Early Life Environments and Cognitive-Behavioral Outcomes of Children: A Life Course Approach

DISSERTATION

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Abstract

With ever increasing prevalence of obesity among reproductive aged women, more attention has been paid to prevention of adverse pregnancy and birth outcomes. In addition, the relationships of maternal prepregnancy obesity with the offspring's future obesity and metabolic syndrome have been well established. However, its effects on the fetal brain are unclear. Obesity-related metabolic alterations may create suboptimal intrauterine environment for rapidly growing brain. Fetal period is a critical period of brain development. Any insult during this period may have lasting effects on cognitive and behavior outcomes. Therefore, it is important to examine the relationship.

The current study uses a life course approach to examine the association between maternal prepregnancy obesity and the offspring's cognitive-behavioral development. A child's health develops over time as his or her biological systems interact with surrounding environments. It is no longer adequate to examine current health status by only looking at contextual factors in present time. Better understanding of current health conditions requires examination of the child's past experiences beginning from prenatal period.

The first chapter introduces a life course model used throughout this dissertation study. This is followed by a review in chapter 2 of risk factors that are associated with the development of type 2 diabetes during childhood. This chapter ascertains the fact that risk factors for shaping one's health are present throughout one's life course and that

early life adverse environment may play an important role setting up one's health trajectory. In the subsequent two chapters, the association between maternal prepregnancy obesity and the offspring's cognitive and behavioral outcomes are examined using data from the National Longitudinal Survey of Youth.

Maternal prepregnancy obesity was associated with reductions in reading and mathematical test scores among term birth children 5 and 6 years old. The association was statistically significant after adjustment for birth weight, maternal prenatal cigarette smoking, home environment, household income, child's factors, and maternal socioeconomic factors including cognitive trainability. In contrast, no consistent association was present between maternal prepregnancy obesity and children's behavior problem scores across two racial groups of children, whites and African Americans at ages 8 and 9 years. In both racial groups, the strong influence of postnatal family and social environments on children's behavior problems was present. Socially disadvantaged characteristics emerged only among white women who were obese prior to pregnancy compared to among those who were non-obese.

This study demonstrated usefulness of a life course approach. Results of the first study suggest maternal prepregnancy obesity adversely affect the offspring's cognitive development through biological pathways. However, inconsistency across the two racial groups in the second study results suggests little evidence for maternal metabolic alterations influencing the offspring's behavior problems. Replications of the study results are recommended using cohorts with diverse racial/ethnic groups of children. Future research should be directed to examine mechanisms associated with maternal

prepregnancy obesity and the offspring's cognitive development, to test effects of weight reduction before conceptions, and to examine timing and methods to support cognitive stimulation of individuals who are exposed to maternal metabolic alterations.

Dedication

This dissertation is dedicated to my family. To my mother and sister for teaching me how to be strong. To my late father for instilling me to pursue higher education—you were the greatest teacher I ever had. I miss hanging around with you. To my sons, Katsu and Hiro for their patience and understanding—you are the most wonderful gifts I ever received. And to my husband, Soichi for his love, endless support, and encouragement—you always stood by me to help me succeed.

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Chapter 1: Tackling Health Consequences of Obesity with a Long View Approach

1.1. Introduction

Maternal prepregnancy obesity has received increasing attention in an effort for preventing childhood obesity and obesity related complications. Currently more than 30% of women in reproductive age are obese (body mass index or BMI $\geq$ 30 kg/m^2) (Flegal, Carroll, Ogden, & Curtin, 2010). Maternal prepregnancy obesity not only complicates pregnancy itself but also adversely affects health of unborn children. Compared to women with lower BMI categories, obese women are especially at a high risk for gestational hypertension and preeclampsia (Crane, White, Murphy, Burrage, & Hutchens, 2009; de la Torre et al., 2011; Gaillard, Steegers, Hofman, & Jaddoe, 2011), both of which compromise placental nutrient transfer and result in increased risks for preterm birth and small for gestational age births (Bakker, Steegers, Hofman, & Jaddoe, 2011). Maternal prepregnancy obesity is also associated with an increased risk for large birth weight and large for gestational age births (Crane et al., 2009; Oken, Kleinman, Belfort, Hammitt, & Gillman, 2009; Park et al., 2010). It is an independent factor for childhood obesity (Salsberry & Reagan, 2005; Whitaker, 2004), development of metabolic syndrome in late childhood (Boney, Verma, Tucker, & Vohr, 2005; X. Wang, Liang, Junfen, & Lizhong, 2007), and early onset of type 2 diabetes (T2DM) (Dabelea et al., 2008). While genetic predisposition along with shared family factors such as

