We will study composite IQ and subtests as both continuous and dichotomous variables (low IQ (≤89) versus average or above IQ (>89) based on the SBIS defined ranges(130)). The average score on the SBIS composite scale in the MHPCD cohort was 91.2 (SD: 11.8).

Table 6: Offspring Performance on Cognition Assessments at age 10

	N(%)
Intelligence	
Stanford Binet Composite Scale	
Overall, Mean(SD)	91.2 (11.8)
≤89 (low average)	280 (44.7)
>89 (average or above)	346 (55.3)
Executive Function	
Wisconsin Card Sorting Task Perseverative Errors	
Overall, Mean(SD)	23.9 (9.9)
Trail Making Test Part B (time)	
Overall, Mean(SD)	103.1(43.1)
ADHD symptoms/ behavior	
Continuous Performance Test	
Average Omission, Mean(SD)	1.5 (1.2)
Average Commission, Mean(SD)	3.7 (4.6)
Child Behavior Checklist Total Score	
Overall, Mean(SD)	52.8 (10.5)
≥67 (borderline clinical)	64 (10.0)
<67 (average)	571 (90.0)
Teacher Report Form Total Score	
Overall, Mean(SD)	53.0 (11.5)
≥67 (borderline clinical)	71 (12.4)
<67 (average)	504 (87.6)
Academic Achievement	
Wide Range Achievement at 10	
Math Score, Mean(SD)	88.7 (13.1)
Reading Score, Mean(SD)	94.2 (15.4)
Spelling Score, Mean(SD)	93.5 (14.6)

The SBIS is the second version of the Stanford Binet Scale, which was developed to compensate for the short-comings in the first version (SBIS L-M), identified as cultural bias, difficulty in scoring, and subjective bias in interpreting the results(131). With the revision, the SBIS lost the ability to accurately identify gifted students due to a ceiling effect on scoring. The ceiling effect should not impact our study since we aim to identify deficient intellectual functioning. The SBIS subscales are an addition from the previous scale and they are not adequate for individual interpretation or comparison(129). We will focus our analyses on the composite IQ score, which has high construct and external validity(131).

Executive function. The MHPCD administered two tests of executive function to children at 10 years of age: Wisconsin Card Sorting Test (WCST) and Trail Making Test (TMT). The *Trail-Making test part B (TMT)* is a measure of attention, speed, and mental flexibility(129). In part B, the test consists of 25 circles that contain both numbers and letters. The participant draws a single line to connect the circles in an ascending pattern while alternating between numbers and letters (i.e. 1, A, 2, B, 3, C, etc.). The time (in seconds) to complete the trail comprises the score. The average time to complete part B is 75 seconds and >273 seconds indicates deficiency(129). The mean time (seconds) on part B was 103.1 (SD: 43.1) in the MHPCD cohort. The Trail-Making Test is limited by an IQ performance effect; individuals with low IQ perform worse on the test. We can address this aspect of the TMT by controlling for child IQ.

The *Wisconsin Card Sorting Test* (WCST) assesses strategic planning, organized searching, and the ability to use feedback to shift cognitive set and goal-oriented behavior (129). The test consists of four stimulus cards that have a different shape, number of shapes, and color of shapes. The participant is told to match each card in a deck of response cards to one of the four stimulus cards. The computer provides feedback after each match to indicate whether the matched response was right or wrong, a method to guide future decisions about matches(129). Scoring is divided into 3 categories: categories completed, number of errors, and number of items in which the participant continues to respond incorrectly after feedback (perseverative errors). Recent data shows that perseverative errors are the most useful in identifying executive dysfunction(132). The average number of perseverative errors in the MHPCD cohort was 23.9 (SD: 9.9)

The WCST is the most commonly used tool to assess executive function(129), but limitations exist. Performance on the WCST can be affected by socioeconomic status; however, we can address this limitation by controlling for income, education, and employment—indicators of socioeconomic status. Additionally, the WCST should not be used as a single assessment of executive function(129). To address this limitation we will use both the WCST and TMT.

ADHD symptoms. ADHD is diagnosed with a psychiatric, psychological, and neurologic evaluation consisting of in-person evaluations and observations, and objective assessment tools (2). Because ADHD diagnosis has a high researcher and subject burden, the

MHPCD did not diagnose ADHD. Rather, the study assessed ADHD behaviors and symptoms consistent with a gold-standard ADHD evaluation: the Child Behavior Checklist (CBCL) and Teachers Report Form (TRF), both subjective tests, and the Connors Continuous Performance Task (CPT), an objective test. Each is discussed below.

Table 7: Psychometric and Scoring information for Cognition Assessment Tools

Measurement Tool	Psychometrics(129)	Scoring
	Intelligence	
Stanford Binet Intelligence Scales-4th edition	Composite score *r* : 0.95 *IC:* 0.96	Average vs. Below average (>89 vs. ≤89) Mean(SD): 100(16) Continuous (Higher=Better)
	Executive Function	
Trail Making Test	*IC*: Part B: 0.65	Time to complete Part B Continuous (Higher=Worse)
Wisconsin Card Sorting	*r*: 0.83	Number of Perseverative Errors Continuous (Higher=Worse)
	ADHD Symptoms and Behavior	
Child Behavior Check List *&* *Teacher Report Form*	Internalizing *r:* 0.89 Externalizing *r:* 0.93 Specificity: 80-90%	Deviant vs. Average (≥67 vs. <67) Continuous (Higher=Worse)
Continuous Performance Test	*IC*: 0.83- 0.93	Number of Errors Continuous (Higher=Worse)
	Academic Achievement	
Wide Range Achievement Test	*r* : 0.91-0.98 *IC*: 0.92-0.95	Mean(SD): 100(15) Continuous (Higher=Better)
Wechsler Individual Achievement Test	*r*: 0.97-0.98 *IC*: 0.80-0.90	Mean(SD): 100(15) Continuous (Higher=Better)

**r*-Test-retest reliability; IC-internal reliability

The Child Behavior Checklist (completed by a parent or caregiver) and the *Teacher Report Form* (completed by the teacher) are questionnaires that address behavior and emotional problems in 9 trait areas: withdrawn, somatic complaints, anxious/depressed, social problems, sex problems, thought problems, attention problems, delinquent behavior and aggressive behavior. These 9 traits are further broken up into summary standardized scores of internalizing problems, externalizing problems, and total behavioral problems. Samples of questions asked include, "Compared with others of the same age, how well does your child carry out chores?" and "On a scale from not true, somewhat true, to always true, how often does your child daydream or get lost in his/her own thoughts?" On each of these scales, a score ≥67 is defined as borderline clinical for deviant behavior(133). In the MCPCD cohort, the mean (standard deviation) score on the CBCL was 52.8 (SD: 10.5) and 53.0 (SD: 11.5) on the TRF.

The CBCL and TRF have limitations. First, it is difficult to test for behavioral differences within the normal range of scores. For example, this test is not valid for determining whether children within the normal range of functioning (score <67) differ by exposure status on attention and thought subscales. We do not anticipate this to affect our study since we are interested in detecting a difference between normal and clinical ranges(134).

The *Continuous Performance Task* (CPT) is a computer-administered task that evaluates attention deficits in children. Various shapes (circle, square, etc.) in different colors are presented on the computer screen and the child must press the space bar only when a blue square appears. The task consists of 3 trials in which the first two present the shapes at a fixed time interval while the last trial varies the interval of speed between shapes depending on whether the child answers correctly or incorrectly (129). For example, the interval speed increases when the child answers correctly but decreases when the child answers incorrectly. The final score is divided into omission errors, which represent inattention or slow-reaction and commission errors, which represent impulsive responding. The CPT is a reliable and sensitive measure for assessing ADHD symptoms(135) . The omission and commission scores will each be averaged across the 3 trials. The mean omission score and commission score was 1.5 (SD: 1.2) and 3.7 (SD: 4.6) in the MHPCD cohort.

Academic Achievement. Offspring academic achievement was assessed using the *Wide Range Achievement Test-Revised (WRAT-R)* at ages 6 and 10 and the *Wechsler Individual Achievement Test (WIAT)* at age 14. The WRAT-R is designed to evaluate basic academic skills

including reading, spelling, and arithmetic. The reading scale tests the child's ability to recognize letters, name letters, and pronounce words out of context. The spelling scale assesses the child's ability to use marks resembling letters to form words. The arithmetic scale tests the child's ability to count, read number symbols, and solve oral and written problems. The WIAT assesses the same academic skills as the WRAT-R, but the WIAT is designed for children 12 years and older. The scales are highly correlated on reading (r=0.84), spelling (r=0.84), and arithmetic (r=0.76). Final scores for reading, spelling, and math skills on both the WRAT-R and WIAT are age-standardized to a mean (SD) of 100 (15). The WRAT-R and WIAT are both reliable and commonly used tools for assessing academic achievement in children(129). Each subtest score will be analyzed continuously. The mean (SD) math, reading, and spelling at age 6 were 92.7 (17.5), 93.7 (13.6), and 88.7 (17.5) on the WRAT-R and at age 14 were 89.6 (13.8), 92.4 (13.1), and 93.2 (13.9) on the WIAT (age 10 scores are listed in Table 6).

The WRAT-R is easy to administer and is an acceptable tool for measuring basic academic skills; however, scores can be affected by socioeconomic status. We can address this limitation by controlling for income, education, and employment—indicators of socioeconomic status(129). The WIAT is the most commonly used and valid tool to assess academic skills in children, but there is a floor and ceiling effect in which the WIAT cannot identify individuals 4 SD below the mean. We do not expect our population to have scores outside this range and therefore this limitation should not impact our findings.

3.3.3 Covariates

We will consider the following covariates as potential confounders in our analysis based on causal diagram theory(136) (**Table 8**). All covariate information was obtained during an interview with trained examiners. Demographic characteristics (i.e. maternal pre-pregnancy BMI, age, race, parity, employment, education, income, marital status) were obtained by maternal self-report during enrollment. Substance use was assessed at enrollment, at the second prenatal visit, and at delivery. At enrollment, women indicated the quantity and frequency of substance use during the year prior to pregnancy and during the first trimester to calculate a more accurate depiction of first trimester use(137). At the second prenatal visit and at delivery, women

indicated the quantity and frequency of use since the previous visit. Alcohol, marijuana, and cocaine use were summarized as average daily drink volume, average daily joints, and cocaine use (yes/no), respectively. Current cigarette smoking was assessed at each trimester during pregnancy and summarized as cigarettes per day. Maternal depression and anxiety were assessed at the first prenatal visit. Depression was measured using the Center for Epidemiological Studies Depression Scale (138)and anxiety was measured using the Spielberger's State-Trait Anxiety Personality Inventory(139). Higher scores on both scales indicate higher depression and anxiety levels. Maternal intelligence was assessed 10 years postpartum using the Wechsler Adult Intelligence Scale (WAIS) a validated scale for adult intelligence. The Home Observation Measurement of Environment (HOME) was administered to mothers or caretakers at 10 years postpartum to determine the cognitive stimulation provided in the home environment. A higher score indicates more stimulation in the home.

Table 8: Potential Confounders

At Enrollment: maternal pre-pregnancy BMI, age, race, parity, employment, education, income, marital status, depression, anxiety
During Pregnancy: substance use during pregnancy (marijuana, alcohol, cocaine), smoking during pregnancy
At 10 years postpartum: maternal intelligence, HOME scale

3.4 STATISTICAL ANALYSIS

Univariate statistics will be used to examine variable distributions, outliers, and skewness. Normality will be assessed using histograms, Q-Q plots, and Shapiro-Wilk Test. Bivariate relationships between GWG and offspring cognitive outcomes, pre-pregnancy BMI and offspring outcomes, and covariates and offspring outcomes will be assessed using chi square tests, Student's t-tests, one-way ANOVA, and non-parametric or repeated measure equivalents when necessary. Linearity will be assessed using lowess plots. To allow for non-linear relationships, cubic, quadratic, and linear spline terms will be tested. Outcomes will be analyzed

continuously and dichotomized for the following scales: the CBCL, the TR, and the SBIS. Multivariable linear regression will be used to model normally distributed outcomes as continuous dependent variables. Poisson and negative binomial regression will be used to model non-normally distributed and over-dispersed outcomes, respectively, as continuous dependent variables. Modified (robust) Poisson models will be used to assess dichotomized dependent variables(140, 141). We will use generalized estimating equations to model academic achievement at 6, 10, and 14 years accounting for the intra-person correlation in scores over time. The primary predictor of interest is maternal GWG z-score, which will be analyzed continuously, categorized into quantiles, and using spline regression. Maternal prepregnancy BMI is another primary predictor of interest and will be analyzed continuously. Effect modification by prepregnancy BMI will be tested at the $p<0.05$ level in all models by including an interaction term that allows the GWG and cognitive outcome relationship to vary by maternal BMI. Effect modification by substance use (Heavy/Non or light users), race (Black/White), and income (<500/≥500) will also be explored. All combinations of exposure, outcome, and interaction terms using continuous, dichotomized, and quantile variables will be tested and then compared using Akaike's information criteria (AIC) and Bayesian information criteria (BIC). Covariates will be selected for inclusion in the model based directed acyclic graph theory (136). Covariates will be retained in models based on the change-in-estimate method, which retains covariates if they change the effect estimate of the primary exposure by >10%(142, 143). Substance use variables will be tested in both models as continuous trimester-specific variables (i.e. use in the first trimester only) and categorized by overall pregnancy use (i.e. no use during pregnancy, used only in 1 trimester, used the entire pregnancy). Substance use variables will be retained a priori. Models will be assessed for influential points, normality of residuals, and heteroscedasticity. Model fit will be assessed for goodness-of-fit using Hosmer-Lemeshow Goodness-of-Fit test, AIC and BIC criteria. Multicollinearity will be assessed using variance covariance estimator (VCE).

Specific Aim 1: The dependent outcomes of interest include child intelligence (IQ) and executive function. IQ was measured using the Stanford Binet Intelligence Scale (SB-4). The SB-4 is comprised of a standardized composite score. Multivariable linear regression will be used to assess child composite IQ as a continuous outcome adjusted for covariates. Modified

Poisson regression models will be used to assess composite IQ as a dichotomous variable (i.e. IQ≤89, IQ>89) to indicate average IQ vs. above average IQ(129) adjusted for covariates.

Executive function was measured using the Wisconsin Card Sorting Test (WCST) and the Trail Making Test Parts A and B (TMT). The WCST is comprised of two summary scales, number of completed categories and perseverative errors, which will be analyzed separately. Negative binomial regression will used to analyze the number of perseverative errors with a higher number of errors indicating lower executive function performance. Multivariable linear regression will be used to examine the time in seconds on part B on the TMT as continuous variables adjusting for covariates.

Specific Aim 2: The dependent outcome of interest is attention and hyperactivity/impulsivity (ADHD symptoms), which was measured using 3 scales: the Continuous Performance Test II (CPT-II), the Child Behavior Checklist (CBCL), and the Teacher Report Form (TRF). The CBCL and TRF are scored the same way and are each comprised of a total score, represented as a normalized t-score. Multivariable linear regression will be used to assess the CBCL and the TRF separately, adjusted for covariates. Modified Poisson models will be used to assess the total CBCL and total TRF score dichotomized as <67 and ≥67, to indicate normal versus deviant behavior. The CPT is comprised of 3 trials and each trial has a commission and omission score to indicate impulsivity and inattention, respectively. The omission and commission scores will each be averaged across the 3 trials and examined continuously. Poisson regression will be used to assess inattention (mean number of omission errors) and negative binomial regression will be used to asses impulsivity (mean number of commission errors) continuously adjusting for covariates.

Specific Aim 3: The dependent outcome of interest is offspring academic achievement, which was measured by math, reading, and spelling skills on the Wide Range Achievement Test-Revised (WRAT-R) at ages 6 and 10, and the Wechsler Individual Achievement Test (WIAT) at age 14. All scores were age-standardized to a mean(SD) of 100(15), which allows for comparability across assessment tools. We will fit generalized estimating equations with an exchangeable covariance structure to estimate the association between pre-pregnancy BMI and each of the offspring achievement scores—math, reading, and spelling. This method will account

for the correlation among child academic assessments at multiple ages. All outcome scores will be examined continuously and adjusted for covariates.

4.0 GESTATIONAL WEIGHT GAIN, PRE-PREGNANCY BODY MASS INDEX, AND OFFSPRING INTELLIGENCE AND EXECUTIVE FUNCTION AT AGE 10

4.1 ABSTRACT

Our objective was to test the hypothesis that high/low gestational weight gain (GWG) and high/low pre-pregnancy BMI were associated with offspring intelligence (IQ) and executive function at age 10. Mother-infant dyads (n=763) enrolled in a birth cohort study were followed from early pregnancy to 10 years postpartum. IQ was assessed by trained examiners using the Stanford Binet Intelligence Scale-4th edition. Executive function was assessed by the number of perseverative errors on the Wisconsin Card Sorting Test and time to complete Part B on the Trail Making Test. Self-reported total GWG was converted to gestational-age-standardized GWG z-scores. Multivariable linear regression and negative binomial regression were used to estimate independent and joint effects of GWG and BMI on outcomes while adjusting for maternal race, parity, income, maternal intelligence, home stimulation, and prenatal substance use. The mean (SD) GWG z-score was -0.5(1.8) and 27% of women had a pregravid BMI≥25. The median (IQR) number of perseverative errors was 23(17-29), the mean (SD) time on Part B was 103(42.6) seconds, and 44% of children had a low IQ (≤89). Maternal obesity was associated with 3.2 lower IQ points (95% CI: -5.6, -0.8) and a slower time to complete the executive function scale Part B (adj β: 12.7 seconds, 95% CI: 2.8, 22.7) compared with offspring of normal weight mothers. Offspring of mothers whose GWG was >+1SD, compared with -1 to +1SD, performed 15.3 seconds slower on the executive function task (95% CI: 2.5, 28.1). There was no association between GWG z-score and offspring composite IQ score (adj β: -0.32, 95% CI: -0.72, 0.10). Pre-pregnancy BMI did not modify these associations. While GWG may be important for executive function, maternal BMI has a stronger relation than GWG with both

offspring intelligence and executive function. Our findings contribute to evidence linking maternal obesity to long-term child outcomes.

4.2 INTRODUCTION

Maternal overweight and obesity affect two-thirds of women of childbearing age in the United States(40) and increase the risk of a number of adverse offspring health outcomes such as preterm birth, infant mortality, offspring obesity(144), insulin resistance(145), and asthma(146). Recent research suggests that offspring of overweight and obese mothers may also have impaired brain development(17, 18). It has been posited that the inflammatory and hormonal (leptin and insulin) milieu of obesity(51, 52) may lead to an over- and under-activation of a number of fetal neurodevelopmental processes(55, 56) including neuron proliferation and differentiation (57), myelination, and synapse formation(57). Studies from three large European cohorts reported that obese mothers had children with lower general intelligence at 3-4 years of age(17) and lower cognitive performance in infancy(18), compared with offspring of normal weight mothers.

Gaining the optimal amount of weight during pregnancy may attenuate the risk of adverse birth outcomes associated with obesity(42), but whether this is true for offspring cognition is not known. Further, gestational weight gain (GWG) itself may be independently associated with cognitive outcomes. The data examining the association between GWG and child cognitive development in humans is limited(9). When the Institute of Medicine revised the GWG guidelines in 2009, the committee stressed the importance of filling this knowledge gap. Subsequently, one study in a large European cohort reported a modest decrease in offspring intelligence with increasing GWG(14), and two studies reported a null finding on the independent relation between maternal GWG and offspring cognition(8, 111).

Understanding how maternal weight and weight gain contribute to offspring cognitive development is important, but key knowledge gaps remain. Intelligence is not the only domain of offspring cognition that may be negatively associated with maternal obesity. Executive function is the coordinating system of the brain, and while interrelated with intelligence, captures goal-directed behavior (78, 147). Additionally, most previous work assessed general offspring cognitive development in infancy or early childhood, but infants are too young to assess domain-

specific disruptions. Therefore, assessments in infancy are less predictive of adult intelligence than assessments in late childhood, which can be domain-specific(148). Importantly, a lack of adequate adjustment for maternal intelligence or stimulation at home may have biased previous findings. Our objective was to assess associations between both pre-pregnancy BMI and GWG with offspring intelligence and executive function at age 10.

4.3 METHODS

The Maternal Health Practices and Child Development (MHPCD) cohort was designed to study the effects of prenatal substance use on long-term offspring outcomes(149). Recruitment for the MHPCD took place at a prenatal care clinic in Magee-Womens Hospital in Pittsburgh, Pennsylvania from 1983-1986. Women ≥18 years and less than 21 weeks gestation were approached and interviewed in a private setting; 1360 women were screened for eligibility (15% refusal rate). From this pool of women, an alcohol cohort and marijuana cohort were selected based on first trimester use. The alcohol cohort was comprised of all women who drank ≥3 drinks per week and an equal sample of women who drank <3 drinks per week. The marijuana cohort was comprised of all women who smoked ≥2 joints per month and an equal sample of women who smoked <2 joints per month. There was a 48% overlap in the combined cohorts. The cohorts were combined for this analysis (n=829 combined). At delivery, 763 mothers remained in the study and most of the cohort was comprised of women who drank <3 drinks per week (n=508; 67%) or smoked <2 joints per month (n=579; 76%) in the first trimester.

Enrollment and the first study visit occurred at a median of 18.7 weeks (IQR: 17.1, 20.7). The second study visit and delivery visit occurred at a median of 31.3 weeks (IQR: 29.4, 33.1) and a median of 39 weeks (IQR: 38-40), respectively. Mother-child pairs were followed for 10 years. At each post-partum visit, sociodemographic status, substance use, maternal psychological status, and offspring cognitive development were assessed. Women provided informed, written consent and the study was approved by the University of Pittsburgh Institutional Review Board (IRB #PRO14020264)

At the 10-year study visit, there were 636 mother-child dyads interviewed (83% of the birth cohort) (**Figure 3**). We further excluded mother-offspring pairs with incomplete data on

BMI (n=4), GWG (n=12), intelligence (n= 6) or executive function (n=51) assessments at age 10, or other covariates (n=33). A total of 530 pairs were used in the final analysis.

Description of Exposure: Pre-pregnancy BMI and Maternal GWG

Pre-pregnancy weight and height were self-reported at the first study visit. Pre-pregnancy BMI [weight (kg)/height (m^2)] was categorized using the World Health Organization (WHO) criteria: BMI <18.5 kg/m^2 as underweight; BMI 18.5-24.9 kg/m^2 as normal weight; BMI 25-29.9 kg/m^2 as overweight; and BMI ≥30 kg/m^2 as obese(117). The total amount of weight women gained during pregnancy was self-reported at delivery. We then classified total GWG according to gestational age-standardized z-scores, a measure of GWG that by design is uncorrelated with gestational age(115). Z-score charts were developed from serial prenatal weight measurements in a random sample of normal weight term pregnancies without complications from Magee-Womens Hospital in Pittsburgh, PA (1998-2008)(115). Z-scores were calculated using charts for normal weight women to allow us to evaluate whether the association between GWG z-scores and offspring intelligence and executive function varied depending on pre-pregnancy BMI.

Description of Outcome: Intelligence and Executive Function

Trained examiners blinded to maternal prenatal and current substance use administered all neuropsychological assessments to children at age 10. Offspring intelligence (IQ) was assessed using the Stanford Binet Intelligence Scale 4th Edition (SBIS)(130). The SBIS has a high internal consistency (0.96) and test re-test reliability (0.95)(129). The scale has four subtests: visual reasoning, verbal reasoning, quantitative reasoning, and short term memory. These subtests are combined to create the composite score, which indicates general intellectual ability. We studied IQ as both a continuous and dichotomous variable (low IQ (≤89) versus average or above IQ (>89) based on the SBIS defined ranges(130)).

Offspring executive function was assessed using the Wisconsin Card Sorting Test (WCST) and Trail Making Test Part B (TMT-B), which are both reliable and commonly used tools(129). The WCST assesses the ability of the subject to use computer feedback to shift and inhibit unwanted responses(129), measured by the number of perseverative errors. A greater number of errors indicate lower executive function. The TMT-B assesses mental flexibility, visual attention, and motor impulsivity(129), indicated by the ability to update working memory

and shift to the appropriate response(150), and is measured by the time in seconds to complete Part B. A longer time to complete the scale indicates lower executive function ability.

Other Covariates

At the first study visit, trained examiners collected information on sociodemographic characteristics (i.e., maternal age, race, parity, employment, education, income, marital status). Alcohol, marijuana, cigarette, and cocaine use were collected by interviewers at both prenatal visits and delivery, and were summarized as average daily drinks, average daily joints, cigarettes per day, and cocaine use (yes/no), respectively. At the first study visit, women indicated the quantity and frequency of substance use during the year prior to pregnancy and during specific segments of the first trimester to calculate a more accurate depiction of first trimester use(137). We categorized each substance into non-users, users during the first trimester when many women do not know they are pregnant, and use throughout pregnancy. Maternal depression at the first study visit was measured using the Center for Epidemiological Studies Depression Scale(138) and anxiety was measured using the Spielberger State-Trait Anxiety Personality Inventory(139). Maternal intelligence was assessed at 10 years postpartum using the two-subtest version of the Wechsler Adult Intelligence Scale (WAIS)(151) . The Home Observation for Measurement of the Environment -Short Form (HOME-SF) was administered to mothers or caretakers at 10 years postpartum to assess the quality and quantity of support for cognitive and social development in the home environment. We included the HOME-SF as a continuous variable in models and as a dichotomized variable for descriptive purposes (lower stimulation (<16) versus higher stimulation (≥16))(152).

4.3.1 Statistical analysis

Student’s t-tests and one-way ANOVA were used to determine differences in child cognitive outcomes, GWG, and BMI by maternal characteristics. Pearson correlation coefficients were used to assess the strength of association between scales. Multivariable linear regression models were used to estimate beta coefficients and their corresponding 95% confidence intervals (CI) for the association between pre-pregnancy BMI and offspring intelligence (SBIS scale) as well as executive function (TMT-B). We estimated incidence rate ratios (IRR) and 95% CI for the

relation between pre-pregnancy BMI and WCST executive function scale (count of errors) using negative binomial regression due to a skewed and over-dispersed distribution. Effect modification by maternal race was tested by including a statistical interaction term between race and BMI (continuous) in fully-adjusted models. Similar models were built for GWG z-scores as the main exposure, with effect modification by pre-pregnancy BMI tested by including a statistical interaction term between BMI and GWG z-score (tested both as continuous and as categorical variables) in fully-adjusted models. Effect modification was present when $\alpha = 0.05$ based on Wald p-value (linear regression) or likelihood ratio test (negative binomial regression).

We examined the non-linear relationship between each child outcome and maternal pre-pregnancy BMI and GWG z-score. The relation between intelligence, executive function and pre-pregnancy BMI was modeled using restricted cubic spline terms with 3 knots at the 10th, 50th, and 90th percentiles and as a linear spline term with one knot. We compared the spline models using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) model comparison criteria to select the best variable specification(153). After model estimation, we used linear combinations to calculate coefficients and 95% CI for selected BMI values compared with 22 as the referent, which was selected based on the observed point of inflection. For ease of interpretation, we categorized GWG as <-1SD, -1 to +1SD, and >+1SD from the mean because the relation between GWG and outcomes did not deviate from linearity. We selected potential confounders based on directed acyclic graph theory(136): maternal race, parity, income, employment status, marital status, education, maternal intelligence, maternal depression, maternal anxiety, home environment stimulation, prenatal substance use, child gender, and pre-pregnancy BMI (GWG models only). Parsimonious models were built by adjusting for confounders that, if removed from the model, changed the effect estimate of the primary exposure by >10%(142). Maternal race, child sex, parity, income, maternal intelligence, pre-pregnancy BMI (GWG models only), and the home environment met confounder inclusion criteria for all models. Prenatal substance use variables were forced into models based on *a priori* decisions. Adjusted predicted IQ and executive function scores and 95% CI's were plotted versus pre-pregnancy BMI with covariates set to population means.

Although substance use was common in this cohort, women were not substance abusers. We performed a sensitivity analysis to address the potential bias of the high substance use by excluding high marijuana (>1 joint a day)(154), alcohol (>1 drink a day)(119), cigarette (≥20

cigarettes per day)(155), cocaine (any use), and illicit drug (any use) users during the 1st or 3rd trimester. Analyses were conducted in Stata software, version 13.0 (StataCorp, College Station, TX)(156).

4.4 RESULTS

There were no differences in GWG, pre-pregnancy BMI, maternal race, substance use, offspring IQ, or executive function between those with and without missing data at 10 years (data available on request). At enrollment, the majority of women in the MHPCD cohort were unmarried, unemployed, and had a family income <$500 a month (<$1,400 per month in 2014 dollars(118)) (**Table 9**). Over half of the women reported their race as Black and nearly half as White. Most of the women did not use illicit drugs or marijuana prenatally. At 10 years postpartum, mothers tended to be moderately depressed, to provide a low stimulating home environment and to have a low average IQ. The mean (SD) gestational weight gain was 14.2 (5.8) kg and mean (SD) pre-pregnancy BMI was 23.4 (5.7) kg/m^2.

The prevalence of children with low IQ (≤89) was 44%, with a mean(SD) IQ score of 91.6 (11.6). On the executive function scales, the median (IQR) number of perseverative errors was 23 (17-29) and the mean (SD) time to complete Trails Part B was 103 (42.6) seconds. The Pearson correlation coefficient comparing the two executive function scales was 0.18. The correlations ranged from 0.3 to 0.4 comparing each executive function scale with the IQ scale.

Offspring IQ and executive function were higher among children of White mothers, married women, mothers with higher income, average or above IQ, or a home environment that provided higher stimulation (**Table 10**). Child IQ was also significantly higher among children of mothers using illicit drugs (i.e., cocaine, heroin etc.), which is likely explained by the fact that illicit drug users were disproportionately White women (70%). Neither offspring IQ nor executive function differed by maternal prenatal alcohol, marijuana, or cigarette use.

There was no difference in offspring IQ or executive function by pre-pregnancy BMI or GWG before confounder adjustment (**Table 11**). After adjusting for maternal race, child sex, parity, income, maternal intelligence, home environment, and prenatal substance use, there was a

significant non-linear relationship between pre-pregnancy BMI and offspring IQ (**Table 12 and Figure 4A**). Offspring IQ was relatively constant when pre-pregnancy BMI was below 22 kg/m^2. In contrast, offspring IQ was 1.1 points (adjβ: -1.1, 95% CI: -1.8, -0.3) lower among women with a BMI of 26 kg/m^2 and 2.5 points (adjβ: -2.5, 95% CI: -4.5, -0.6) lower among women with a BMI of 32 kg/m^2, compared with women with a BMI of 22kg/m^2. A similar trend was observed on the IQ subscales (**Table 14**). Similarly, on the Trails B, offspring executive function time to complete was longer as pre-pregnancy BMI increased beyond 22 kg/m^2 (**Table 12 and Figure 4B**). Offspring time to complete the scale was 4.1 seconds slower (adjβ: 4.1, 95% CI: 0.9, 7.3) when their mothers had a BMI of 26 kg/m^2 compared with 22 kg/m^2. There was no association between maternal BMI and the number of executive function perseverative errors.

High and low maternal GWG z-scores were not associated with offspring SBIS composite IQ score (**Table 13**) or subscales (Table 15): visual reasoning (adjβ:-0.2, 95% CI: -0.9, 0.5), verbal reasoning (adjβ -0.8, 95% CI: -1.4, 0.1), quantitative reasoning (adjβ: 0.2, 95% CI: -0.9, 0.4), or short-term memory (adjβ: -0.2, 95% CI: -0.9, 0.5), compared with GWG z-score -1 to +1SD. Compared with children of mothers who gained from -1 to +1SD, offspring of mothers who had GWG >+1SD from the mean had lower executive function performance (adjβ: 15.3, 95% CI: 1.8, 28.1), indicated by a longer time to complete the TMT-B scale, after adjustment for confounders (**Table 13**). GWG was not associated with the number of perseverative errors on the WCST. These results did not vary by pre-pregnancy BMI.

None of the associations varied by maternal race, and the addition of other potential confounders had no meaningful impact on the results. Results were not meaningfully different after excluding high substance users (data available on request).

4.5 DISCUSSION

In a longitudinal cohort of mother-child pairs followed for 10 years, we observed that offspring IQ score and executive function performance decreased as pre-pregnancy BMI rose above 22 kg/m^2. Mothers with GWG >+1SD from the mean (>23 kg at 40 weeks) were more likely to have a child with lower executive function than a woman who gained less weight, but there were no differences with offspring intelligence. These associations were observed after adjusting for a

number of important confounders including maternal race, child sex, parity, income, maternal intelligence, the home environment, and prenatal substance use.

Executive function is used every day to plan, organize, and adjust to novel situations(5), yet is complex and remains difficult to define and measure. One accepted model suggests three main executive function constructs exist: 'inhibition', 'shifting', and 'updating'(157). The Trail Making Test Part B assessed 'shifting' and 'updating' constructs and the Wisconsin Card Sorting Test assessed 'shifting' and 'inhibition' constructs. Our results suggest the 'updating' dimension of executive function may be susceptible to excessive maternal weight gain or pre-pregnancy BMI, while 'inhibition' and 'shifting' may be more resilient. We are aware of only one other study that has assessed the independent relation between executive function with pre-pregnancy BMI and GWG. Buss et al. (2012) measured the 'inhibition' construct of executive function using the Go No-Go Task in a sample of 174 mother-child pairs(158). Consistent with our findings, this study observed no association between GWG and the 'inhibition' construct of executive function(158). In contrast to our findings, they observed lower offspring 'inhibition' performance among children of obese mothers. However, their study is limited by the use of total GWG (which cannot untangle effects of weight gain from effects of shortened gestational age) and adjustment for factors on the causal pathway (e.g., gestational age and birthweight), which may bias the findings. While executive function overall appears to be associated with maternal obesity, the null finding in `inhibition' may be null because it is difficult to measure construct-specific functioning.

Our results are consistent with the majority of literature that has reported lower intelligence among children of mothers with a higher BMI, even after adjusting for important confounders (14, 17, 18, 35, 38, 87). Bliddal et al. (2014) and Huang et al. (2014) identified a similar non-linear association between maternal BMI and offspring intelligence, with offspring intelligence peaking at a maternal BMI of 20-22 kg/m^2 (88, 159). Huang et al. (2014) reported a 2-point deficit in IQ scores among children of obese mothers compared with normal weight mothers, which is similar to the 3-point difference reported in our study. Although a 2-3 point difference in IQ is modest, this difference may be more drastic among offspring of severely obese women—a group of women rapidly increasing(40). We had too few severely obese women to evaluate this relationship directly. Additionally, while other factors such as genetics

may have a stronger impact on offspring IQ than maternal obesity, pre-pregnancy BMI has the advantage of being modifiable.

Few studies have examined the association between GWG and IQ, and the findings are mixed. Gage et al. (2013) reported a <1 point increase in child IQ with increasing trimester-specific GWG (14), with first and second trimester GWG having the strongest relationship with IQ. Despite the statistical significance, this increase in IQ may be too small to have clinical implications. Consistent with our findings, the remainder of studies reported no independent association between GWG and offspring IQ(8, 91, 111) . While the majority of the evidence suggests no independent relation between GWG and offspring intelligence, GWG may still be important for offspring intelligence when modified by pre-pregnancy BMI. However, the cohort used in our study and cohorts in previous studies may be too small to detect effect modification by BMI.

The extent to which our findings can be generalized to all obstetrical populations is uncertain. The MHPCD cohort consists of lower socioeconomic status women from the 1980s, some of whom used substances prenatally. These women were not substance abusers, but higher substance use was reported during the first trimester, when many women do not know they are pregnant. When we examined the impact of excluding these high substance-using women on our results, our estimates remained unchanged.

A potential limitation of this study is the reliance on self-reported pre-pregnancy weight, height, and total GWG. While some data suggest that BMI is correctly classified in 85% of women, other studies have shown that the accuracy of self-reported weight, height, and BMI varies by how heavy the mother is and other maternal characteristics including race/ethnicity and education(126). Unfortunately, we do not have information on the validity of self-reported weight and weight gain in this population. Lastly, the longitudinal nature of this study lends itself to attrition bias. However, the retention rate at 10 years was 83% and there was no difference in GWG, BMI, maternal race, or substance use between those with and without missing data at age 10, making it unlikely that this bias is of concern.

Our study had several unique strengths. The longitudinal nature of this study allowed us to assess offspring cognition at 10 years, a time point when domain-specific dysfunction can be measured. The objective nature and high construct validity and reliability of the cognitive assessment tools instills confidence that children are correctly classified. In addition, we

controlled for a number of important confounders including socioeconomic status, maternal intelligence, and home environment. Lastly, this study used a measure to assess GWG that is independent of gestational age, which is important when studying outcomes such as cognitive development that are associated with early delivery(80).

This study provides valuable insight into the relation between maternal obesity and long-term offspring intelligence and executive function in children at 10 years of age. In general, pre-pregnancy BMI remained more strongly associated with cognitive outcomes than GWG. Our findings bolster the notion that offspring of obese mothers may be at an increased risk of impaired cognition. Future research should expand on our findings by examining constructs of executive function and other domains of cognition potentially impacted by maternal obesity, and evaluate whether there is merit to screening children of obese mothers for cognitive delays.

4.6 TABLES AND FIGURES

Table 9: Maternal Characteristics at Enrollment and 10 years Postpartum (n=530)

	Overall N(%)
Enrollment	
Maternal Race	
White	254 (47.9)
Black	276 (52.1)
Marital Status	
Never Married	360 (67.9)
Married	170 (32.1)
Maternal Employment[1]	
No	389 (73.4)
Yes	141 (26.6)
Family Income ($ per month)	
<500	321 (60.6)
≥500	209 (39.4)
Prenatal alcohol use (any)	
Never used	131 (24.7)
Drank 1st trimester only	157 (29.6)
Drank 2+ trimesters	242 (45.7)
Prenatal Marijuana use (any)	
Never used	263 (49.6)
Smoked 1st trimester only	126 (23.8)
Smoked 2+ trimesters	141 (26.6)
Prenatal Cigarette use (any)	
Never used	197 (37.2)
Smoked 1st trimester only	44 (8.3)
Smoked 2+ trimesters	289 (54.5)
Prenatal Illicit Drug Use	
No	467 (88.1)
Yes	63 (11.9)
10 years Postpartum	
Maternal Depression	
Moderately Depressed ≥40	299 (56.4)
Not Depressed <40	231 (43.6)
HOME Stimulation Scale	
Lower stimulation <16	457 (86.3)
Higher Stimulation ≥16	73 (13.8)
Maternal IQ	
Low Average (≤89)	319 (60.2)
Average or Above (>89)	211 (39.8)

[1]Includes school attendance; **HOME**: Home Observation for Measurement of the

Table 10: Offspring Intelligence and Executive Function by Maternal Characteristics (n=530)

	Intelligence (IQ) Mean(SD)	Executive Function Perseverative Errors Mean(SD)	Executive Function Time to complete Part B Mean(SD)
Enrollment			
Maternal Race			
White	95.9 (11.3)*	22.5 (10.3)*	93.7 (38.9)*
Black	87.6 (10.3)	24.9 (9.0)	111.8 (44.1)
Marital Status			
Never Married	90.1 (11.2)*	24.2 (9.4)	103.7 (42.7)
Married	94.7 (11.8)	23.0 (10.5)	102.2 (42.7)
Maternal Employment[1]			
No	91.0 (11.6)	23.9 (9.6)	104.5 (43.7)
Yes	93.2 (11.5)	23.2 (10.1)	99.6 (39.4)
Family Income ($ per month)			
<500	90.0 (10.9)*	24.3 (9.7)	107.1 (44.8)*
≥500	94.0 (12.0)	22.9 (9.7)	97.2 (38.5)
Prenatal alcohol use (any)			
Never used	91.2 (11.6)	23.4 (9.2)	103.2 (41.6)
Drank 1st trimester only	91.3 (11.4)	23.6 (10.3)	102.6 (45.7)
Drank 2+ trimesters	91.9 (11.7)	24.1 (9.7)	103.5 (41.3)
Prenatal Marijuana use (any)			
Never used	92.2 (11.6)	23.2 (10.1)	102.7 (42.3)
Smoked 1st trimester only	91.6 (11.8)	24.1 (8.8)	100.7 (40.2)
Smoked 2+ trimesters	90.4 (11.4)	14.6 (9.9)	106.3 (45.5)
Prenatal Cigarette use (any)			
Never used	90.9 (11.3)	23.6 (9.7)	106.2 (42.9)
Smoked 1st trimester only	91.3 (12.9)	23.3 (8.4)	104.1 (41.2)
Smoked 2+ trimesters	92.1 (11.6)	23.9 (10.0)	100.9 (42.8)
Illicit Drug Use			
No	90.1 (11.4)*	23.9 (9.6)	104.5 (43.4)
Yes	96.2 (11.6)	22.4 (10.8)	93.6 (35.6)
Maternal Depression			
Moderately Depressed ≥40	90.9 (11.5)	24.3 (9.7)	104.5 (45.5)
Not Depressed <40	92.4 (11.6)	23.1 (9.7)	101.5 (38.7)
10 years Postpartum			
HOME Stimulation Scale			
Lower Stimulation <16	90.7 (11.3)*	24.2 (9.8)*	105.8 (42.8)*
Higher Stimulation ≥16	97.5 (11.7)	21.3 (9.3)	86.8 (38.1)
Maternal IQ			
Low Average (≤89)	87.9 (10.7)*	25.2 (9.5)*	109.3 (44.1)*
Average or Above (>89)	97.2 (10.7)	21.6 (9.7)	94.0 (38.7)