obesogenic dietary habit and lifestyle may be largely responsible for childhood obesity and obesity-related complications, intrauterine programming (Hales & Barker, 1992) is thought to play an important role in developing metabolic derangement in the offspring (Rooney & Ozanne, 2011).

Perhaps more concerning is that the consequences of obesity-related metabolic disorders may not be limited to peripheral organs but also extend to the central nervous system (CNS) (Banks, 2004; Reagan, 2007; Starr & Convit, 2007). Advancement of medical treatment coupled with the obesity epidemic has enabled researchers to examine the relationship between T2DM and the risk of developing dementia in older adults (Strachan, Reynolds, Frier, Mitchell, & Price, 2008). Older adults with T2DM are 1.5 to 3 times more likely to develop dementia compared to those without (Strachan et al., 2008). It is suggested that lengths of the exposure to hyperinsulimic state or insulin resistance may play a significant role in cognitive function (Convit, 2005; Reagan, 2007; Starr & Convit, 2007).

Maternal high insulin resistance, often accompanied by obesity and gestational diabetes, fails to store excess glucose as glycogen in the placenta, resulting in high glucose supply to fetus. This, in turn results in adaptive changes in fetal metabolism, such as fetal fat deposit, hyperinsulinemia, and accelerated growth (Desoye, Gauster, & Wadsack, 2011). Although maternal insulin does not cross the placenta, the fetus of an obese woman may develop insulin resistance (Catalano, Presley, Minium, & Hauguel-de Mouzon, 2009). It is conceivable that maternal metabolic derangement may leads to multiple physiological changes in the fetus and this in turn (1) programs for T2DM with

an increasingly earlier onset if faced with repeated exposures to postnatal obesogenic environments, and/or (2) interferes with normal development of fetal brain. In the chapters that follow, a life course approach is used to appreciate how maternal obesity during very early life period of a child and throughout his or her childhood may impact development of T2DM, and show similarities and differences in how maternal prepregnancy obesity affects development of cognitive-behavioral health in the offspring using the same approach. The purpose of this chapter is to introduce the Life Course Health Development (LCHD) framework, a life-course model developed by Halfon and Hochstein (2002), to provide a conceptual foundation for this dissertation study, and to discuss potential mechanisms that may explain how early life experiences, specifically to maternal prepregnancy obesity, is important to determine the offspring's CNS functions.

1.2. Overview of Life Course Health Development Framework

A life-course model provides a powerful tool for understanding health and disease trajectories, and for developing strategies to prevent and treat disease. Often times, looking for a causal association between contemporaneous exposure and ill health fails to fully explain health disparities that exist among different socioeconomic racial and ethnic groups (Braveman & Barclay, 2009). While one's health may be influenced by current surroundings interacting with his/her biological and psychological systems, the symptoms may not be apparent until more harm to the body accumulates and a certain threshold is reached. The use of the life-course approach provides the ability to connect remote experiences with current health (Halfon & Hochstein, 2002). Early life experiences and

cumulative risk exposures are important components of the life-course approach that help explain shaping of one's health trajectory (Halfon & Hochstein, 2002).