SD-standard deviation; HOME- Home Observation for Measurement of the Environment
* P<0.05 [1]Includes school attendance

Table 11: Unadjusted Association between Offspring Intelligence and Executive Function and Pre-pregnancy Body Mass Index and Gestational Weight Gain (n=530)

	N	Intelligence (IQ) Mean (SD)	Executive Function Perseverative Errors Mean (SD)	Executive Function Time to complete Part B (in seconds) Mean (SD)
Pre-pregnancy Body Mass Index[1]				
Underweight	74	92.9 (11.2)	21.6 (8.8)	102.6 (42.3)
Normal Weight	311	92.2 (11.4)	24.2 (10.1)	101.5 (42.2)
Overweight	94	90.2 (11.5)	24.1 (9.4)	103.0 (39.6)
Obese	51	88.4 (12.5)	23.8 (9.2)	114.8 (50.4)
GWG z-score				
<-1 SD	130	92.1 (9.8)	25.3 (10.1)	100.0 (39.6)
-1 to +1SD	354	91.6 (11.9)	23.6 (9.7)	102.3 (42.3)
>+1 SD	45	90.4 (12.5)	22.3 (9.6)	116.6 (49.3)

Underweight (BMI <18.5 kg/m^2); Normal weight (BMI 18.5-24.9 kg/m^2); Overweight (BMI 25-29.9 kg/m^2); Obese (BMI ≥30 kg/m^2); SD-standard deviation

[1]None of the above comparisons were statistically different at $p<0.05$

Table 12: Association between Pre-pregnancy Body Mass Index and Offspring Intelligence and Executive Function (n=530)

	Intelligence (IQ) adjustedβ (95% CI)[1]	Executive Function Perseverative Errors adjIRR (95% CI)[1]	Executive Function Time to complete Part B adjβ (95% CI)[1]
Pre-pregnancy Body Mass Index[2]			
18	-0.3 (-2.6, 1.9)	0.93 (0.9, 1.0)	3.3 (-6.0, 12.6)
20	-0.2 (-1.3, 0.9)	0.97 (0.9, 1.0)	1.7 (-3.1, 6.4)
22	Reference	Reference	Reference
24	-0.5 (-0.9, -0.1)	1.0 (1.0, 1.4)	2.0 (0.4, 3.6)
26	-1.1 (-1.8, -0.3)	1.0 (0.9, 1.1)	4.1 (0.9, 7.3)
28	-1.5 (-2.6, -0.4)	1.0 (0.9, 1.1)	6.0 (1.3, 10.8)
30	-2.1 (-3.6, -0.5)	0.9 (0.9, 1.1)	8.1 (1.8, 14.5)
32	-2.5 (-4.5, -0.6)	0.9 (0.9, 1.1)	10.1 (2.2, 18.0)
34	-3.2 (-5.6, -0.8)	0.9 (0.8, 1.1)	12.7 (2.8, 22.7)

β-Beta coefficient; IRR- Incidence Rate Ratio; CI- Confidence Interval

[1]Adjusted for maternal race, child sex, parity, income, maternal intelligence, the home environment, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs)

[2] Pre-pregnancy body mass index modeled using a linear spline with a single knot specified at a BMI of 22 kg/m^2

Table 13: Association between Gestational Weight Gain z-score and Offspring Intelligence and Executive Function (n=530)

	Intelligence (IQ) adjustedβ (95% CI)[1]	Executive Function Perseverative Errors adjIRR (95% CI)[1]	Executive Function Time to complete Part B adjβ (95% CI)[1]
GWG z-score			
<-1 SD	1.6 (-0.4, 3.7)	1.05 (0.9, 1.2)	-0.33 (-8.8, 8.1)
-1 to +1 SD	Reference	Reference	Reference
>+1 SD	-1.0 (-4.2, 2.2)	0.94 (0.8, 1.1)	15.3 (1.8, 28.1)

β-Beta coefficient; IRR- Incidence Rate Ratio; CI- Confidence Interval, SD-standard deviation
[1]Adjusted for maternal race, child sex, parity, income, maternal intelligence, the home environment, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs)

Table 14: Association between Gestational Weight Gain z-score and Offspring Intelligence Subscales (n=530)

	IQ Visual adjβ (95% CI)[1]	IQ Verbal adjβ (95% CI)[1]	IQ Quantitative adjβ (95% CI)[1]	IQ Short term memory adjβ (95% CI)[1]
GWG z-score				
<-1 SD	1.3 (-1.1, 3.8)	2.2 (-0.1, 4.5)	0.6 (-1.8, 3.0)	1.7 (-0.9, 4.4)
-1 to +1 SD	Reference	Reference	Reference	Reference
>+1 SD	-1.9 (-5.8, 1.9)	0.8 (-2.8, 4.4)	-1.4 (-5.0, 2.4)	-1.2 (-5.4, 2.9)

β-Beta coefficient; CI- Confidence Interval; SD-standard deviation
[1]Adjusted for maternal race, child sex, parity, income, maternal intelligence, the home environment, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs)

Table 15: Association between Pre-pregnancy Body Mass Index and Offspring Intelligence Subscales (N=530)

	IQ Visual adjβ (95% CI)[1]	IQ Verbal adjβ (95% CI)[1]	IQ Quantitative adjβ (95% CI)[1]	IQ Short term memory adjβ (95% CI)[1]
BMI[2]				
18	0.7 (-0.1, 1.4)	0.7 (-0.03, 1.3)	0.9 (0.2, 1.6)	0.6 (-0.2, 1.4)
22	Reference	Reference	Reference	Reference
25	-0.5 (-1.0, 0.1)	-0.5 (-1.0, 0.02)	-0.7 (-1.2, -0.2)	-0.5 (-1.0, 0.1)
30	-1.3 (-2.7, 0.1)	-1.3 (-2.7, 0.06)	-1.8 (-3.2, -0.4)	-1.2 (-2.8, 0.4)
35	-2.1 (-4.5, 0.2)	-2.1 (-4.4, 0.1)	-2.9 (-5.2, -0.7)	-1.9 (-4.5, 0.6)

β-Beta coefficient; CI- Confidence Interval
[1]Adjusted for maternal race, child sex, parity, income, maternal intelligence, the home environment, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs)
[2] Pre-pregnancy body mass index modeled using a linear spline with a single knot specified at a BMI of 22 kg/m^2

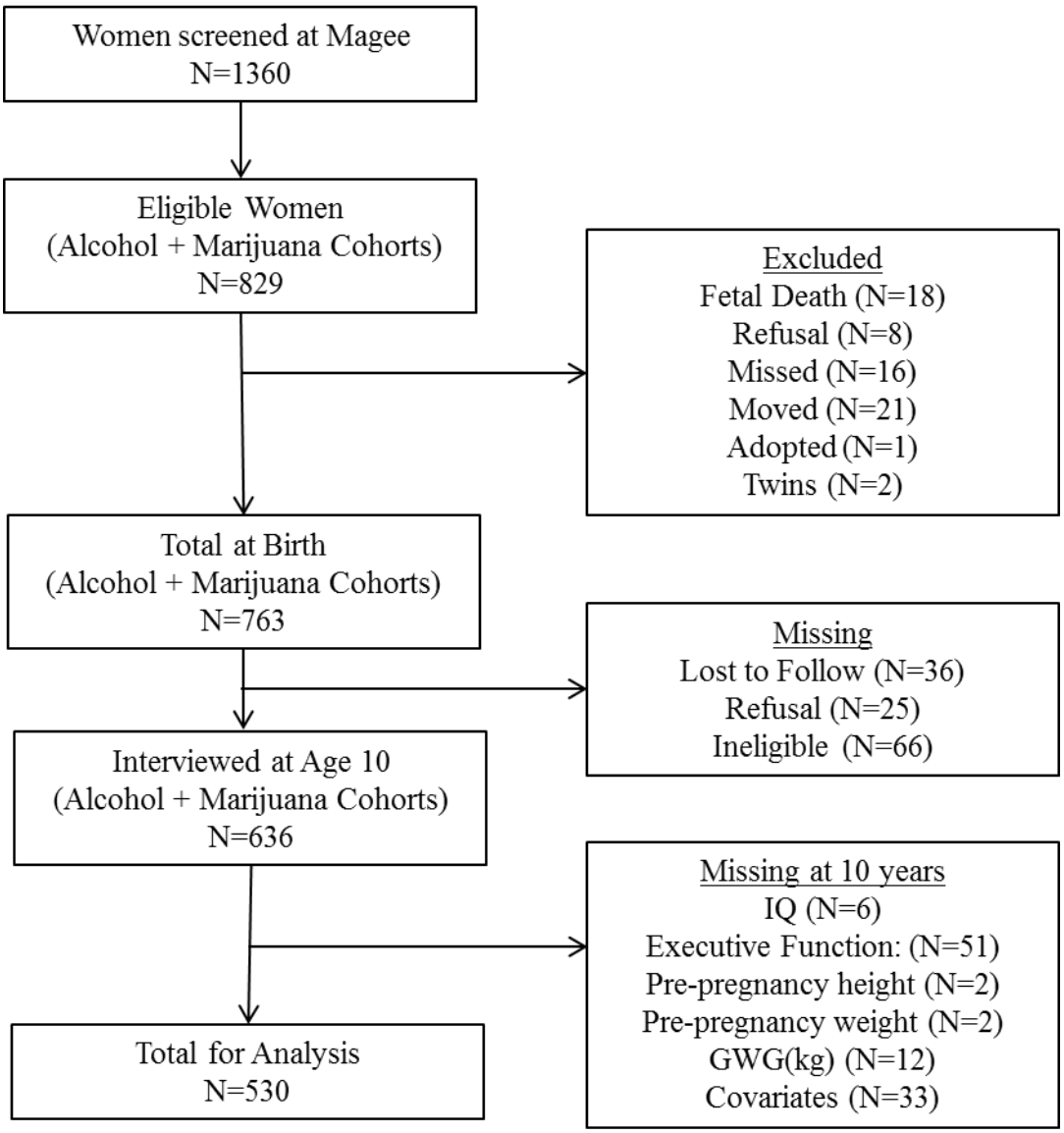

Figure 3: Participant Flow Diagram for Maternal Health Practices and Child Development cohort, 1983-1986

A) B)

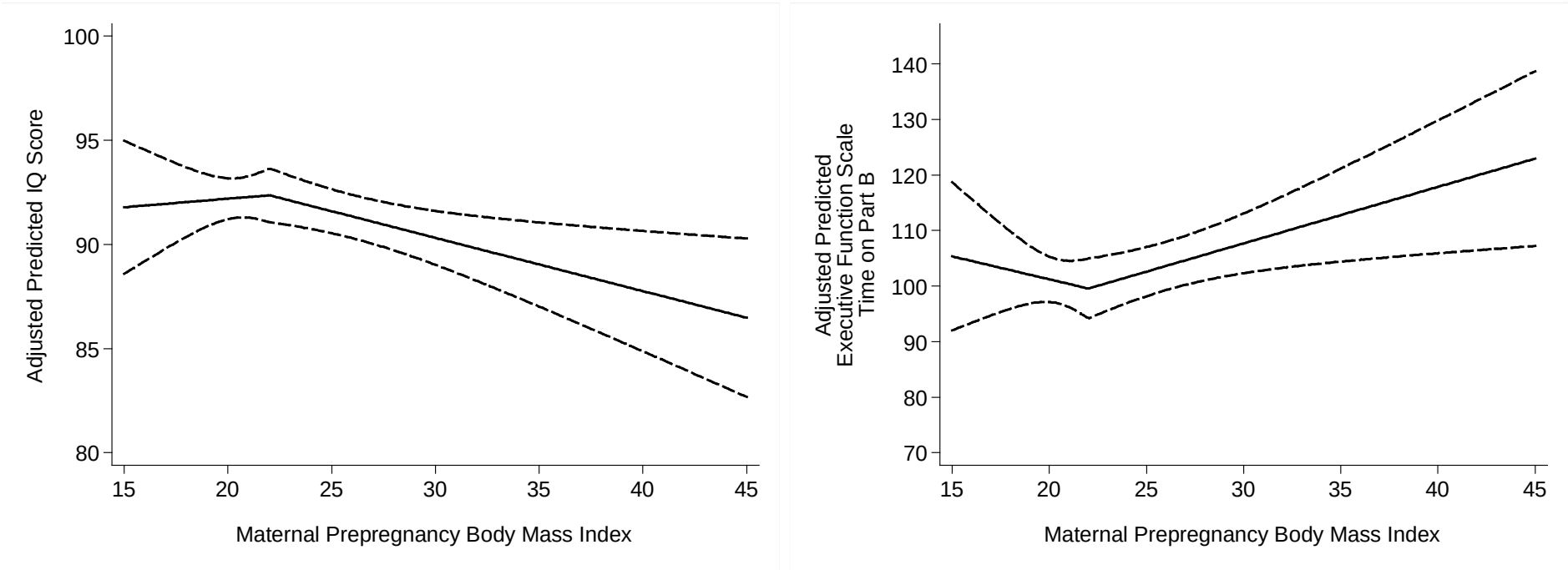

Figure 4: Association between Pre-pregnancy Body Mass Index and Offspring Intelligence (Panel A) and Offspring Executive Function (Panel B), n=530

5.0 GESTATIONAL WEIGHT GAIN, PRE-PREGNANCY BODY MASS INDEX, AND OFFSPRING ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS AND BEHAVIOR AT AGE 10

5.1 ABSTRACT

Our objective was to assess offspring attention-deficit hyperactivity disorder (ADHD) symptoms (inattention and impulsivity) and emotional/behavioral impairments at age 10 in relation to gestational weight gain (GWG) and pre-pregnancy body mass index (BMI). Mother-infant dyads (n=763) enrolled in a birth cohort study were followed through pregnancy to 10 years. Child ADHD symptoms were assessed with the Conners' Continuous Performance Test. Child behavior was assessed by parent and teacher ratings on the Child Behavior Checklist and Teacher Report Form, respectively. Self-reported total GWG was converted to gestational-age-standardized z-scores. Multivariable linear and negative binomial regressions were used to estimate effects of GWG and BMI on outcomes while adjusting for maternal race, child sex, parity, income, employment, maternal intelligence, home stimulation, and prenatal substance use. The mean(SD) total GWG(kg) was 14.5(5.9), and 28% of women had a pregravid BMI ≥25. On the Child Behavior Checklist, pre-pregnancy obesity was associated with increased offspring problem behaviors including withdrawn or somatic complaints (adj β: 4.9 points, 95% CI: 1.7, 8.1), delinquent or aggressive behaviors (adj β: 4.2 points, 95% CI: 1.1, 7.3), and attention problems (adj β: 3.5 points, 95% CI: 1.2, 5.8), compared with children of normal weight mothers. There were non-significant trends towards increased offspring impulsivity with low GWG among lean mothers (adj IRR: 1.2, 95% CI: 0.9, 1.5) and high GWG among overweight mothers (adj IRR: 1.7, 95% CI: 0.9, 2.8), but additional behavior and ADHD symptoms did not differ by GWG z-score. We found little evidence that GWG is related to child ADHD symptoms

or behavior at age 10. Interventions to reduce maternal obesity may have an impact on child ADHD and behavioral development.

5.2 INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is the most common developmental disability among children in the United States, affecting 7% to 9% of 5-17 year olds (19). Annually, the United States spends an excess of $42 billion dollars on medical treatment as well as individual and parental lost wages (31) related to ADHD. ADHD is diagnosed after a psychiatric, psychological, and neurologic assessment consisting of in-person observations and evaluations to identify if a child presents with at least 6 symptoms of inattention and hyperactivity/impulsivity in more than one setting (e.g. school, home, etc.)(2). When diagnosis is not feasible due to the demanding protocol, characteristics of ADHD, including somatic complaints, anxious/depressed feelings, and deviant or aggressive behaviors(160), are often measured by parent and/or teacher assessments(25). These symptoms, though not required for diagnosis of ADHD, are beyond the expected behaviors from an average child or adolescent. They limit a child's ability to learn and behave, contributing to lower academic achievement, fewer social relationships, and decreased professional employment and relationship success(26). There is no cure for ADHD, and treatments vary in effectiveness(6). Medications are costly and may have unfavorable side effects, while behavioral therapy and social skills training are not always fully effective without the addition of pharmacotherapy(7). Understanding potential preventive measures to reduce ADHD is a public health priority (161).

Biological evidence suggests maternal pre-pregnancy body mass index (BMI) and weight gain during pregnancy are potentially modifiable factors for offspring ADHD or related emotion/behavior disruptions(8, 62). Obesity is often accompanied by high blood concentrations of pro-inflammatory cytokines and leptin(51, 52), which may cross the placenta and cause over- and under-activation of a number of fetal neurodevelopmental processes(55, 56), including neuron proliferation and differentiation (57), myelination, and synapse formation (57). Animal studies have also reported that offspring of mothers consuming a high-fat diet contributing to

excessive weight gain during pregnancy had increased circulating pro-inflammatory cytokines in the hypothalamus and hippocampus, where behavioral regulation systems are located (61) (62).

Nevertheless, few studies have rigorously explored these associations in humans. A small body of evidence suggests that maternal obesity is associated with a modest increase in deviant and aggressive offspring problem behaviors (16, 101) and an increased risk of learning disability diagnosis (including ADHD) in early childhood (100). A single study examining GWG reported no relation with offspring problem behaviors (158). Moreover, most previous research has not controlled for important confounders such as socioeconomic status or stimulation in the home environment. The majority of studies assessed ADHD and behavior problems in children less than 6 years, yet the updated Diagnostic Statistical Manual-V increased the age range of ADHD diagnosis to before 12 years(162). Therefore, assessment of behavior later in childhood may capture more children affected by behavioral disruptions. Our objective was to assess offspring ADHD symptoms (inattention and impulsivity) and emotional/behavioral impairments at age 10 in relation to GWG and pre-pregnancy BMI while controlling for a number of important confounders.

5.3 METHODS

We used data from a birth cohort designed to study the effects of prenatal substance use on long-term offspring outcomes(149). Women ≥18 years old were approached at a prenatal clinic at Magee-Womens Hospital in Pittsburgh, Pennsylvania from 1983-1986. Women were enrolled in this cohort based on 1st trimester use of alcohol and marijuana. The alcohol cohort included women who drank ≥3 drinks per week and an equal sample who drank <3 drinks per week. The marijuana cohort included women who smoked ≥2 joints per month and an equal sample who smoked <2 joints per month. From the pool of 1360 women screened for eligibility during the 1st trimester, 15% refused participation, and 763 women were followed through pregnancy and delivered a live-born singleton infant (Figure 1). The majority of women were low substance users during the first trimester (drank <3 drinks per week (n=508, 66%) or smoked <2 joints per month (n=516, 67%)). There was 48% overlap in the alcohol and marijuana groups.