The LCHD framework is discussed by Neal Halfon and Miles Hochstein in 2002 to explain development of heath trajectory of an individual over life course and to guide appropriate health policy development (Halfon & Hochstein, 2002). Unlike other explanatory models of health and disease development, which may only provide cross-sectional views of health outcomes, the LCHD framework uniquely includes time context to allow room to consider human development, past experiences, and cumulative effects of health risk and protective factors from one's past experiences.

The LCHD framework views health as a dynamic process over time (Halfon & Hochstein, 2002). The LCHD framework is based on four principles of health development: (1) multiple causations of health development, (2) design and process of health development, (3) mechanisms that shape individual's unique health trajectory, and (4) integration of time dimension for health development (Halfon & Hochstein, 2002). These four principles facilitate comprehensive approach for understanding health development. In this approach, one's early life experiences are viewed as critical components that contribute to building foundations of one's health and therefore provide an important linkage to the current health status and future health development.

1.2.1. Multiple Causations of Health Development

Multiple environments surround an Individual. Examples of the environmental contexts provided by the LCHD framework include genetic endowment, physical environment, social environment, family environment, psychological environment,

cultural and policy environment, and health care system. Each environmental context does not singularly influence an individual's health development but rather it is the dynamic interactions of multiple environmental factors collectively shaping his or her health development. This is because often times each environment is correlated with each other, or smaller environments are embedded within larger more influential ones. For example, poor family economic status may limit those families to reside in certain neighborhoods where housing is only affordable for them. Physical and built environments of the neighborhood may not be favorable for developing optimal health.

The magnitude of influential force that each environment exerts on an individual's health development may also differ by the developmental stage at which he or she stands. An influence from immediate caregivers may be strongest during infancy and early childhood, whereas peer and social media pressure may be greater than parental control to shape one's behavior during the adolescent period. Thus, trying to change only one system at one time point may hardly change the course of one's health development.

1.2.2. Design and Process of Health Development

Through the evolutionary process, living organisms that developed multiple fail-proof systems to maintain functionality have survived through natural selection pressure. Regulatory processes are the ways in which body attempt to maintain stability. The regulatory systems such as nervous, endocrine, and immune systems serve as information systems and help produce functional adaptation in response to the internal or external environmental changes (Halfon & Hochstein, 2002). Development of one's adaptive ability may be influenced by early experiences and life events over the life course

(Halfon, Russ, & Regalado, 2005). For example, fetuses that are exposed to low nutrient environment during intrauterine period are thought to develop insulin resistance to regulate and maintain glucose supply to their brain through alteration in the hypothalamic-pituitary-adrenal (HPA) axis activity (Barker & Bagby, 2005). Individuals' adaptive abilities may not be fully functional at birth, but can be programmed over time through exposures to different or repeated experiences.

1.2.3. Mechanisms

Mechanisms are defined as the effects that influence health outcome. Two types of mechanisms are described in the LCHD framework: cumulative and programming. Cumulative mechanism is defined as the effects that are due to repeated exposures through one's life course but independent from timing of the event. Thus, the body's adaptive process occurs in a dose dependent fashion. On the other hand, programming mechanism is a strong effect of risk exposure that occurs in critical or sensitive periods of development and produce permanent changes in body's functions or structures without repeated exposures to the same environment (Halfon & Hochstein, 2002). Programming events are said to occur especially in early life, and critical components to determine health development trajectories.

1.2.4. Developmental Time Frames

Developmental time frames are temporal overarching structures that influence an individual's health trajectory. Developmental time frames include patterns of critical or sensitive periods of certain organ development or disease progression, and the transitions

and turning points. As described in Halfon and Hochstein (2002), the fetal period is the most vulnerable period for neuronal cells in the brain because sequenced events that are under genetic program must occur during this period for the cells to attain normal functions. This is described as experience expectant as opposed to experience dependent (Halfon & Hochstein, 2002). One example is neuronal development, where at a certain period of development during infancy, neural connection becomes complete and an infant starts to use binocular vision (Siegler & Alibali, 2005). Disturbances to optic nerve area of the brain during or prior to this period may lead to delayed or disruption in binocular vision development. In summary, the timing of the events may be crucial for particular organ functions, and produce lasting effects on one's health development trajectory.