The first and second prenatal visits took place at a median of 18.7 weeks (IQR: 17.1, 20.7) and 31.1 weeks (IQR: 29.4, 33.1), respectively. Mother-child pairs were followed up at delivery [median 39 weeks (IQR: 38-40)], 8 months, 18 months, 3, 6, and 10 years postpartum. At each visit, children and mothers were assessed by separate trained interviewers who gathered data on maternal sociodemographic status, substance use, maternal psychological status, and offspring cognitive development. Our analysis focused on the 10 year postpartum visit to capture the most children with behavioral problems. Women provided informed, written consent and this study was approved by the University of Pittsburgh Institutional Review Board (IRB #PRO14020264)

Women self-reported their pre-pregnancy weight and height at the first study visit. Pre-pregnancy BMI [weight (kg)/ height (m^2)] was categorized as underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight(BMI 25-29.9 kg/m^2), or obese (BMI ≥30 kg/m^2)(117). Mothers were asked at delivery, "How much total weight did you gain during this pregnancy?" Total GWG was converted to z-scores according to gestational age-standardized charts for normal weight women(115). We applied the normal weight z-score charts to all women because we aimed to evaluate whether the association between GWG z-scores and outcomes varied by pre-pregnancy BMI.

At the 10-year follow-up visit, parents (or primary care-givers) and teachers assessed child behavior using the Child Behavior Checklist (CBCL) and the Teacher Report Form (TRF), respectively. Both scales have a high test-retest reliability (0.89 on the CBCL and 0.92 on the TRF)(163, 164) and address the same child behavior and emotional problems. To best characterize impairments consistent with ADHD, we focused on internalizing behaviors (withdrawn behavior, somatic complaints, and anxious/depressed), externalizing behaviors (delinquent behavior and aggressive behavior), and attention problems. The internalizing and externalizing behavior summary scores and the individual score for the attention subscale were standardized based on the child's age and gender. A higher score indicates worse behavior problems(163, 164). We studied each score as a continuous variable and as a dichotomous variable (average behavior problems(<67) versus borderline clinically significant behavior problems (≥67))(163, 164).

Child ADHD symptoms were also assessed using an objective test: the Connors' Continuous Performance Test (CPT)(165). The CPT is a computerized task where various shapes

in different colors are flashed across a screen and the child is instructed to respond only when a specified target appears. The number of times the child misses the target is measured by omission errors, which indicate inattention. The number of times the child incorrectly responds to the target is measured by commission errors, which indicate impulsivity. Children were given 3 trials of the CPT, and the mean number of omission and commission errors were calculated.

At the first study visit during pregnancy, trained interviewers collected information on sociodemographic characteristics (i.e. maternal age, race, parity, employment, education, income, marital status) and the quantity and frequency of substance use during the year before pregnancy and during specific segments of the first trimester to calculate a more accurate depiction of first trimester use (137). At two prenatal study visits and delivery, alcohol, marijuana, cigarette, and cocaine use were collected and summarized as average daily drink volume, average daily joints, cigarettes per day, and cocaine use (yes/no) for each trimester, respectively. We categorized each substance into overall pregnancy use to best capture non-users throughout pregnancy, users during the first trimester only when many women do not know they are pregnant, and use throughout pregnancy. Maternal depression at the first study visit was measured using the Center for Epidemiological Studies Depression Scale (138)and anxiety was measured using the Spielberger's State-Trait Anxiety Personality Inventory(139). The Home Observation for Measurement of the Environment (HOME) was administered to mothers or caretakers at 10 years postpartum to assess the quality and quantity of support for cognitive and social development in the home environment(152). We studied the HOME scale as a continuous variable in models and as a dichotomous variable for descriptive statistics (under stimulated (<16) versus adequate stimulation (≥16)). Maternal intelligence was assessed at 10 years postpartum using the two-subtest version of the Wechsler Adult Intelligence Scale full scale (WAIS)(151).

5.3.1 Statistical analysis

Student's t-tests and one-way ANOVAs were used to determine differences in child ADHD symptoms and behavior, GWG, and BMI by maternal characteristics. Pearson correlation coefficients were used to assess the strength of association between scales. Multivariable regression models were used to estimate beta coefficients or incidence rate ratios (IRR) and their

corresponding 95% confidence intervals (CI) for associations between pre-pregnancy BMI and offspring behaviors. Linear regression was used for modeling internalizing, externalizing, and attention scores. Multivariable Poisson regression was used for the inattention score due to its skewed distribution. Negative binomial regression was used for modeling the impulsivity score, which had an over-dispersed distribution. Similar models were built for GWG z-scores as the main exposure.

To allow for flexible, non-linear relationships, we modeled the relation between pre-pregnancy BMI and outcomes using splines. To select the best fitting spline, we compared restricted cubic spline terms with 3 knots at the 10th, 50th, and 90th percentiles and linear spline terms with 1 or 2 knots using Akaike information criterion (AIC) and Bayesian information criterion (BIC) (153). For all outcomes, we selected a linear spline term with 1 knot at the observed point of inflection at a BMI of 22kg/m^2. After model estimation, we used the '`xblc`' command in Stata to calculate adjusted coefficients and 95% CI for select BMI values compared with a BMI of 22kg/m^2 as the referent. Associations between GWG and behavioral outcomes did not deviate from linearity, so we categorized z-scores into 3 groups (<-1SD, -1 to +1SD, >+1SD) for ease of interpretation.

To test for effect modification between pre-pregnancy BMI and race, pre-pregnancy BMI and offspring sex, and GWG and pre-pregnancy BMI, statistical interaction terms were introduced into fully adjusted models. Effect modification was tested using an $\alpha = 0.05$ threshold based on the Wald p-values (linear regression) or likelihood ratio tests (Poisson and negative binomial regression). We built parsimonious models by adjusting for confounders that, if removed from the model, changed the effect estimate of the primary exposure by >10%(142). We included maternal race, parity, income, employment status, marital status, education, maternal intelligence, maternal depression, maternal anxiety, home environment stimulation, substance use, child gender, and pre-pregnancy BMI (in GWG models only) as potential confounders. Prenatal substance use variables were forced into models based on *a priori* decisions. Adjusted predicted behavior scores and ADHD symptom scores along with 95% CI were plotted with covariates set to population means.

We performed a sensitivity analysis by excluding high marijuana (>1 joint per day)(154), alcohol (>1 drink a day)(119), cigarette (>=20 cigarettes per day)(155), cocaine (any use), and

illicit drug (any use) users during the 1st or 3rd trimester. Analyses were conducted in STATA, version 13.0, software(156).

5.4 RESULTS

At delivery, there were 763 mother-child dyads. At the 10 year study visit, 636 (83%) pairs remained. We excluded records with incomplete data on pre-pregnancy weight and height (n=4), GWG (n=13), ADHD symptoms or behavioral assessments at age 10 (n=79), or other covariates (n=29) (**Figure 5**). A total of 511 mother-child pairs were used in the final analysis. Maternal GWG, pre-pregnancy BMI, maternal race, prenatal substance use, and child behaviors of interest did not differ between those with and without missing data (data available on request).

The mean (SD) pre-pregnancy BMI was 23.4 (5.7) kg/m^2 and the mean (SD) gestational weight gain in the cohort was 14.2 (5.9) kg. The majority of women at study enrollment were unmarried, unemployed, normal weight, had an income <$500 a month (<$1,400 per month in 2014(118)) and were moderately depressed (**Table 16**). Over half of the women reported their race as Black. Most women reported no prenatal use of illicit drugs or marijuana. At 10 years postpartum, mothers tended to provide a low stimulating home environment for their offspring and to have a below average IQ.

Parents rated 10% (n=49) and 12% (n=63) of children as having borderline clinically significant externalizing or internalizing behaviors, respectively. These respective values were 15% (n=77) and 8% (n=40) based on teacher-ratings. Only 5% (n=23) and 2% (n=11) of children were rated by both informants as having borderline clinically high externalizing and internalizing symptoms, respectively. The median (range) number of objective omission errors was 1 (0-6) and the median (range) number of commission errors was 2 (0-24). There was low to moderate correlation between parent and teacher ratings for externalizing (r=0.33), internalizing (r=0.21), and attention (r=0.40) scales. The correlation was also low between objective attention and impulsivity scales (r=0.23).

Maternal and child characteristics that were associated with child internalizing and externalizing behaviors and attention scores differed based on whether they were rated by a parent or teacher (**Table 17**). Teacher-rated behaviors tended to be worse among children of

Black mothers, mothers providing a low stimulating home environment, mothers with below average IQ, mothers with moderate depression, and mothers with a monthly income <$500 (<$1,400 per month in 2014(118)) compared with their counterparts. Parent-rated behaviors differed from teacher-rated behaviors in that they tended to be worse among children of White mothers, mothers with above average IQ, and mothers who used cigarettes during two trimesters. Apart from these differences, parent and teacher ratings of offspring behavior were similarly associated with maternal and child characteristics. There were fewer objective impulsivity errors among children of mothers with average or above IQ, but objective inattention errors did not differ by any maternal characteristics (Appendix A: **Table 26**).

In bivariate analyses, maternal pre-pregnancy obesity was associated with ADHD symptoms and behaviors (Table 17). Children of obese mothers scored 3 to 4 points worse on the parent-rated internalizing, externalizing, and attention scales, compared with children of normal weight mothers. However, there were no differences in behavior scores by GWG categories. This same trend in pre-pregnancy BMI and GWG persisted in unadjusted associations (Appendix A: **Tables 27 & 28**).

Maternal race, parity, income, employment status, maternal intelligence, maternal depression, home environment stimulation, child gender, and pre-pregnancy BMI (GWG models only) met our definition of confounding in all models. After adjusting for confounders, maternal obesity was significantly associated with 4.9-, 4.2-, and 3.5-point increases in parent-rated offspring internalizing, externalizing, and attention scores, respectively, compared with children of normal weight mothers (**Table 18**). We observed a similar, but non-significant, trend for teacher-rated behavior problems. Using spline regression, we found that parent- and teacher-rated offspring internalizing, externalizing, and attention behavior problems tended to be lowest among mothers with pregravid BMI of 22 kg/m^2 and increased with both lower and higher BMI values (**Figure 6; Table 19**). For instance, a pregravid BMI of 28 kg/m^2 was associated with a 2.2-point (95% CI: 1.1, 3.4) increase in parent-rated and a 1.2 point (95% CI: -0.1, 2.5) increase in teacher-rated offspring externalizing problems, compared with a BMI of 22kg/m^2. Associations were similar for low BMI values, but were only borderline statistically significant for parent-rated scales.

When we examined objective measurements of offspring attention and impulsivity errors, we found that after confounder adjustment, maternal underweight was associated with 20%

fewer offspring attention errors (adjusted IRR: 0.8, 95% CI: 0.6, 0.9) and maternal obesity was associated with 40% more impulsivity errors (adjusted IRR: 1.4, 95% CI: 1.0, 1.8), compared with children of normal weight mothers (Table 18).

The association between GWG and offspring impulsivity errors varied by pre-pregnancy BMI. Among lean mothers (BMI <25), low GWG was associated with 20% more offspring impulsivity errors (adj IRR: 1.2, 95% CI: 0.9, 1.5) compared with GWG -1 to +1SD (**Table 20**). Among overweight mothers (BMI ≥25), high GWG was associated with 70% more impulsivity errors (adj IRR: 1.7, 95% CI: 0.9, 2.8, 3.2) compared with GWG -1 to +1SD (Table 20). Maternal GWG z-score was not associated with parent- or teacher-rated offspring behavior outcomes or objective measurements of offspring attention after confounder adjustment (Table 20) and the associations did not vary by pre-pregnancy BMI.

Neither maternal race nor child sex modified any of the relations above. Results were not meaningfully different after excluding high substance users or after the addition of other potential confounders (data available on request).

5.5 DISCUSSION

In this longitudinal birth cohort followed to 10 years, we assessed ADHD symptoms and behavioral problems using tools that are consistent with those administered during an ADHD diagnostic evaluation(166). We found that maternal obesity was associated with more objectively-assessed offspring impulsivity errors, and both high and low pre-pregnancy BMI were associated with more offspring behavior problems. The results were generally consistent whether parents or teachers rated behaviors. Maternal GWG was associated with offspring impulsivity errors depending on pre-pregnancy BMI. In contrast, GWG was not related to any other offspring ADHD symptoms or behavior problems. These relations remained after adjustment for factors including socio-economic status and the postnatal home environment.

Our study was the first to our knowledge to use both objective and subjective tools to evaluate offspring ADHD symptoms and behaviors in relation to both pre-pregnancy BMI and GWG. Our results relating BMI to subjectively-assessed offspring behaviors are consistent with those from an Australian cohort of 2,900 2-year-olds and their mothers, which found that for

each 4-kg/m^2 increase in maternal pre-pregnancy BMI, there was a 0.5-point increase in externalizing problems as assessed using the Child Behavior Checklist(101). In a Swedish cohort of over 1,000 pairs of mothers and their 5-year-old children, Rodriguez et al. (2010) reported that obese compared with normal weight mothers had a 2-fold increase in teacher-rated, but not parent-rated, attention problems as assessed by the Strengths and Difficulties Questionnaire. Additionally, in a European cohort, maternal overweight was associated with increased parent-rated externalizing problems in offspring 3-4 years of age(17). We observed larger effect sizes than these aforementioned studies, which may be due to our study of older children, in whom behavior problems may be more fully developed(167).

Two studies found no association between pre-pregnancy BMI and offspring behavior(102, 103). Chen et al. (2014) reported an increased risk of offspring ADHD diagnosis after 3 years of age among over 600,000 children of obese mothers, but the association was null after adjustment for familial confounding through a sibling analysis(103). This study highlights the importance of unmeasured confounding from the postnatal environment, a potential bias limiting previous studies. Our study, however, adjusted for a measure of the postnatal environment. Our findings may differ from Chen et al. (2014) because they ascertained ADHD diagnosis based on registry and medical record data. This captures only the most severe cases, while our study and previous studies assessed offspring behavioral symptoms consistent with ADHD, which may include a larger number of children with a range of symptoms. A sibling analysis is a more rigorous method to control for the postnatal environment than confounder adjustment alone, but limitations in this method still exist.

Consistent with the only other study that we are aware of(158), we found no independent relation between maternal GWG and offspring internalizing, externalizing, and attention behaviors or offspring impulsivity and attention errors. We did observe that offspring of lean mothers with low GWG and offspring of overweight mothers with high GWG had an increased number of objective impulsivity errors. Excessive GWG may increase the already high concentrations of inflammatory markers present in the blood of obese women(168). Similarly, underweight women may have nutrient deficiencies that are exacerbated with low GWG. Both excessive inflammation and nutrient deficiency pathways may interfere with offspring brain development(76, 169).We may not have observed the same trend with attention errors because of the limited variation in the number of attention errors in this cohort.

Our findings may have limited generalizability to common obstetric populations. The MHPCD cohort is a lower socio-economic group of women from the 1980's, who used substances prenatally. Yet, even among this somewhat higher-risk population, we still observed an important relation between maternal obesity and child behavioral development. Furthermore, substance use was reported during the first trimester when many women do not know they are pregnant(170) and our conclusions did not change when we excluded women with heavy use 1st trimester use.

An additional limitation is that we were not able to diagnose ADHD using gold-standard methodology; rather, we assessed attention and impulsivity, two of the core symptoms required for ADHD diagnosis. Additionally, we used two informants to assess emotional and behavioral symptoms often identified in children with ADHD, although not part of the diagnostic criteria(25). Despite the low correlation between parent- and teacher-rated scales, the overall relation with pre-pregnancy BMI and GWG was consistent across informants. The use of multiple informants provided more valid estimates of behavior.

The longitudinal nature of this study lends itself to attrition bias. However, the 83% retention rate at 10 years and the lack of difference in GWG, BMI, and other key variables between those with and without missing data at 10 years provides confidence that selection bias may not be a major concern. Additionally, this study was able to assess prenatal exposures and long-term offspring cognition, which contributes new information since most previous studies only assessed children younger than 6 years of age.

Lastly, this study is limited by the reliance on self-reported pre-pregnancy weight, height, and total GWG. Studies have shown that the accuracy of self-reported weight, height, and BMI may vary by maternal weight, race/ethnicity, or other factors (126), which makes it difficult to predict the direction and magnitude of the bias this may cause(128).

A unique strength of this study is our use of gestational age-standardized GWG z-scores to classify weight gain. This classification allows us to separate the effect of weight gain from the effect of early gestational age at delivery, which is important when studying cognitive development and other outcomes related to preterm birth(80). Additionally, adjustment for prenatal substance use, socioeconomic factors, maternal psychological status, and home environment allowed us to address important confounding factors.

In order to better understand the joint relation between maternal BMI and GWG with offspring ADHD, larger cohort studies with diverse, representative populations are needed. Future studies should also aim to assess offspring ADHD using a gold-standard diagnosis in addition to behavior/emotion symptoms in late childhood to inform an inclusive group of affected children. The 3- to 4-point increase we observed in offspring externalizing and internalizing behavior scores among children of obese mothers compared with children of normal weight mothers may not be meaningful at an individual level, but may have a substantial impact on child behavior in the population. Preconception counseling to reduce weight before pregnancy may be an important step towards alleviating the familial and societal burden of ADHD. However, since nearly 50% of pregnancies are unplanned (41), future studies should aim to assess the underlying etiologic mechanisms of behavioral development and determine whether interventions during pregnancy would be an effective method to reduce the impact of obesity on offspring behavior.

5.6 TABLES AND FIGURES

Table 16: Characteristics of the Maternal Health Practices and Child Development Cohort, Pittsburgh, PA (1983-1986) at Enrollment and 10 years Postpartum in Pittsburgh, PA (n=511)

	Overall N(%)
Enrollment or Delivery	
Maternal Race	
White	250 (48.9)
Black	261 (51.1)
Marital Status	
Never Married	342 (66.9)
Married	169 (33.1)
Maternal Employment[1]	
No	372 (72.8)
Yes	139 (27.2)
Family Income ($ per month)	
<500	311 (60.9)
≥500	200 (39.1)
Pre-Pregnancy Body Mass Index	
Underweight	73 (14.3)
Normal Weight	297 (58.1)
Overweight	92 (18)
Obese	49 (9.6)
Prenatal Alcohol use	
Never used	129 (25.2)
Drank 1 trimester	145 (28.4)
Drank 2+ trimesters	237 (46.4)
Prenatal Marijuana use	
Never used	254 (49.7)
Smoked 1 trimester	125 (24.5)
Smoked 2+ trimesters	132 (25.8)
Prenatal Cigarette use	
Never used	194 (37.9)
Smoked 1 trimester	44 (8.6)
Smoked 2+ trimesters	273 (53.4)
Prenatal Illicit Drug Use	
No	452 (88.5)
Yes	59 (11.5)
Maternal Depression Scale	
Not Depressed <40	231 (43.6)
Moderately Depressed ≥40	299 (56.4)
Child Sex	

Table 16 Continued

Female	253 (49.5)
Male	258 (50.5)
10 years Postpartum	
HOME Stimulation Scale	
Under stimulated <16	437 (85.6)
Stimulated ≥16	74 (14.5)
Maternal IQ	
Below Average (≤89)	300 (58.7)
Above Average (>89)	211 (41.3)

Underweight (BMI <18.5 kg/m^2); Normal weight (BMI 18.5-24.9 kg/m^2); Overweight (BMI 25-29.9 kg/m^2); Obese (BMI ≥30 kg/m^2)

[1]Includes school attendance; HOME: Home Observation for Measurement of the Environment

Table 17: Offspring Parent and Teacher-rated Offspring Behaviors by Maternal Characteristics (n=511)

	Maternal Rated: Internalizing Mean(SD)	Maternal Rated: Externalizing Mean(SD)	Maternal Rated: Attention Mean(SD)	Teacher Rated: Internalizing Mean(SD)	Teacher Rated: Externalizing Mean(SD)	Teacher Rated: Attention Mean(SD)
			Enrollment or Delivery			
Maternal Race						
White	54.0 (10.7)*	53.1 (9.9)	56.4 (7.1)	50.1 (10.9)	51.5 (10.8)*	55.5 (7.9)*
Black	51.9 (10.3)	53.1 (9.9)	56.2 (7.1)	50.1 (10.1)	56.4 (11.2)	57.4 (8.9)
Family Income ($ per month)						
<500	53.5 (10.3)	53.1 (10.2)	56.7 (7.5)	50.2 (10.4)	55.2 (11.8)*	56.9 (8.5)
≥500	52.1 (10.8)	51.4 (10.0)	55.6 (7.2)	49.9 (10.7)	52.1 (10.2)	55.8 (8.3)
Body Mass Index						
Underweight	52.0 (10.8)*	52.9 (11.5)*	56.1 (7.8)*	50.9 (9.9)	55.3 (12.8)	57.0 (9.0)
Normal Weight	52.8 (10.4)	52.1 (10.1)	55.9 (7.2)	49.6 (10.6)	53.7 (10.9)	56.1 (8.1)
Overweight	51.7 (10.5)	51.2 (9.4)	55.9 (7.6)	50.3 (10.7)	52.6 (11.8)	56.0 (8.5)
Obese	56.8 (10.7)	56.0 (9.5)	59.1 (7.7)	51.3 (10.3)	56.2 (9.7)	58.7 (9.4)
Prenatal alcohol use						
Never used	52.6 (11.5)	51.3 (10.7)	56.3 (7.8)	50.8 (10.4)	55.2 (11.6)	56.9 (8.7)
Drank 1 trimester	53.4 (10.6)	53.2 (9.9)	56.5 (6.9)	49.4 (10.4)	52.9 (11.4)	56.2 (8.1)
Drank 2+ trimesters	52.8 (9.9)	52.6 (10.0)	56.2 (7.5)	50.1 (10.7)	53.9 (11.1)	56.4 (8.5)
Prenatal Cigarette use						
Never used	52.1 (10.6)*	50.7 (9.9)*	55.4 (6.3)	49.6 (10.2)	53.6 (10.8)	56.2 (8.5)
Smoked 1 trimester	50.4 (8.7)	50.5 (9.8)	56.4 (6.5)	52.8 (11.0)	56.0 (11.1)	58.1 (9.4)
Smoked 2+ trimesters	53.9 (10.7)	53.9 (10.2)	56.9 (8.2)	50.0 (10.6)	53.8 (11.6)	56.5 (8.2)
GWG z-score						
<-1 SD	51.6 (10.6)	52.0 (10.4)	56.0 (7.1)	48.5 (9.4)	52.4 (10.6)	55.6 (7.7)
-1 to +1SD	53.3 (10.7)	52.4 (10.0)	56.3 (7.5)	50.8 (10.7)	54.5 (11.5)	56.9 (8.7)
>+1 SD	54.4 (9.4)	53.4 (10.8)	57.1 (7.9)	49.8 (11.1)	54.5 (11.7)	55.9 (8.3)
			10 years Postpartum			

Table 17 Continued

Maternal Depression Scale						
Not Depressed <40	50.8 (10.1)*	50.6 (9.6)*	55.4 (6.5)*	49.5 (10.1)	53.0 (11.3)	55.8 (7.9)
Moderately Depressed ≥40	54.6 (10.6)	53.9 (10.4)	57.1 (8.1)	50.6 (10.8)	54.8 (11.3)	57.0 (8.8)
HOME Stimulation Scale						
Under stimulated <16	53.2 (10.7)	52.8 (10.2)	56.5 (7.5)	50.4 (10.7)	54.4 (11.4)*	56.8 (8.6)*
Stimulated ≥16	51.2 (9.3)	49.9 (9.7)*	54.9 (6.5)	48.4 (9.2)	51.3 (10.2)	54.3 (6.6)
Maternal IQ						
Below Average (≤89)	52.1 (10.5)*	51.9 (10.3)	55.7 (7.1)*	50.6 (10.2)	55.7 (11.4)*	57.2 (8.7)*
Above Average (>89)	54.1 (10.5)	53.1 (9.9)	57.1 (7.8)	49.3 (10.9)	51.5 (10.6)	55.6 (7.9)

Underweight (BMI <18.5 kg/m^2); Normal weight (BMI 18.5-24.9 kg/m^2); Overweight (BMI 25-29.9 kg/m^2); Obese (BMI ≥30 kg/m^2); SD-standard deviation; HOME: Home Observation for Measurement of the Environment
*P<0.05

Table 18: Offspring Parent and Teacher-rated Offspring Behaviors and Objective Attention and Impulsivity by Pre-Pregnancy Body Mass Index Categories (n=511)

	Underweight N=73	Normal Weight N=297	Overweight N=92	Obese N=49
Assessment Tool	adjβ[1] (95% CI)	adjβ (95% CI)	adjβ (95% CI)	adjβ (95% CI)
Parent-Rated				
Internalizing	-0.5 (-3.2, 2.1)	Reference	0.2 (-2.2, 2.6)	4.9 (1.7, 8.1)
Externalizing	1.2 (-1.3, 3.7)	Reference	0.6 (-1.7, 2.9)	4.2 (1.1, 7.3)
Attention	0.4 (-1.5, 2.3)	Reference	0.8 (-0.9, 2.6)	3.5 (1.2, 5.8)
Teacher-Rated				
Internalizing	1.8 (-0.8, 4.6)	Reference	1.4 (-1.1, 3.9)	2.0 (-1.3, 5.3)
Externalizing	2.6 (-0.2, 5.5)	Reference	-0.4 (-3.0, 2.2)	2.2 (-1.2, 5.7)
Attention	1.4 (-0.8, 3.5)	Reference	0.5 (-1.4, 2.5)	2.5 (-0.1, 5.1)
Objective	adjIRR (95% CI)	adjIRR (95% CI)	adjIRR (95% CI)	adjIRR (95% CI)
Attention	0.8 (0.6, 0.9)	Reference	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)
Impulsivity	0.8 (0.6, 1.1)	Reference	1.0 (0.8, 1.2)	1.4 (1.0, 1.8)

Underweight (BMI <18.5 kg/m^2); Normal weight (BMI 18.5-24.9 kg/m^2); Overweight (BMI 25-29.9 kg/m^2); Obese (BMI ≥30 kg/m^2)
β-Beta coefficient; IRR- Incidence Rate Ratio; CI- Confidence Interval
[1]Adjusted for maternal race, child sex, parity, income, employment, maternal depression, maternal intelligence, the home environment, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs)

Table 19: Offspring Parent and Teacher-rated Offspring Behaviors by Pre-Pregnancy Body Mass Index (n=511)

	Maternal Rated: Internalizing adjβ (95% CI)[1]	Maternal Rated: Externalizing adjβ (95% CI)[1]	Maternal Rated: Attention adjβ (95% CI)[1]	Teacher Rated: Internalizing adjβ (95% CI)[1]	Teacher Rated: Externalizing adjβ (95% CI)[1]	Teacher Rated: Attention adjβ (95% CI)[1]
BMI (kg/m^2) [2]						
18	1.3 (-1.1, 3.6)	2.1 (-0.1, 4.3)	0.9 (-0.7, 2.6)	2.6 (0.2, 5.0)	2.9 (0.5, 5.5)	1.2 (-0.7, 3.1)
20	0.6 (-0.5, 1.8)	1.1 (-0.1, 2.2)	0.5 (-0.4, 1.3)	1.3 (0.1, 2.5)	1.5 (0.2, 2.8)	0.6 (-0.4, 1.6)
22	Reference	Reference	Reference	Reference	Reference	Reference
24	0.8 (0.4, 1.2)	0.7 (0.4, 1.1)	0.6 (0.3, 0.9)	0.4 (-0.1, 0.8)	0.4 (-0.1, 0.8)	0.3 (-0.01, 0.7)
26	1.7 (0.8, 2.5)	1.5 (0.7, 2.3)	1.1 (0.5, 1.7)	0.7 (-0.2, 1.6)	0.8 (-0.1, 1.7)	0.7 (-0.01, 1.3)
28	2.5 (1.3, 3.8)	2.2 (1.1, 3.4)	1.7 (0.8, 2.6)	1.0 (-0.2, 3.1)	1.2 (-0.1, 2.5)	1.0 (-0.01, 1.9)
30	3.3 (1.7, 4.9)	2.9 (1.4, 4.6)	2.3 (1.1, 3.4)	1.4 (-0.3, 3.1)	1.6 (-0.2, 3.4)	1.3 (-0.01, 2.7)
32	4.1 (2.1, 6.2)	3.7 (1.8, 5.7)	2.8 (1.4, 4.3)	1.8 (-0.4, 3.9)	2.0 (-0.2, 4.3)	1.7 (-0.01, 3.3)
34	5.1 (2.6, 7.6)	4.6 (2.2, 6.9)	3.5 (1.7, 5.3)	2.2 (-0.5, 4.8)	2.5 (-0.2, 5.2)	2.1 (-0.02, 4.1)

β-Beta coefficient; CI- Confidence Interval
[1]Adjusted for maternal race, child sex, parity, income, employment, maternal depression, maternal intelligence, the home environment, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs)
[2] Pre-pregnancy body mass index modeled as a linear spline with a single knot at a BMI of 22kg/m^2

Table 20: Offspring Parent and Teacher-rated Offspring Behaviors and Objective Attention and Impulsivity by Gestational Weight Gain z-score (n=511)

Scales	GWG z-score <-1 SD Adjβ[1] (95% CI)	GWG z-score -1 to +1SD Adjβ[1] (95% CI)	GWG z-score >+1SD Adjβ[1] (95% CI)
Parent-Rated			
Internalizing	-0.8 (-2.9, 1.4)	Reference	1.6 (-1.5, 4.8)
Externalizing	-0.4 (-2.5, 1.7)	Reference	1.8 (-1.2, 4.8)
Attention	-0.1 (-1.6, 1.5)	Reference	1.7 (-0.5, 3.9)
Teacher-Rated			
Internalizing	-1.8 (-4.0, 0.5)	Reference	0.1 (-3.1, 3.4)
Externalizing	-2.2 (-4.6, 0.1)	Reference	0.7 (-2.6, 4.1)
Attention	-1.2 (-2.9, 0.6)	Reference	-0.2 (-2.8, 2.4)
Objective	adjIRR[1] (95% CI)	adjIRR[1] (95% CI)	adjIRR[1] (95% CI)
Attention	1.1 (0.9, 1.3)	Reference	1.1 (0.8, 1.4)
Impulsivity			
Lean (<25kg/m^2)	1.2 (0.9, 1.5)	Reference	0.8 (0.6, 1.2)
Overweight (≥25 kg/m^2)	0.8 (0.6, 1.1)	Reference	1.7 (0.9, 2.8)

β-Beta coefficient; IRR- Incidence Rate Ratio; CI- Confidence Interval; SD-Standard Deviation
[1]Adjusted for maternal race, child sex, parity, income, employment, maternal depression, maternal intelligence, the home environment, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs)

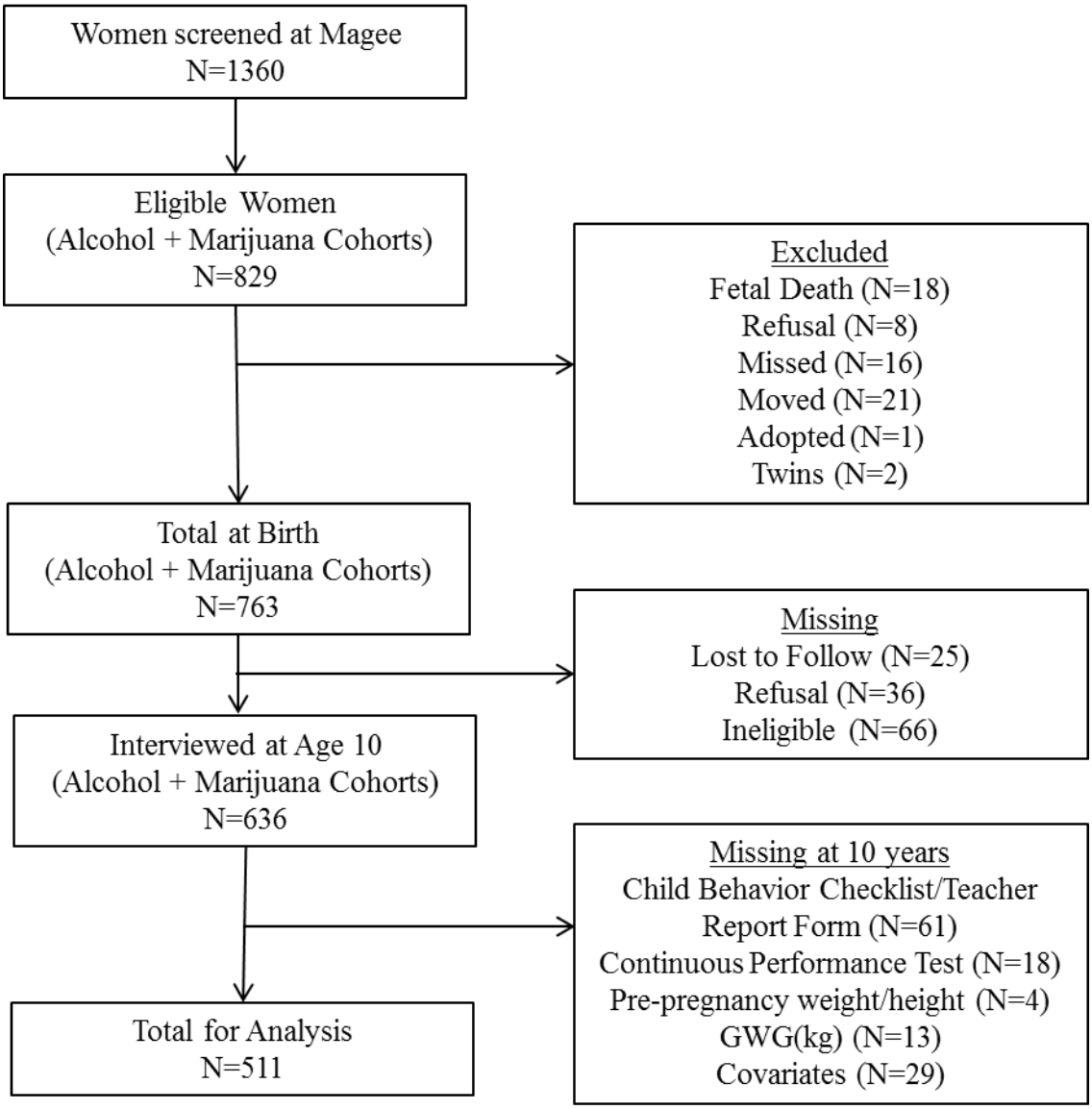

Figure 5: Participant Flow Diagram for the Maternal Practices and Child Development Cohort, 1983-1986

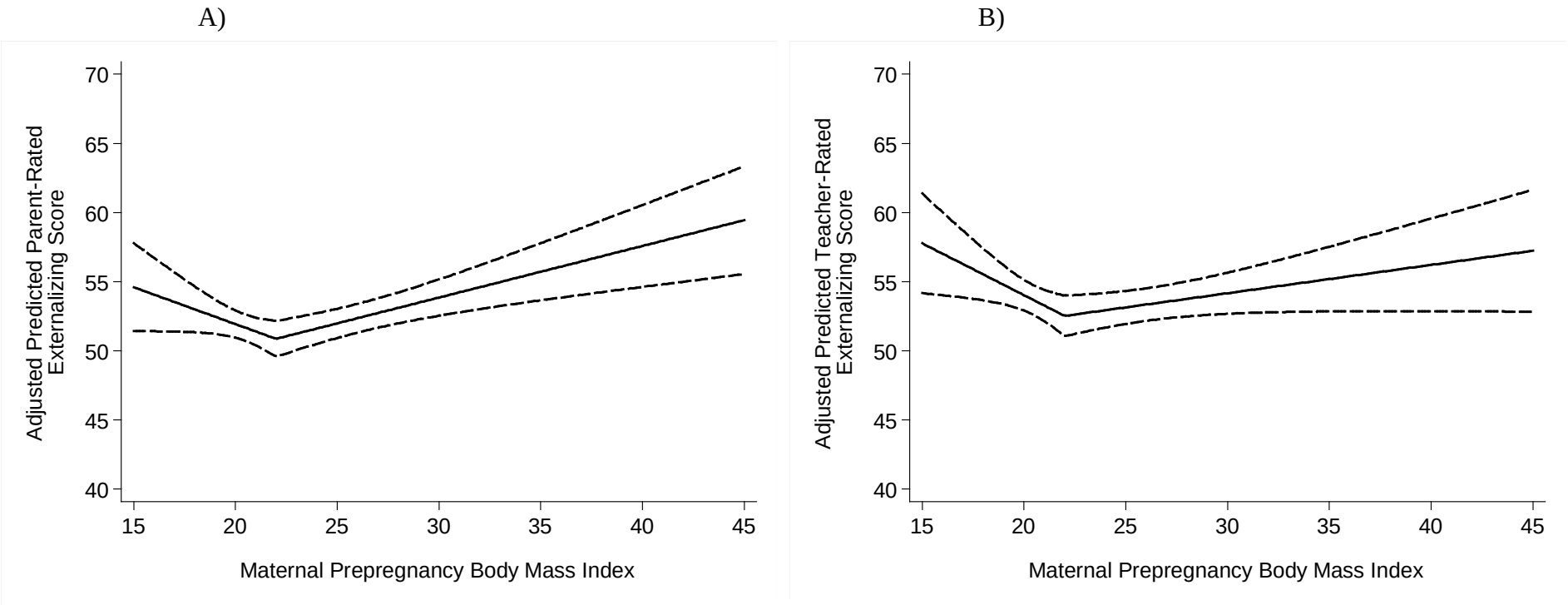

Figure 6: Association between Pre-pregnancy Body Mass Index and Offspring Externalizing Behavior on the Parent-Rated Scale (Panel A) and Teacher-Rated Scale (Panel B), n=511

Adjusted predicted scores of parent- and teacher-rated externalizing behavior problems by pre-pregnancy body mass index. The solid lines represent the point estimates and dashed lines represent its 95% confidence bands. Predicted scores were estimated using linear regression and were set at the population average for maternal race, child sex, parity, income, employment, maternal depression, maternal intelligence, the home environment, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs). Pre-pregnancy body mass index was modeled using a single knot (BMI=22kg/m^2) linear spline.

6.0 CHILD ACADEMIC ACHIEVEMENT IN RELATION TO PRE-PREGNANCY OBESITY AND GESTATIONAL WEIGHT GAIN

6.1 ABSTRACT

Our objective was to assess offspring academic achievement at ages 6, 10, and 14 in relation to maternal pre-pregnancy body mass index (BMI) and gestational weight gain (GWG). Mother-infant dyads enrolled in a birth cohort study in Pittsburgh, Pennsylvania (1983-1986) were followed from early pregnancy to 14 years postpartum (n=574). Math, reading, and spelling achievement was assessed at ages 6 and 10 using the Wide Range Achievement Test-Revised and at age 14 using the Wechsler Individual Achievement Test Screener. Self-reported total GWG was converted to gestational-age-standardized z-scores. Generalized estimating equations were used to estimate the effects of GWG and pre-pregnancy BMI on academic achievement at 6, 10, and 14 years, while adjusting for maternal race, child sex, parity, employment, family income, maternal intelligence, maternal depression, pre-pregnancy BMI (in GWG models only), and the home environment. The mean (SD) BMI was 23.4 (5.7) kg/m^2 and the mean (SD) GWG reported at delivery was 14.4 (5.9) kg. There was a non-linear association between pre-pregnancy BMI and offspring academic achievement. At 6, 10, and 14 years, offspring academic scores were inversely associated with pre-pregnancy BMI beyond 22kg/m^2. High GWG (≥1 standard deviation) was associated with approximately 4-point lower reading (adjβ: -3.75, 95% CI: -7.1, -0.4) and spelling scores (adjβ: -3.90, 95% CI: -7.8, -0.2), compared with GWG -1 to +1standard deviation. Future studies in larger and socioeconomically diverse populations are needed to confirm maternal weight and weight gain are associated with child academic skills and whether this effect persists to adulthood.

6.2 INTRODUCTION

Children of mothers who are obese before pregnancy or who gain too much weight during pregnancy are at high risk of a number of adverse short- and long-term outcomes, including preterm birth(171), stillbirth, obesity(144, 172), asthma(146, 173), and later-life cardiovascular disease(174). Recent data suggests that maternal obesity and/or mothers who gain excessive weight during pregnancy may also have children who are at increased risk of cognitive impairments (e.g., deficits in intelligence(14, 17) and executive function(158)) and problem behaviors that are consistent with attention deficit hyperactivity disorder (ADHD) (17, 101). These deficits may interfere with academic success (106); however, less is known about the impact of maternal weight and weight gain on offspring academic achievement.

Academic achievement is a key outcome because it not only synthesizes how behavioral and cognitive problems impact real-life functioning, but also predicts professional attainment and long-term job success (175). Four previous studies have sought to establish the association between maternal BMI or weight gain and offspring academic achievement (8, 14, 100, 111), but only 2 adequately adjusted for socioeconomic status or other critical confounders such as the cognitive enrichment in the home (8, 100). Additionally, all 4 studies assessed child achievement at a single time-point in children 7 years or younger. Therefore, it is unclear whether underachievement related to maternal weight that is observed in kindergarten, for instance, is transient or persists into late childhood and early adolescence(176). Our objective was to assess offspring math, reading, and spelling scores at ages 6, 10, and 14 in relation to maternal pre-pregnancy BMI and GWG in a cohort of Black and White low-income mother-child pairs.