Health development is a consequence of "lifelong adaptive process that builds and maintains optimal functional capacity and disease resistance" (Halfon & Hochstein, 2002, p. 437). Life expectancy, functional capacities, disease, disability, and dysfunction, and school and job readiness and performance are all outcomes of health development. It is clear that outcomes of health development are not limited to disease process but inclusive to every function of human development including metabolic, cognitive and behavioral health.

1.3. Potential Mechanisms linking Maternal Prepregnancy Obesity to Cognitive-Behavioral Development of Offspring

Several potential mechanisms have been proposed for maternal prepregnancy obesity to cause detrimental effects on offspring's CNS development. One of the proposed mechanisms involves in insulin, insulin-related peptides, or insulin receptors in

the brain. Insulin receptors in the brain differ from peripheral insulin receptors, and are present in diverse structural forms (Chiu & Cline, 2010; Zhao, Chen, Quon, & Alkon, 2004). These brain insulin receptors have binding affinity to Insulin-like-growth-factor I (IGF-1) and IGF-2 as well as insulin. Together, insulin, IGF-1, and IGF-2 are thought to be responsible for neuronal cell development, including synapse maturation, maintenance, elimination, and dendrite development (Chiu & Cline, 2010). Level of brain insulin receptor expression is increased during the late fetal period. Increased number of neuronal cells and synapses are present during early development until these cells undergo selection processes for selective and refined synapse formation. New synapse formation occurs as the need for transmitting new information is presented during which time pre- and post-synaptic terminals recruit needed materials to transport and receive the particular information. Chiu and Cline (2010) suggest that early events during which neuronal and synaptic selections are actively organized during early development may play an important role in dynamics of synapse formations in later life. In other words, disruptive events that may cause brain insulin receptor abnormalities in critical period of neuronal cell development may result in either decreased number of dendrites in a neural cell, or disruption in recruitment of correct materials to form mature synaptic connections.

In animal models, diet induced maternal obesity have shown altered physiological and behavioral consequences in offspring. For example, the study results by Niculescu & Lupu (2009) suggest that maternal diet may permanently alter structures and functions of the brain. They found that rat fetuses born to HFD-fed obese dams displayed delayed

neural cell development evidenced by decreased number of apoptotic cell markers, were growth restricted at embryonic day 17. Tozuka and colleagues found a lower level of brain-derived neurotrophic factors (BDNF) and evidence of increased oxidative stress in the brain of young offspring born to HFD-fed obese dams (Tozuka et al., 2010). Accompanied with this were underdeveloped neural cells in the hippocampus and a reduction in maze learning ability in behavioral tests among the young, but not adult, offspring of HFD-fed obese dams compared to those born to regular chow-diet fed normal weight dams. Bilbo and Tsang on the other hand found increased inflammatory markers in the brain, increased anxiety-like behavior, but no impairment in spatial learning among adult offspring of HFD-fed dams compared to those of chow-diet fed dams (Bilbo & Tsang, 2010). Results of the latter two studies suggest that both prenatal and postnatal nutritional environments are important in influencing offspring's cognitive outcome, but that early experiences may cause lasting effects to later life.

While the above studies focus on changes in the brain structures and functions of offspring born to obese mothers, others attempt to explain the mechanisms through the changes that occur in maternal and placental physiology. Maternal nutritional status and her ability to transport essential nutrition are critical for fetal development. During pregnancy, the maternal body and the placenta undergo numerous adaptations to supply sufficient nutrients to meet fetal growth demand. The placenta adapts its shape, size, and nutrient transport systems to optimize survival of fetus and mother (Fowden, Sferruzzi-Perri, Coan, Constancia, & Burton, 2009). Maternal prepregnancy obesity may results in accelerated fetal growth, premature birth, or intrauterine growth restriction. Imbalance of

nutrient supply and fetal growth can occur either with too rapid fetal growth or low nutrient transfer through the placenta. This could result in increased oxidative stress (Hayes et al. 2012) and lead to cellular inflammation and insulin resistance in fetus, which may occur both in peripheral organs and the CNS.