6.3 METHODS

We used data from the Maternal Practices and Child Development Cohort. This study recruited women in Pittsburgh, PA who were ≥18 years and attended the prenatal clinic at Magee-Womens Hospital from 1983-1986. Study staff members screened 1360 eligible women (15% refusal rate) and selected women for inclusion based on their 1st trimester alcohol and marijuana use. An equal sample of women who drank <3 drinks per week and all women who drank ≥3

drinks per week were included in the cohort, as were an equal sample of women who smoked <2 joints per month and all women who smoked ≥2 joints per month. A total of 829 women were included in the combined cohorts (48% overlap). There were 763 women followed through pregnancy who delivered a singleton live-born infant. A majority of these women were light marijuana and alcohol users in their first trimester, a time when many women do not know they are pregnant (n=508 drank <3 drinks per week; n=516 smoked <2 joints per month).

Enrollment and the first study visit occurred at a median of 18.7 weeks (IQR: 17.1, 20.7). The second study visit and delivery visit occurred at a median of 31.3 weeks (IQR: 29.4, 33.1) and a median of 39 weeks (IQR: 38-40), respectively. Mother-child pairs were followed and interviewed at multiple post-partum time points. Included in this analysis are post-partum assessments at ages 6, 10 and 14 years. At each visit, sociodemographic status, substance use, maternal psychological status, and offspring cognitive development and academic achievement were assessed. Women provided informed, written consent and the study was approved by the University of Pittsburgh Institutional Review Board (IRB #PRO14020264)

Pre-pregnancy weight and height were self-reported at the first study visit. We categorized pre-pregnancy BMI [weight (kg)/height (m^2)] using the World Health Organization (WHO) criteria: BMI <18.5 kg/m^2 as underweight; BMI 18.5-24.9 kg/m^2 as normal weight; BMI 25-29.9 kg/m^2 as overweight; and BMI ≥30 kg/m^2 as obese(117). At delivery, women were asked to self-report the total amount of weight gained during the incident pregnancy. We then classified total GWG according to gestational age-standardized z-scores, a measure of GWG that by design is uncorrelated with gestational age (115). Z-score charts were developed from serial prenatal weight measurements in a sample of normal weight term pregnancies without complications from Magee-Womens Hospital in Pittsburgh, PA (1998-2008)(115). Z-scores were calculated using charts for normal weight women to allow us to evaluate whether the association between GWG z-scores and offspring academic scores varied depending on pre-pregnancy BMI.

Trained assessors blinded to maternal prenatal and current substance use evaluated child academic achievement using the Wide Range Achievement Test-Revised (WRAT-R)(177) at ages 6 and 10 and the Wechsler Individual Achievement Test (WIAT)(178) at age 14. The WRAT-R and WIAT have a high test-retest reliability (r=0.91-0.98 on the WRAT-R and r=0.90 on WIAT). Both tools assess skills in math (counting and solving oral and written problems),

reading (naming letters and words), and spelling (writing symbols and words). The final score on each scale is age-standardized to a mean (SD) of 100 (15), allowing for comparability across tools. The subscales of the WRAT-R and WIAT are highly correlated on reading (0.84) and spelling (0.84) and moderately correlated on math (0.76). We analyzed all scales as continuous variables.

In addition, offspring intelligence and behavior were assessed at age 10. The Stanford-Binet Intelligence Scale-4th edition (SBIS)(130) was used to measure child intelligence. For these analyses, the composite scale was dichotomized as low IQ (≤89) versus average or above IQ (>89))(130). Parent-ratings on the Child Behavior Checklist assessed offspring internalizing (withdrawn, anxious/depressed, or somatic complaints), externalizing (deviant or aggressive), and attention behaviors (all scales dichotomized as borderline clinical (≥67) versus average (<67))(163).

At the first study visit, trained interviewers collected information on sociodemographic characteristics, maternal depression using the Center for Epidemiological Studies Depression Scale(138), and anxiety using the Spielberger State-Trait Anxiety Personality Inventory(139). Alcohol, marijuana, cigarette, and cocaine use were collected by interviewers at both prenatal visits and delivery, and were summarized as average daily drinks, average daily joints, cigarettes per day, and cocaine use (yes/no), respectively. At the first study visit, women indicated the quantity and frequency of substance use during the year prior to pregnancy and during specific segments of the first trimester to calculate a more accurate depiction of first trimester use(137). We categorized each substance into overall pregnancy use to best capture non-users throughout pregnancy, users during the first trimester only when many women do not know they are pregnant, and use throughout pregnancy. Maternal intelligence was assessed at 10 years postpartum using the two-subtest version of the Wechsler Adult Intelligence Scale (WAIS)(151) . Mothers completed the Home Observation for Measurement of the Environment -Short Form (HOME-SF) at 10 years postpartum as a measure of the quality and quantity of support for cognitive and social development in the home environment. We included the HOME-SF as a continuous variable in all models(152).

6.3.1 Statistical analysis

We tested for differences in BMI and GWG by maternal characteristics using the Student's t-test and one-way ANOVA. We used a paired t-test to examine whether there was a significant and meaningful change in children's math, reading, and spelling scores across the three assessment points and a repeated measures ANOVA to examine whether this change varied by GWG z-score group or BMI category. To visualize the longitudinal pattern of each academic score by BMI and GWG, we plotted mean math, reading, and spelling scores by age. We used the Student's t-test to examine differences in academic achievement scores by offspring intelligence and behavior scores at age 10 (the age at which intelligence and behavior were measured).

We fit generalized estimating equations with an exchangeable covariance structure (Gaussian family, identity link) to estimate beta coefficients and their corresponding 95% confidence intervals (CI) for the association between pre-pregnancy BMI or GWG and each of the offspring achievement scores (math, reading, and spelling). Generalized estimating equations were used to account for the intra-individual correlation of child academic assessments at multiple ages and varying data completeness over time.

We explored non-linear relationships between child academic skills and maternal pre-pregnancy BMI and GWG z-score using splines. We compared the fit of cubic and linear spline terms using Akaike's Information Criteria(153) and selected a linear spline with a single knot at a BMI of 22kg/m^2, which was the observed point of inflection in all models. Since the relation between GWG and academic scores did not deviate from linearity, we categorized GWG as <-1SD, -1 to +1SD, and >+1SD for ease of interpretation.

The ages at the time of assessment (i.e. 6, 10 or 14 years) were coded as dummy variables and included in all models to account for time. Potential confounders were identified using theory-based causal diagrams(136): maternal race, child sex, parity, baseline employment, family income, education, maternal depression, maternal anxiety, marital status, maternal intelligence, pre-pregnancy BMI (in GWG models only), and the home environment at age 10. To select the most parsimonious model, we retained potential confounders that, if removed from the model, changed the primary exposure effect estimate by >10% (142, 143). Maternal race, child sex, parity, employment, family income, maternal intelligence, maternal depression, pre-pregnancy BMI (in GWG models only), and the home environment met our definition of confounding. We

calculated the difference between the actual age the child was assessed and the age for which the test was standardized (e.g. 6.4 years minus 6 years) and included this variable in all models as a continuous confounder. Prenatal substance use variables were forced into models based on *a priori* decisions. We separately tested for effect modification by maternal race, child sex, prepregnancy BMI (in GWG models only), and the age at assessment (time), by including statistical interaction terms with BMI or GWG z-score (tested both as continuous and categorical for all models) in fully adjusted models. Effect modification was present when $\alpha = 0.05$. We plotted adjusted predicted math, reading, and spelling scores and 95% CI according to pre-pregnancy BMI with covariates set to population means.

We re-ran our analyses after limiting to mother-child pairs with complete data and after excluding high marijuana (>1 joint a day)(154), alcohol (>1 drink a day)(119), cigarette (≥20 cigarettes per day)(155), cocaine (any use), and illicit drug (any use) users during the 1st or 3rd trimester. Analyses were conducted in Stata software, version 13.0 (StataCorp, College Station, TX)(156).

6.4 RESULTS

Of the 763 mother-child pairs at delivery, we excluded 65 pairs without child follow-up data as well as 22 with missing data on BMI or GWG and 102 with missing covariates in the final model. The final analytic sample included 574 mother-child pairs contributing 1567 observations (n=542 pairs at age 6, n=557 pairs at age 10, and n=468 pairs at age 14). There were no differences in GWG, pre-pregnancy BMI, maternal race, child sex, prenatal substance use, or offspring academic scores between those with and without missing data (data available on request). At the time of enrollment, the majority of the women were Black, unmarried, unemployed, had a family income of <$500 per month (<$1,400 per month in 2014 dollars(118)), were normal weight and gained an average amount of weight (-1 to +1SD) (Table 1). Most women reported no illicit drug use, 50% reported no marijuana use during pregnancy, and about one-third of women reported no prenatal alcohol or cigarette use (**Table 21**).

The mean (SD) prepregnancy BMI was 23.4 (5.7) kg/m^2 and the mean (SD) total GWG was 14.4 (5.9) kg. Mean math, reading, and spelling scores did not meaningfully differ by age

and were all within the expected age-normed range of 85-115 (corresponding to a mean(SD) of 100(15); Appendix B: **Table 29**) (177, 178).

Table 22 shows the differences in math, reading, and spelling scores at age 10 by maternal characteristics (results were similar for 6 and 14 years, Appendix B: **Table 30**). At age 10, academic scores were significantly higher among children of White mothers and married mothers, and tended to be higher among children of working mothers and families with an income ≥$500 per month at enrollment, compared with their counterparts. Children of mothers who did not use marijuana prenatally had significantly higher reading scores at age 10, and all scores were higher among children whose mothers used illicit drugs prenatally (likely explained by the disproportionate number of white women using illicit drugs). Offspring academic scores did not differ by prenatal alcohol or cigarette use.

Table 23 shows the difference in offspring academic achievement by intelligence and behavior at age 10. Children with average or above intelligence scored 12-14 points higher on the math, reading, and spelling skills test compared with children scoring lower on the intelligence test. Lower academic achievement scores were observed among children with externalizing behavior problems (deviance and aggression) and inattention, but not internalizing (withdrawn, anxious/depressed) behaviors.

The difference in mean academic scores by pre-pregnancy BMI were similar at ages 6, 10, and 14 (**Figure 7**). Among children of obese mothers, mean math, reading, and spelling scores were 4-6 points lower at age 6 and 14 and 5-6 points lower at age 10 compared with normal weight mothers, although the level of significance varied. In unadjusted multivariable models, child reading and spelling scores were significantly lower among obese compared with normal-weight mothers across ages 6, 10, and 14 years, while differences in math scores were of borderline statistical significance (**Table 24**). After adjusting for age, maternal race, parity, maternal intelligence, employment status, family income, the home environment, maternal prenatal depression, and prenatal substance use, the relationship between prepregnancy BMI and math scores at 6, 10, and 14 years was non-linear (**Figure 8**, results were similar for spelling and reading scores). Offspring academic scores at 6, 10, and 14 years were inversely associated with pre-pregnancy BMI beyond 22kg/m^2. Mothers with BMI values of 26, 28, or 30 kg/m^2 had children with math scores that were -1.3 (95% CI: -2.2, -0.4), 1.9 (95% CI: -3.2, -0.6), or 2.6 (95% CI: -4.4, -0.8) points lower, respectively, compared with children whose mothers had a

BMI of 22kg/m^2 (**Table 25**). Associations were similar for offspring reading and spelling scores (Table 24). These associations did not statistically vary by age at assessment (time).

The magnitude of the difference in mean academic scores by GWG z-score group did not vary significantly at ages 6, 10, and 14 **(Figure 9)**. Mean reading and spelling scores were 5-6 points lower among children of mothers gaining >+1SD compared with -1 to +1SD at ages 6 and 10, and the magnitude of this difference appeared to diminish at age 14 (**Table 25**). After adjustment, high GWG (>+1SD) was significantly associated with a nearly 4 point lower score in reading (adjβ: -3.75, 95% CI: -7.1, -0.4) and spelling (adjβ: -3.90, 95% CI: -7.8, -0.2), compared with GWG -1 to +1SD. Math scores were also lower, but this difference was not statistically significant. These associations did not vary by pre-pregnancy BMI or by age at assessment, despite the appearance that this effect was attenuated at 14.

None of the above findings varied by race or child sex (interaction p>0.05). Results were not meaningfully different after including other potential confounders in the models (child sex, marital status, maternal education, and maternal anxiety), limiting the analysis to those with data at all 3 visits (n=439), or excluding high substance users (data available on request).

6.5 DISCUSSION

Academic performance is an indicator of a child's general cognitive functioning, social acuity, and behavioral control, and strongly predicts adult employment and work success (106, 175). Our findings suggest that children born to obese mothers or mothers with high GWG have lower math, reading, and spelling scores across 6, 10, and 14 years. These relations remained after adjustment for measures of cognitive stimulation in the home, socioeconomic status, prenatal depression, prenatal substance use, and other confounders.

Our results on pre-pregnancy BMI confirm findings with kindergarten-aged children in two previous nationally representative studies in the US. Data from the National Longitudinal Study of Youth (NLSY) (1986-2008, n=3,412) found that 5-7 year old children of obese mothers scored 2-3 points lower on math and reading portions of the Peabody Individual Achievement Test compared with children of normal weight mothers(8). In a second study of 5,200 children ages 5-6 in the Early Childhood Longitudinal Birth Cohort (2001-2008)(100), children of

overweight and obese mothers had a modest decrease in reading, but not math scores, on standardized tests developed for this study(100). Our work extends these findings to illustrate that associations between maternal obesity and children's academic performance persist at 10 and 14 years, and therefore may have long-term effects.

The existing literature on GWG and child academic performance is small and mostly found no association, which conflicts with the 3-4 point lower scores we observed in offspring reading and spelling skills with excessive GWG. In a study of 8,704 seven-year-old siblings in the Collaborative Perinatal Project (1959-1973), GWG above the 2009 IOM guidelines was not associated with offspring math or reading scores (as assessed using the WRAT, the same tool we used) compared with GWG within the guidelines, after controlling for individual factors and shared factors among siblings such as maternal intelligence and cognitive stimulation at home (111). In nearly 6,000 four-year-old children from the Avon Longitudinal Study in the United Kingdom (1991-1997), GWG below the IOM guidelines was associated with a clinically insignificant decrease (<0.1 point) in offspring composite academic scores(14). A third study in the NLSY reported a non-significant trend towards lower reading and math scores among children of mothers with GWG above the guidelines(8). Previous studies used large nationally representative cohorts while we used a higher-risk, low income sample, which may explain the difference in findings. Socioeconomic status (SES) may modify the impact of GWG on offspring academic achievement, yet no previous studies mentioned differences in outcomes by SES. We were unable to test effect modification by socioeconomic status since the MHPCD population only represents a lower-SES group of women. However, the compounding stressors associated with low SES may contribute to a more susceptible environment for excessive GWG to impact academic achievement.

Our results were generally consistent with those from studies in this cohort relating maternal BMI to domain-specific cognition (i.e., child intelligence and behavior) (179, 180). Unlike domain-specific cognition measurements, academic achievement synthesizes how behavioral and cognitive problems impact real-life functioning. Combined, these findings suggest that lower intelligence and clinically significant problem behaviors at age 10 due to maternal BMI and GWG translate into significantly worse functional skills such as academic achievement. However, the associations with GWG differed in previous studies where we observed only a (non-significant) trend towards increasing deficits associated with high maternal

GWG. While the impact of GWG on individual domains may have been too small to detect a significant difference, the totality of intelligence and behavior impairments may have impacted academic achievement enough to detect lower scores with excessive GWG.

These results must be considered in the context of the study's limitations. This study is observational and cannot determine causality. The pregnancy cohort is comprised of lower socioeconomic status women; therefore, our results may only be generalizable to similarly disadvantaged populations. There is also the potential for attrition bias due to the longitudinal follow-up over 14 years. However, the retention rate was high in this cohort at 6 (88%), 10 (83%), and 14 (76%) years. It is unlikely this bias is of major concern since those with and without missing data at postpartum assessments did not differ by GWG, BMI, maternal race, or prenatal substance use. Multiple follow-up assessments strengthened this study because we could obtain a more accurate depiction of academic skills, which tend to vary over time (109, 110). We relied on self-reported pre-pregnancy weight, height, and total GWG, which may result in misclassification bias(126). However, it is difficult to know how this would affect our results because self-reporting bias may have differed in the 1980s than today. Nevertheless, we used a measure of GWG that by design is independent of gestational age, which allows us to separate the effect of gestational age from GWG. This is especially important when studying outcomes correlated with preterm birth such as academic performance (80) (181). The objective nature and high construct validity and reliability of the WRAT-R and WIAT instills confidence that children are correctly classified. In addition, we controlled for a number of important confounders including socioeconomic status, maternal depression, prenatal substance use, maternal intelligence, and child stimulation at home.

Our finding that low GWG was not associated with child's academic performance in the present study, or intelligence and behavior in previous work in the same cohort (179, 180) is important. The National Academy of Sciences/Institute of Medicine Committee to Reevaluate Gestational Weight Gain Recommendations expressed concern that low weight gain or weight loss, particularly among obese women, may impair offspring cognitive function (9). While our results and others (8, 14, 111) suggest no relationship with low weight gain, we were limited by a mostly lean cohort and few women with very low weight gain or weight loss during pregnancy. Future studies should aim to fill this knowledge gap.

Future studies in larger and socioeconomically diverse populations are needed to confirm that maternal weight and weight gain are modifiable factors related to child academic skills and whether this effect persists to adulthood. The 2-3 point decrease in academic achievement scores that we observed with maternal obesity and excessive GWG may not be meaningful for an individual, but the downward shift in the population average may have an impact on college attendance, employment, and work success (107, 175).

6.6 TABLES AND FIGURES

Table 21: Characteristics of the Maternal Health Practices and Child Development Cohort, Pittsburgh, PA (1983-1986) at Enrollment or Delivery (n=574 mother-child pairs)

	Overall N (%)
Enrollment	
Maternal Race	
White	276 (48.1)
Black	298 (51.9)
Marital Status	
Never Married	388 (67.6)
Married	186 (32.4)
Maternal Employment[1]	
No	420 (73.2)
Yes	154 (26.8)
Family Income ($ per month)	
<500	351 (61.2)
≥500	223 (38.9)
Maternal Depression Scale	
Not Depressed <40	256 (44.6)
Moderately Depressed ≥40	318 (55.4)
PrePregnancy Body Mass Index [2]	
Underweight	81 (14.1)
Normal Weight	338 (58.9)
Overweight	100 (17.4)
Obese	55 (9.6)
Delivery	
Gestational Weight Gain Z-score	
<-1 SD	136 (23.7)
-1 to +1 SD	384 (66.9)
>+1 SD	54 (9.4)
Prenatal Alcohol use (any)	
Never used Drank 1	152 (36.5)
trimester Drank 2+	161 (28.1)
trimesters	261 (45.5)
Prenatal Marijuana use (any)	
Never used	287 (50.0)
Smoked 1 trimester	136 (23.7)
Smoked 2+ trimesters	151 (26.3)
Prenatal Cigarette use (any)	

Table 21 Continued

Never used	220 (38.3)
Smoked 1 trimester	44 (7.7)
Smoked 2+ trimesters	310 (54.0)
Prenatal Illicit Drug Use throughout pregnancy (any)	
No	508 (88.5)
Yes	66 (11.5)
Child Sex	
Female	288 (50.2)
Male	286 (49.8)

[1]Includes school attendance
[2]Underweight (BMI <18.5 kg/m^2); Normal weight (BMI 18.5-24.9 kg/m^2); Overweight (BMI 25-29.9 kg/m^2); Obese (BMI ≥30 kg/m^2)

Table 22: Offspring Academic Scores on the Wide Range Achievement Test at age 10 (n=574) by Maternal Characteristics at Enrollment or Delivery

	Math Mean(SD)	Reading Mean(SD)	Spelling Mean(SD)
	Enrollment		
Maternal Race			
White	92.1 (13.3)*	97.7 (14.5)*	95.9 (14.1)*
Black	85.8 (12.0)	90.9 (15.6)	91.3 (14.6)
Marital Status			
Never Married	88.1 (12.3)*	93.1 (15.8)*	92.9 (14.7)
Married	90.3 (14.5)	96.4 (14.5)	94.6 (14.2)
Maternal Employment[1]			
No	88.3 (13.1)	93.8 (15.5)	93.1 (14.9)
Yes	90.2 (12.8)	95.1 (15.4)	94.6 (13.6)
Family Income ($ per month)			
<500	87.5 (13.0)	92.8 (15.9)	92.0 (14.9)
≥500	90.8 (12.8)	96.2 (14.9)	95.6 (13.9)
Maternal Depression Scale			
Not Depressed <40	89.1 (12.3)	95.1 (14.8)	94.0 (14.2)
Moderately Depressed ≥40	88.6 (13.6)	93.4 (15.9)	93.1 (14.8)
	Delivery		
Prenatal Alcohol use (any)			
Never used	88.8 (14.0)	93.2 (16.4)	92.4 (15.2)
Drank 1 trimester	89.4 (12.3)	94.8 (14.6)	94.5 (13.5)
Drank 2+ trimesters	88.4 (13.0)	94.3 (15.5)	93.4 (14.9)
Prenatal Marijuana use (any)			
Never used	89.0 (13.0)	95.4 (15.3)*	94.2 (14.2)
Smoked 1 trimester	89.7 (13.0)	94.3 (15.3)	93.7 (14.6)
Smoked 2+ trimesters	87.5 (13.1)	91.5 (15.7)	91.8 (15.2)
Prenatal Cigarette use throughout pregnancy (any)			
Never used	89.2 (12.6)	94.3 (14.6)	93.4 (13.4)
Smoked 1 trimester	86.6 (13.8)	90.7 (17.8)	91.1 (16.6)
Smoked 2+ trimesters	88.9 (13.2)	94.5 (15.6)	93.9 (15.0)
Prenatal Illicit Drug Use (any)			
No	88.5 (12.9)	93.6 (15.5)*	92.9 (14.5)*
Yes	91.2 (13.6)	98.6 (14.1)	97.5 (14.1)
Child Sex			
Female	89.7 (12.8)	95.0 (13.6)	95.1 (13.4)*
Male	87.8 (13.3)	93.3 (17.1)	91.8 (15.5)

* $p<0.05$

[1]Includes school attendance

Table 23: Offspring Academic Scores by Intelligence and Parent-Rated Behavior Scores at Age 10 (n=557)

Scales	Math Mean(SD)	Reading Mean(SD)	Spelling Mean(SD)
Intelligence[1]			
Below average (<89)	82.1 (10.4)*	86.1 (14.9)*	86.9 (14.2)*
Average or above (≥89)	94.0 (12.4)	100.6 (12.6)	98.7 (12.5)
Externalizing[2]			
Clinically significant (≥67)	83.2 (13.2)*	84.5 (16.5)*	84.4 (15.3)*
Normal	89.2 (12.8)	95.5 (16.5)	94.4 (14.2)
Internalizing[2]			
Clinically significant (≥67)	86.5 (14.5)	92.0 (18.2)	90.9 (16.3)
Normal	89.0 (12.7)	94.4 (15.0)	93.8 (14.3)
Attention[2]			
Clinically significant (≥67)	84.8 (13.9)*	86.4 (16.9)*	86.2 (15.3)*
Normal	89.3 (12.8)	95.3 (14.9)	94.5 (14.1)

*$p<0.05$

[1] Stanford Binet Intelligence Test: Composite Scale

[2] Parent-Rated Symptoms on the Child Behavior Checklist: Externalizing symptoms include deviant or aggressive behavior; Internalizing symptoms include withdrawn, anxious/depressed feelings, and somatic complaints

Table 24: Unadjusted and adjusted non-linear association between pre-pregnancy body mass index and offspring math, reading and spelling scores at ages 6, 10, and 14 (n=574 unique pairs contributing 1567 observations)

	Math	Reading	Spelling
Pre-Pregnancy Body Mass Index[1]	β (95% CI)	β (95% CI)	β (95% CI)
Underweight	-0.95 (-3.9, 1.9)	-0.06 (-3.0, 3.0)	0.69 (-2.5, 3.9)
Normal Weight	Reference	Reference	Reference
Overweight	0.59 (-2.1, 3.2)	1.62 (-0.9, 4.1)	2.71 (0.01, 5.4)
Obese	-5.47 (-9.2, 1.7)	-4.63 (-8.5, -0.8)	-4.99 (-8.9, -1.0)
Pre-Pregnancy Body Mass Index (kg/m^2) [2]	adjβ[3] (95% CI)	adjβ[3] (95% CI)	adjβ[3] (95% CI)
18	-0.72 (-3.6, 1.7)	-1.33 (-3.9, 1.3)	-1.25 (-4.1, 1.5)
20	-0.36 (-1.8, 0.9)	-0.67 (-2.1, 0.7)	-0.63 (-2.1, 0.7)
22	Reference	Reference	Reference
24	-0.65 (-1.1, -0.2)	-0.54 (-1.0, -0.1)	-0.62 (-1.1, -0.2)
26	-1.31 (-2.2, -0.4)	-1.09 (-2.1, -0.1)	-1.26 (-2.2, -0.3)
28	-1.94 (-3.2, -0.6)	-1.62 (-3.1, -0.1)	-1.86 (-3.2, -0.5)
30	-2.61 (-4.4, -0.8)	-2.18 (-4.1, -0.2)	-2.51 (-4.4, -0.6)
32	-3.25 (-5.5, -0.9)	-2.70 (-5.1, -0.2)	-3.12 (-5.5, -0.8)

β-Beta coefficient; CI- Confidence Interval; SD-Standard Deviation

[1]Underweight (BMI <18.5 kg/m^2); Normal weight (BMI 18.5-24.9 kg/m^2); Overweight (BMI 25-29.9 kg/m^2); Obese (BMI ≥30 kg/m^2)

[2] Linear spline terms with a single knot at a BMI of 22kg/m^2

[3]Adjusted for age, maternal race, parity, employment, family income, maternal intelligence, home environment, maternal prenatal depression, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs)

Table 25: Unadjusted and Adjusted Associations between Gestational Weight Gain and offspring Math, Reading, and Spelling scores at ages 6, 10, and 14 (n=574 unique pairs)

	Math		Reading		Spelling	
	β (95% CI)	adjβ[2] (95% CI)	β (95% CI)	adjβ[2] (95% CI)	β (95% CI)	adjβ[2] (95% CI)
GWG Z-score[1]						
<-1SD	0.41 (-1.9, 2.7)	1.77 (-0.3, 3.8)	0.81 (-1.5, 3.1)	2.01 (-0.2, 4.2)	0.32 (-2.1, 2.8)	1.33 (-1.0, 33)
-1 to +1SD	Reference	Reference	Reference	Reference	Reference	Reference
>+1SD	-2.47 (-6.1, 1.1)	-2.17 (-5.6, 1.1)	-4.39 (-7.8, -0.9)	-3.75 (-7.1, -0.4)	-4.41 (-8.1, -0.7)	-3.90 (-7.8, -0.2)

β-Beta coefficient; CI- Confidence Interval ; SD-Standard Deviation

[1] <-1SD (<11.2kg at 40 weeks gestation); -1 to +1SD (11.2- 22.9kg); >+1SD (>22.9kg)

[2]Adjusted for age, maternal race, parity, employment, family income, maternal intelligence, home environment, maternal prenatal depression, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs)

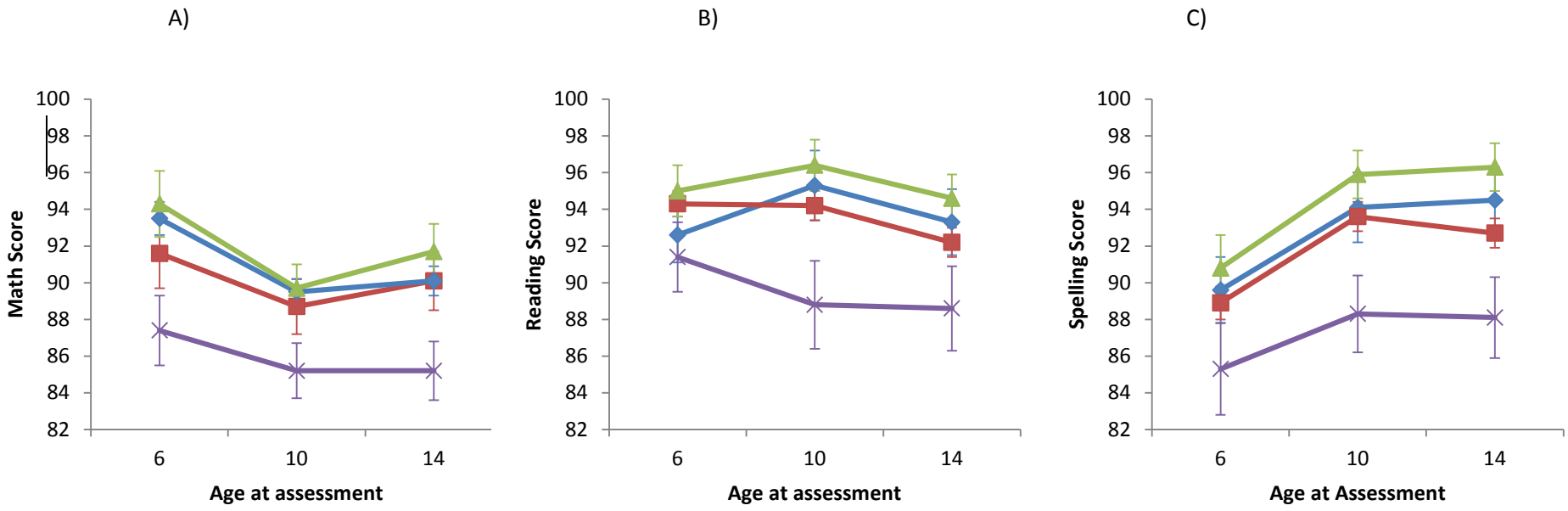

Figure 7: Mean (SEM) Academic Scores at ages 6 (n=542 pairs), 10 (n=557 pairs), and 14 (n=468 pairs) by Pre-pregnancy Body Mass Index

Legend: Math (Panel A), Reading (Panel B), and Spelling (Panel C) scores, by Underweight (Blue), Normal Weight (Red), Overweight (Green), and Obese (Purple) Women; SEM-standard error of the mean

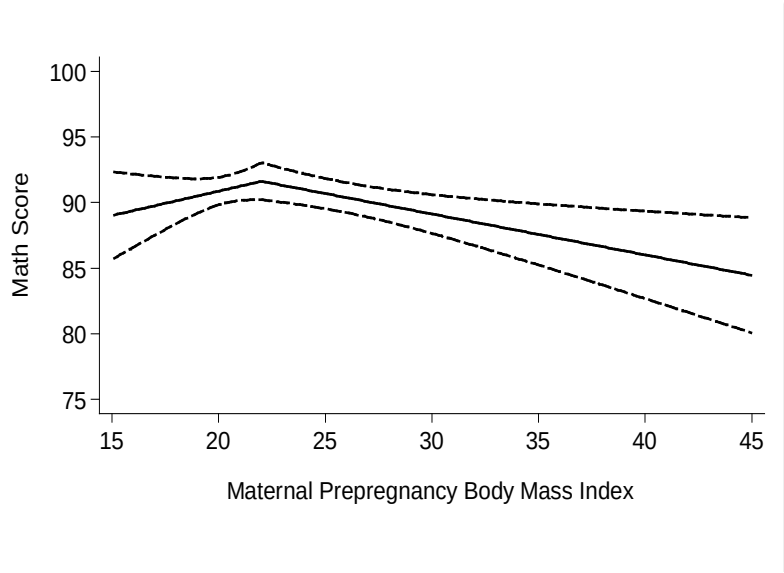

Figure 8: Adjusted predicted child math scores by pre-pregnancy body mass index

Legend: The solid lines represent the point estimates and dashed lines represent its 95% confidence bands. Predicted scores were estimated using linear regression and were set at the population average for child age, maternal race, parity, employment, family income, maternal intelligence, home environment, maternal prenatal depression, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs). Pre-pregnancy body mass index was modeled using a single knot (BMI=22kg/m^2) linear spline.

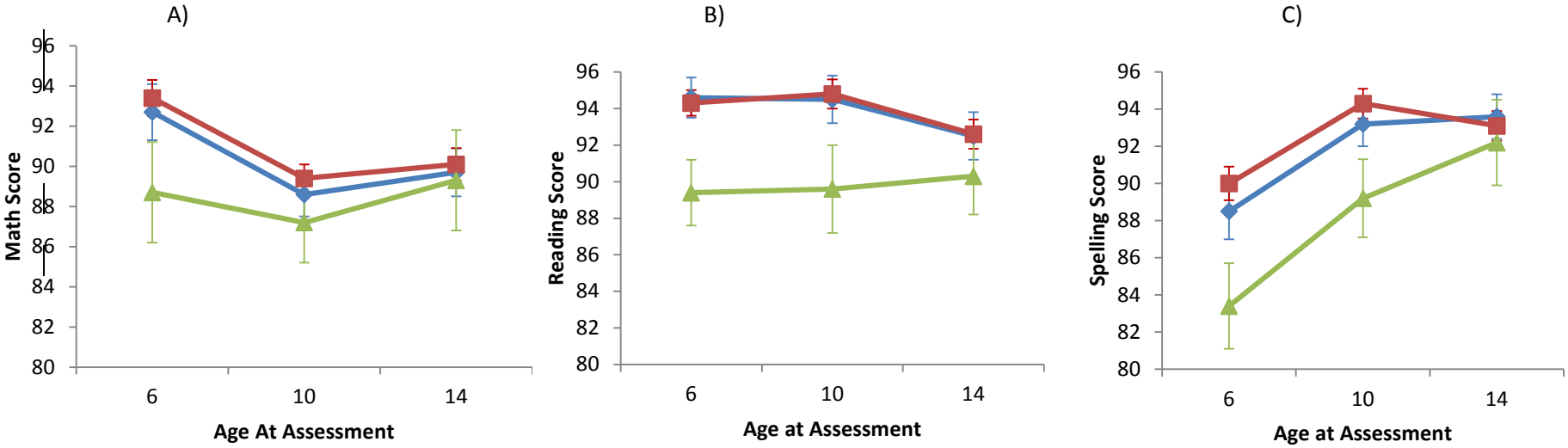

Figure 9: Mean (SEM) Academic Scores at ages 6 (n=542 pairs), 10 (n=557 pairs), and 14 (n=468 pairs) by Gestational Weight Gain Z-score Category

Legend: Mean Math (Panel A), Reading (Panel B), and Spelling (Panel C) scores at ages 6, 10, and 14, by GWG <-1 SD (blue), GWG -1 to +1SD (Red), and GWG >+1SD (Green); SEM-standard error of the mean

7.0 SYNTHESIS

7.1 OVERVIEW OF RESEARCH FINDINGS

This dissertation used data from the Maternal Health Practices and Child Development Study, a longitudinal birth cohort of mother-child pairs followed from pregnancy to 14 years postpartum. The goal of this dissertation was to assess areas of cognition, behavior, and academic achievement that are often impaired in children with ADHD in relation to gestational weight gain and pre-pregnancy BMI, two potentially modifiable risk factors. Below we outline the findings presented in this dissertation.

1.) <u>Determine the association between pre-pregnancy body mass index, gestational weight gain, and offspring intelligence and executive function at age 10</u>

Maternal self-reported measurements of height, weight, and total weight gain were used to calculate pre-pregnancy BMI and GWG. Trained interviewers assessed offspring intelligence (IQ) and executive function using the Stanford Binet Intelligence Scale-4th edition, the Wisconsin Card Sorting Test (executive function), and the Trail Making Test (executive function), all validated and commonly used tools. We found that offspring IQ and executive function were lowest in children whose mothers had a BMI above 22 kg/m^2 and the magnitude of this deficit increased as maternal BMI increased. This finding was consistent with other studies that also explored offspring IQ, though this study was one of the first to assess offspring executive function and use a low-income and racially diverse population.

Independently from pre-pregnancy BMI, we also observed lower executive function, but not IQ, in children of mothers with high GWG (>+1SD; >22.9kg), compared with GWG -1 to +1SD (11.2 to 22.9kg). There is a paucity of evidence examining GWG as a primary exposure, which our study aimed to fill. In general, we found that maternal BMI had a stronger relation

than GWG with both offspring intelligence and executive function. Our study was observational and cannot establish causality, but our results support the notion that women entering pregnancy at a normal weight have fewer adverse outcomes. Since nearly two-thirds of women of child-bearing age are overweight or obese, even a modest decrease in child cognition, like the deficit we observed, could have an important impact on population health.

2.) Determine the association between pre-pregnancy body mass index, gestational weight gain and offspring attention-deficit hyperactivity disorder symptoms and behavior at age 10

Offspring behavior and ADHD symptoms were assessed using tools consistent with those used during a typical ADHD diagnostic evaluation. Parents and teachers rated child externalizing, internalizing, and attention behaviors and a computerized test assessed child inattention and impulsivity symptoms. We found that parent- and teacher-rated child problem behaviors increased in a dose-response relation as maternal pre-pregnancy BMI increased and decreased from 22 kg/m^2. This result was consistent with other studies that examined parent- and teacher-rated problem behaviors, yet our study was the first to objectively assess inattention and impulsivity.

We observed a non-significant trend towards increased offspring impulsivity with low GWG among lean mothers and high GWG among overweight mothers, but additional behavior and ADHD symptoms did not differ by GWG z-score. There is a lack of evidence examining GWG independently and in combination with pre-pregnancy BMI, which our study aimed to fill. Future studies need to confirm this finding and further explore the potential interaction between GWG and pre-pregnancy BMI on offspring behaviors. In general, we observed a small increase in offspring internalizing, externalizing, and attention behaviors among children of obese mothers, which may not be meaningful for individuals but could have a substantial impact on child behavior in the population.

3.) Determine the association between pre-pregnancy body mass index, gestational weight gain, and offspring academic achievement

Academic achievement was measured at ages 6 and 10 using the Wide Range Achievement Test and at age 14 using the Wechsler Individual Achievement Test, both validated and standardized assessment tools. In a multivariable analysis using generalized estimating

equations and adjusting for a number of important confounders we found that offspring academic scores at 6, 10, and 14 years were inversely related to pre-pregnancy BMI above 22kg/m^2. This finding is consistent with the small body of literature that also assessed academic achievement, yet this study was the first to evaluate whether academic underachievement persisted over time.

We found that high GWG (>+1 standard deviation), independent of pre-pregnancy BMI, was associated with a modest decrease in reading and spelling scores, compared with GWG -1 to +1 standard deviation. This finding differed from the existing literature, which mostly reported no association. However, previous studies used large nationally representative and mostly White cohorts while we used a low-income and racially-diverse sample. It is possible that GWG may be more important among women with compounding risk factors such as poverty and stress. In general, the decrease in academic achievement scores associated with maternal obesity and excessive GWG may not be meaningful for an individual, but the downward shift in the population average may have an impact on offspring college attendance, employment, and work success.

7.2 STRENGTHS AND LIMITATIONS

Our results should be considered within the context of our limitations.

Generalizability:

Prenatal substance using women may have limited generalizability to the current U.S. population. However, light substance use among pregnant women in the general population is not uncommon, according to a recent report in 2013. In the U.S., 16% of pregnant women smoked cigarettes, 6% used illicit drugs (i.e. marijuana, cocaine, heroin), 8.5% used alcohol and 2.7% reported binge drinking, (182) but these are likely underestimates of the true prevalence due to the stigma of reporting substance use during pregnancy(183). Heavy substance use was present in our population, but when we examined the impact of excluding these women on our results; our results remained unchanged. The generalizability of this cohort may remain limited to Black and White racial groups from a low socioeconomic (SES), but this population is under-

represented in the literature and our findings contribute to the predominately White and European samples currently studied.

Selection Bias:

There is a possibility for attrition bias due to the longitudinal follow-up over 14 years. However, this cohort had a high retention rate at 6, 10 and 14 years (88 to 76%), which reduces the potential for attrition bias. There was no difference in GWG, BMI, or important maternal characteristics such as income, parity, race, and education between those remaining in the study and lost to follow up.