Long-chain polyunsaturated fatty acids (LC-PUFA) involve in membrane formation, and synapse formations and myelination of neuronal cells (Georgieff, 2007). A surge of LC-PUFAs including essential fatty acids during the third trimester is critical for the fetal brain development (Cetin, Alvino, & Cardellicchio, 2009; Georgieff, 2007). Obesity and gestational diabetes change placental function, thereby compromise transferring of LC-PUFA to fetus (Larque et al., 2011). As for the fetuses born prematurely, the supply of LC-PUFA from placenta will be cut short. Loss of LC-PUFA supply is thought to be responsible for behavioral problems among children born prematurely. For those who are carried to term but with growth restriction, placental LC-PUFA transport systems may be altered, resulting in changes in fatty acids compositions transported to fetus (Cetin et al., 2009). An example of epidemiological studies associated with this is an Australian study reporting that adolescent girls, but not boys, from full-term births with growth restriction, are more likely to have teacher-rated attentional problems compared to normal birth size counterparts (O'Keeffe, O'Callaghan, Williams, Najman, & Bor, 2003).

Some amino acids are neurotransmitters or precursors of neurotransmitters, and play important roles in the development of fetal brain. Amino acid transfer through the placenta to fetus may be compromised by maternal prepregnancy obesity. For example,

in humans, a high level of leptin resistance, which has a well-established association with obesity, has shown to be linked with a reduction in amino acid transfer to fetus independent of fetal size (Farley et al., 2010). In rodent studies, high maternal testosterone level reduces the activity of a membrane transport protein (e.g. SNAT-2), resulting in a reduction of amino acids transfer across placental membranes (Sathishkumar et al., 2011). Not surprisingly, high circulating testosterone levels are often found among obese women (Soderberg et al., 2001; Sowers, Beebe, McConnell, Randolph, & Jannausch, 2001) and smokers (Sowers et al., 2001). In addition, elevated testosterone levels during pregnancy are associated with reduced fetal size (Carlsen, Jacobsen, & Romundstad, 2006). Other micronutrients, such as vitamin D and iron both of which are found at a low level among obese women, are also considered as possible candidates that may tie maternal prepregnancy obesity to delayed fetal brain development.

1.4. Summary

This chapter described my motivation for this dissertation project, introduced the LCHD framework, discussed how it fits to both T2DM and cognitive -behavioral development, and offered potential mechanisms linking maternal prepregnancy obesity and its effects on offspring's brain function. Because of the brain's remarkable plasticity, postnatal experiences may have large impacts on its functions. Social and physical contexts therefore exert many important influences on one's cognitive-behavioral development. However, the fetal period is a critical period of brain development and the brain is most vulnerable to environmental insults during this period. The life course

approach is useful in identifying risk factors not only from the current but also in past periods through which an individual lived, and to understand the contributions of these risk factors in shaping one's health trajectory. Maternal prepregnancy obesity may adversely impact unborn children's brain function through various intrauterine mechanisms, but whether or not it has lasting effects on child's brain functions is yet to be established in humans. Investigations using the life course approach may provide some insightful answers to this question.

Chapter 2: Integrating Risks for Type 2 Diabetes across Childhood: A Life Course Perspective[1]

2.1. Introduction

Current approaches for understanding the risk for developing type 2 diabetes (T2DM) in children are focused primarily upon overweight and obesity at the time of diagnosis. This cross sectional approach has been helpful in providing an understanding of this new phenomenon, but increasingly it is clear that preventive and treatment strategies need to begin earlier. Models that take a longer view of health development are needed to conceptualize risk profiles differently so that new ways of thinking about prevention, treatment and research may emerge. This paper explores the known risks for T2DM across critical periods of child development (prenatal period, infancy, childhood, adolescence) and integrates these factors with a life course model of health development.