Misclassification Bias:

Pre-pregnancy height and weight were self-reported by mothers and used to calculate pre-pregnancy BMI, which may lead to exposure misclassification bias. Heavy women tend to underreport their weight, which may bias our findings towards the null. However, in reality it is difficult to know how this would affect our results because self-reporting bias may have differed in the 1980s than today. BMI is highly correlated with more invasive and direct measures of body fat such as underwater weighing(120) and continues to be a universal and accessible assessment method to monitor population obesity trends.

Outcome misclassification may also bias our results. We did not have a measurement of ADHD diagnosis; rather, we used assessments of ADHD symptoms consistent with gold-standard methodology. To supplement these assessments, we used parent- and teacher-reports of offspring emotional and behavioral symptoms often identified in children with ADHD, although not part of the diagnostic criteria(25). The combination of gold-standard assessment tools and subjective assessments of behavior instills confidence that child behaviors and ADHD symptoms were accurately classified. The high construct validity and reliability of the other cognitive and academic assessment tools we used support our notion that child intelligence, executive function, and academic skills were also correctly classified.

Residual and unmeasured Confounding:

Importantly, our research was observational and we cannot establish causality; our findings may be attributed to shared factors such as genetics or the environment due to residual

or unmeasured confounding. There is potential for residual confounding by substance use. Women were asked to self-report substance use over the past trimester. However, recall of alcohol use has been shown to be moderately reliable over a 3-month and 5-month period(184), and we believe that this likely can be applied to recall of other substances such as marijuana use and smoking. Residual confounding from cognitive stimulation in the home environment may also be present. A single questionnaire, the HOME-SF, was used to assess the quality of the home environment. Although this questionnaire is a widely employed and reliable tool, it might not adequately cover all areas of cognitive stimulation, which may bias our findings away from the null.

Unmeasured confounding by genetics may have biased our results. We were unable to control for genetic profiles that may result in maternal obesity and lower child cognitive/behavioral development, but we did control for a measure of maternal intelligence. Additionally, we adjusted for number of other important maternal confounding factors such as prenatal substance use, psychological status, socioeconomic status, and assessments of the amount of cognitive stimulation provided in the home environment.

A unique strength of this study was our use of gestational age-standardized GWG z-scores to accurately classify weight gain and separate the effect of weight gain from the effect of early gestational age at delivery. Previous studies used total GWG (kg), which may bias their results by inducing a spurious association based on the amount of time available to gain weight (i.e. gestational age). We conducted a sensitivity analysis to see how our results would be affected when we examined our outcomes using total GWG (kg) adjusted for gestational age. Although our findings remained the same, it is unclear how previous study results were impacted since adjustment for gestational age may not appropriately reduce the bias from the correlation between gestational age and child cognition.

7.3 PUBLIC HEALTH SIGNIFICANCE

This dissertation has important implications for public health. Attention-deficit hyperactivity disorder (ADHD) is on the rise and affects 7-9% of children in the United States. Cognitive, behavioral, and academic deficits related to ADHD can impair professional attainment and long-

term job success. Therefore, understanding potentially modifiable risk factors such as maternal obesity or gestational weight gain can have major public health contributions.

The findings from this dissertation suggest maternal pre-pregnancy obesity and potentially excessive GWG may impair offspring cognitive, behavioral, and academic development related to ADHD. However, reducing obesity and excessive GWG would not eliminate ADHD since it is a multi-factorial disorder with different causes including genetics, environmental exposures, and brain injuries (6). Rather, it may alleviate the steady increase in prevalence, which may ease the familial and societal burden due to ADHD.

Multidimensional targets are necessary to change maternal weight and weight gain, which remain complex with psychological, environmental, political, and genetic causes and consequences. Addressing obesity and excessive GWG is a public health priority and can be done through clinical education and counseling as well as environmental and policy changes.

Public health would benefit from increased clinical counseling and education for women of child-bearing age both before and during pregnancy. Weight loss counseling should be a part of continuing care for overweight and obese women in the reproductive-age span. Counseling should not be limited to preconception care for women attempting to conceive. Physicians and other healthcare providers (e.g. dietitian, physical therapists) need to gather accurate weight and height information and have frank discussions with women about the risks of being overweight or obese. During pregnancy, obstetricians need to identify a woman's optimal gestational weight gain, convey her target weight, and provide tools for obtaining this weight (i.e. caloric increase, physical activity). At each visit, clinicians should track weight gain and counsel women who are gaining too much or too little and discuss the risks associated with inadequate or excessive GWG. Electronic medical records may be a useful tool to achieve this goal (185). While targeting obesity and GWG through clinical education and counseling requires few resources, it can be difficult due to time constraints and a lack of patient interest.

Environmental and policy changes will have the biggest impact on reducing obesity, though they require more societal and political movement (186-188). Evidence suggests that humans are largely influenced by systemic and environmental default conditions. Systemic conditions are driven by cost and accessibility; therefore, today's current default foods include sugary sweets and oils/fats, high-density and low nutrient foods, which are cheap and accessible. Environmental defaults include increased proximity to fast food restaurants and large portion

sizes. Systemic and environmental drivers of the food environment currently promote obesity but need to be updated to include low-cost nutrient rich options, increased proximity and density of grocery stores/farmers markets, and smaller portion sizes(187).

Societal changes to reduce an obesogenic environment will be gradual; therefore, a more immediate public health intervention could be screening infants of obese mothers or mothers with excessive GWG. Infants of obese mothers may benefit from additional learning or cognitive stimulation tools such as toys, music, or books since brain development continues in early childhood. Public health may also be improved by implementing early childhood screening programs where children of obese mothers are screened by teachers for cognitive delays or behavioral impairments. Children need to be identified at a young age when their brains are still developing and interventions are early enough to preclude later difficulties in academic performance. However, additional studies are needed to determine the feasibility and effectiveness of such interventions.

7.4 DIRECTIONS FOR FUTURE RESEARCH

This dissertation should be used to inform the design of future cohort studies. Larger cohort studies that include more women with high/low BMI and GWG are needed. The negative impact of maternal BMI on offspring development may be strengthened as maternal obesity increases, but we were limited by a lean population. It is critical to assess offspring of severely obese women to quantify cognitive and behavioral impairments and to determine whether a dose-response relation with obesity persists or plateaus in very high BMI's. Additionally, there is a critical knowledge gap in understanding the impact of low weight gain or weight loss on offspring cognition, particularly in severely obese women. We had too few women with low GWG to inform this gap. It is imperative that future studies assess this question to inform the optimal range of weight gain for severely obese women that balances both child and maternal health.

Future studies would benefit from more precise measures of pre-pregnancy body composition and markers of systemic inflammation to elucidate the pathogenesis for how maternal fat may disrupt offspring development. The biologically plausible support for this

dissertation is rooted in how maternal adiposity contributes to inflammatory dysregulation, which interferes with fetal brain development. However, BMI is an imperfect measure of maternal adiposity and may not accurately correlate with systemic inflammation. Measures of body composition by ultrasound or bioelectrical impedance analysis can be used to identify the amount of fat versus fat-free mass. Biomarkers of inflammation such as C-reactive protein and interleukin-6 can be collected to assess inflammation. These tools complement one another and can be used in combination to more accurately classify women and their risk of impaired child cognition (66). This may also help to focus resources to the most at-risk women.

How women gain weight, as measured by trajectories, may be more important than the total amount of weight gained. This dissertation suggests that excessive total GWG may impair child academic achievement, yet the evidence is mixed. Trajectories of GWG may be important to fill this knowledge gap. There are varying periods of critical fetal brain development and those times in particular may be more susceptible to weight gain. For example, two women with the same total GWG may gain differently such that one woman has high GWG early in pregnancy but then levels off while another may gain little in the beginning but gain rapidly towards the end of pregnancy. Currently, it is unclear whether one trajectory is more beneficial than the other.

Future studies should assess ADHD and related deficits in children by brain response and areas of brain activity. Event-related potential (ERP) and fMRI evaluations are new methods to identify functional brain activation and can be applied to developmental questions such as child cognition(189). These two methods provide complementary information on neural activity and spatial location, respectively. Future studies could use these tools to identify areas of brain activation during cognitive tasks such as the Continuous Performance Test or Trail-Making Test. Comparing activation in children of obese mothers with children of non-obese mothers may provide insight into where brain development is impaired and could be useful to develop interventions. It is important for studies using these methods to continue to incorporate measures of real-life functioning such as academic performance to link brain response with actual life impairment.

More advanced methodologic approaches are needed to account for the postnatal environment or genetics. A common criticism of this literature is that BMI and GWG are merely a proxy of unmeasured genetic or environmental confounding. Methodologically advanced studies may include quasi-experimental methods such a sibling analysis, which can control for

unmeasured environment, or in vitro fertilization cohorts, which aim to tease apart genetics and intrauterine effects. While a randomized control trial would be an ideal way to answer this question, there is too little evidence, particularly on GWG, to support such a study.

Lastly, future studies should build on our findings and investigate modifiable factors such as breastfeeding that may attenuate the adverse effect of obesity and GWG. Obesity and excessive GWG are potentially modifiable, yet may prove difficult to change. Breastfeeding has been associated with improved child intelligence and even future academic achievement(190). However, little is known about whether the amount, duration, or frequency of breastfeeding can modify the impact of maternal adiposity on offspring cognition, behavior, and academic achievement.

The conclusions from this dissertation are all based on findings from observational studies and cannot confirm causality. Additional studies are needed to confirm our findings, address gaps in the literature, and improve our understanding of the underlying mechanisms before randomized control trials can be recommended and interventions can be tested.

APPENDIX A: SUPPLEMENTARY TABLES FOR MANUSCRIPT 2

Table 26: Offspring Objective Attention and Impulsivity by Maternal Characteristics (n=511)

	Objective Attention Mean(SD)	Objective Impulsivity Mean(SD)
Enrollment or Delivery		
Maternal Race		
White	1.4 (1.2)	3.7 (4.9)
Black	1.5 (1.2)	3.5 (3.9)
Family Income ($ per month)		
<500	1.5 (1.3)	3.7 (4.9)
≥500	1.4 (1.1)	3.3 (3.5)
Pre-Pregnancy Body Mass Index		
Underweight	1.2 (1.1)	3.2 (4.2)
Normal Weight	1.5 (1.2)	3.6 (4.5)
Overweight	1.5 (1.2)	3.2 (3.7)
Obese	1.6 (1.1)	4.9 (5.4)
Prenatal alcohol use		
Never used	1.4 (1.2)	4.0 (5.1)
Drank 1 trimester	1.5 (1.2)	3.1 (3.2)
Drank 2+ trimesters	1.4 (1.2)	3.6 (4.7)
Prenatal Cigarette use		
Never used	1.4 (1.2)	3.8 (5.2)
Smoked 1 trimester	1.3 (1.1)	2.8 (2.2)
Smoked 2+ trimesters	1.5 (1.2)	3.5 (4.1)
GWG z-score		
<-1 SD	1.5 (1.2)	3.8 (5.5)
-1 to +1SD	1.4 (1.2)	3.4 (3.9)
>+1 SD	1.5 (1.0)	4.1 (5.8)
10 Years Postpartum		
Maternal Depression Scale		
Not Depressed <40	1.4 (1.1)	3.4 (4.1)
Moderately Depressed ≥40	1.6 (1.2)	3.7 (4.7)
HOME Stimulation Scale		
Under stimulated <16	1.5 (1.2)	3.7 (4.5)
Stimulated ≥16	1.3 (1.2)	2.6 (3.6)

Table 26 Continued

Maternal IQ		
Below Average (≤89)	1.4 (1.1)	3.9 (5.1)
Above Average (>89)	1.4 (1.2)	3.1 (3.3)

Underweight (BMI <18.5 kg/m^2); Normal weight (BMI 18.5-24.9 kg/m^2); Overweight (BMI 25-29.9 kg/m^2); Obese (BMI ≥30 kg/m^2)
SD-Standard Deviation
HOME: Home Observation for Measurement of the Environment

Table 27: Unadjusted Association between Parent and Teacher-rated Offspring Behaviors, Objective Attention and Impulsivity and Pre-pregnancy Body Mass Index (n=511)

Scales	Underweight	Normal Weight	Overweight	Obese
	Unadjusted β (95% CI)	Unadjusted β (95% CI)	Unadjusted β (95% CI)	Unadjusted β (95% CI)
Parent-Rated				
Internalizing	-0.9 (-3.6, 1.8)	Reference	-1.2 (-3.6, 1.3)	3.9 (0.8, 7.2)
Externalizing	0.8 (-1.8, 3.4)	Reference	-0.9 (-3.2, 1.5)	3.9 (0.9, 7.0)
Attention	0.1 (-1.8, 1.9)	Reference	-0.1 (-1.8, 1.7)	3.1 (0.9, 5.4)
Teacher-Rated				
Internalizing	1.3 (-1.3, 4.0)	Reference	0.7 (-1.8, 3.2)	1.7 (-1.5, 4.9)
Externalizing	1.6 (-1.3, 4.5)	Reference	-1.1 (-3.7, 1.6)	2.5 (-0.9, 5.9)
Attention	0.9 (-1.3, 3.1)	Reference	-0.1 (-2.1, 1.9)	2.6 (0.1, 5.1)
	Unadjusted IRR (95% CI)	Unadjusted IRR (95% CI)	Unadjusted IRR (95% CI)	Unadjusted IRR (95% CI)
Objective				
Attention	-0.3 (-0.6, 0.1)	Reference	0.0 (-0.3, 0.3)	0.1 (-0.3, 0.4)
Impulsivity	-0.1 (-0.4, 0.1)	Reference	-0.1 (-0.3, 0.1)	0.3 (0.1, 0.6)

Underweight (BMI <18.5 kg/m^2); Normal weight (BMI 18.5-24.9 kg/m^2); Overweight (BMI 25-29.9 kg/m^2); Obese (BMI ≥30 kg/m^2)
β-Beta coefficient; IRR- Incidence Rate Ratio; CI- Confidence Interval

Table 28: Unadjusted Offspring Parent and Teacher-rated Offspring Behaviors and Objective Attention and Impulsivity by Gestational Weight Gain z-score (n=511)

Scales	GWG z-score <-1SD	GWG z-score -1 to +1SD	GWG z-score >+1SD
	Unadjusted β (95% CI)	Unadjusted β (95% CI)	Unadjusted β (95% CI)
Parent-Rated			
Internalizing	-1.7 (-3.9, 0.4)	Reference	1.1 (-2.1, 4.2)
Externalizing	-0.4 (-2.5, 1.7)	Reference	0.9 (-2.1, 3.9)
Attention	-0.3 (-1.8, 1.3)	Reference	0.8 (-1.4, 3.1)
Teacher-Rated			
Internalizing	-2.4 (-4.5, -0.2)	Reference	-0.9 (-4.1, 2.1)
Externalizing	-1.9 (-4.3, 0.3)	Reference	0.02 (-3.3, 3.4)
Attention	-1.3 (-3.1, 0.4)	Reference	-0.9 (-3.5, 1.5)
	Unadjusted IRR (95% CI)	Unadjusted IRR (95% CI)	Unadjusted IRR (95% CI)
Objective			
Attention	0.1 (-0.1 0.3)	Reference	0.1 (-0.1, 0.4)
Impulsivity	0.1 (-0.1 0.3)	Reference	0.1 (-0.1, 0.4)

β-Beta coefficient; IRR- Incidence Rate Ratio; CI- Confidence Interval; SD-Standard Deviation

APPENDIX B: SUPPLEMENTARY TABLES FOR MANUSCRIPT 3

Table 29: Mean (SD) Offspring Academic Scores at age 6 (n=542), age 10 (n=557) and age 14 (n=468)

	Age 6 Mean(SD)	Age 10 Mean(SD)	Age 14 Mean(SD)
Math	92.9 (17.2)	89.1 (12.9)	90.0 (13.9)
Reading	93.9 (13.2)	94.3 (15.6)	92.5 (13.4)
Spelling	89.2 (16.5)	93.5 (14.6)	93.1 (13.9)

Table 30: Offspring Academic Scores on the Wide Range Achievement Test at age 6 (n=542) and age 14 (n=468) by Maternal Characteristics at Enrollment or Delivery

	Math		Reading		Spelling	
	Age 6	Age 14	Age 6	Age 14	Age 6	Age 14
Enrollment						
Maternal Race						
White	94.5 (15.8)*	95.4 (13.8)*	94.9 (13.4)*	96.5 (11.9)*	90.8 (15.8)*	96.0 (13.3)*
Black	90.8 (18.6)	84.9 (11.9)	92.6 (13.7)	89.1 (13.1)	86.7 (18.7)	90.8 (13.9)
Marital Status						
Never Married	92.3 (18.1)	88.0 (13.4)*	93.4 (13.5)	91.0 (13.2)*	88.1 (18.1)	92.2 (13.8)*
Married	93.4 (16.1)	93.1 (14.0)	94.3 (13.7)	95.7 (12.3)	89.8 (16.2)	95.2 (13.9)
Maternal Employment [1]						
No	91.8 (17.3)	89.1 (13.6)	93.3 (13.2)	92.0 (13.1)	88.7 (16.4)	92.4 (13.8)*
Yes	94.8 (17.8)	91.3 (14.5)	94.7 (14.6)	93.8 (13.1)	88.8 (19.8)	95.3 (13.9)
Family Income ($ per month)						
<500	91.8 (17.3)	87.5 (13.2)	93.4 (13.4)	90.6 (13.5)	88.2 (17.4)	91.2 (14.2)
≥500	94.2 (17.4)	93.2 (14.1)	94.2 (13.8)	95.5 (11.9)	89.8 (17.0)	96.1 (13.1)
Prenatal Alcohol use (any)						
Never used	92.3 (17.4)	89.8 (14.9)	92.8 (13.8)	92.8 (13.7)	88.2 (16.5)	92.8 (14.9)
Drank 1 trimester	91.8 (17.7)	90.5 (13.7)	93.5 (13.5)	92.1 (12.6)	87.4 (18.6)	93.5 (13.4)
Drank 2+ trimesters	93.4 (17.3)	88.9 (13.3)	94.3 (13.6)	92.5 (13.0)	89.9 (17.3)	93.2 (13.6)
Maternal Depression Scale						
Not Depressed <40	94.2 (17.1)*	89.8 (14.0)	94.3 (13.4)	92.6 (13.3)	89.3 (17.3)	93.7 (13.4)
Mod Depressed ≥40	91.4 (17.6)	89.5 (13.7)	93.2 (13.7)	92.4 (12.9)	88.2 (17.6)	92.7 (14.3)
Delivery						
Prenatal Marijuana use (any)						
Never used	92.9 (17.4)	90.5 (14.4)*	93.7 (13.6)	93.8 (12.5)*	89.3 (16.8)	93.9 (13.4)
Smoked 1 trimester	93.5 (16.8)	90.6 (13.2)	94.7 (13.7)	93.3 (13.4)	88.4 (19.6)	94.2 (14.8)

Table 30 Continued

Smoked 2+ trimesters	91.3 (18.2)	87.1 (13.0)	92.6 (13.4)	89.4 (13.5)	87.8 (16.9)	90.8 (13.7)
Prenatal Cigarette use (any)						
Never used	91.9 (17.4)	89.5 (14.7)	93.1 (13.0)	92.9 (12.3)	87.5 (16.8)	93.3 (13.4)
Smoked 1 trimester	91.9 (17.2)	87.5 (12.8)	94.8 (12.1)	89.6 (15.9)	86.8 (19.8)	89.5 (17.2)
Smoked 2+ trimesters	93.2 (17.6)	92.0 (13.4)	93.9 (14.2)	92.6 (13.2)	89.8 (17.6)	93.6 (13.6)
Prenatal Illicit Drug Use throughout pregnancy (any)						
No	92.1 (17.4)*	88.9 (13.8)*	93.3 (12.9)*	92.0 (13.1)*	88.1 (17.0)*	92.8 (13.8)
Yes	96.9 (17.1)	94.8 (13.4)	96.9 (17.5)	95.9 (12.5)	93.9 (20.1)	95.8 (13.8)
Child Sex						
Female	93.2 (17.2)	89.1 (13.0)	94.6 (13.1)	94.2 (12.0)*	90.1 (17.9)*	96.1 (12.9)*
Male	92.1 (17.7)	90.2 (14.6)	92.7 (14.0)	90.7 (13.9)	87.4 (17.0)	90.2 (14.3)

* $p<0.05$

[1]Includes school attendance

[2]Underweight (BMI <18.5 kg/m^2); Normal weight (BMI 18.5-24.9 kg/m^2); Overweight (BMI 25-29.9 kg/m^2); Obese (BMI ≥30 kg/m^2)

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