[1] Reprinted from Journal of Pediatric Nursing 2012, 27(4), 310-318, Tanda, R. and Salsberry, P.J., Integrating Risks for Type 2 Diabetes across Childhood: A Life Course Perspective, ©2012, with permission from Elsevier.

2.2. Background

The prevalence of obesity in children (body mass index ≥ 95th percentile) has nearly tripled over the past three decades in the United States (Ogden, Carroll, & Flegal, 2008; Ogden, Flegal, Carroll, & Johnson, 2002). In 2007, the World Health Organization (WHO) reported that nearly 22 million children under the age of five years were overweight worldwide (WHO, 2007). Race and ethnic differences in overweight status are apparent in childhood (Dabelea et al., 2007; Mayer-Davis, 2008). Significantly higher proportions of Hispanic and African American children ages five to 18 years old are overweight and obese when compared with similarly aged white children. These overweight and obese children are more likely to be male, from families with low-income status, and engage in less physical activities (Lutfiyya, Garcia, Dankwa, Young, & Lipsky, 2008). Although both boys and girls from low socioeconomic status (SES) are at greater risk for being overweight, a recent study indicates that boys are more likely to *remain* overweight and girls to *become* overweight during childhood (Sherwood, Wall, Neumark-Sztainer, & Story, 2009). The WHO estimates that more than 75% of overweight children are from low to middle-income countries and consistent with U.S. data, adolescent boys are more likely to be overweight than girls in many European countries (WHO, 2007).

Type 2 diabetes (T2DM), once known to be a late adult disease has emerged among children due in large measure to a strong physiological link between increased weight states and T2DM. Using the National Health and Nutrition Examination Survey data, researchers have found that the rates of T2DM have doubled among U.S. children aged

12 to 19 years over the last 15 years (Ogden, Carroll, & Flegal, 2008). The obesity epidemic alongside these increasing rates of T2DM in children has been tagged the 'twin epidemics' (Smyth & Heron, 2006) and is worrisome as together they portend of a future of worsening health due to the devastating consequences of T2DM. These include chronic renal failure, blindness, coronary artery disease, limb amputation, and central nervous system manifestation (Reagan, 2007). Furthermore, T2DM disproportionately affects youth from racial minority groups when compared to white youth (Lee, 2008). The SEARCH for diabetes in youth study, a national multicenter study, has established rates of T2DM in 15 to 19 year olds ranging from a low in non-Hispanic whites of 0.19 per 1000 to 1.05 per 1000 in African-Americans to a high of 1.74 per 1000 in Native Americans (Liese et al., 2006).

T2DM is most often diagnosed in children during mid to late adolescence, but the risk factors for T2DM operate across childhood. It is well established that T2DM in children is inextricably linked with childhood obesity, but it is also becoming clear that there is a cluster of risks that begin in early childhood and interact and cumulate over the child's life to increase the likelihood of T2DM. The stress response mechanism may be underlying several of these risks and there is growing interest in the relation between psychological stress and the development of T2DM (Black, 2006). It is postulated that stress hormones (e.g. cortisol and norepinephrine) activate the immune and inflammatory response. Insulin resistance is usually present during the inflammatory process and beta-adrenergic stimulation. Increased cytokine activities, such as tumor necrosis factor and interleukin-6, are believed to increase lipolysis in adipocytes, releasing free fatty acids.

This ultimately leads to impairment of insulin signaling by blocking insulin receptors in target tissues (Tsiotra & Tsigos, 2006). Insulin has been found to attenuate the stress response. In studies where insulin was administered intranasally, there was a decrease in the levels of stress hormones circulating in the body (Bohringer, Schwabe, Richter, & Schachinger, 2008). This result suggests that insulin may play an important role in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Conversely, increased adiposity may alter mood through pro-inflammatory cytokines, which may in turn affect the function of HPA axis (Elenkov, 2008; Reagan, 2007). Underlying these physiological processes is the increasing evidence that the fetal environment may set up the child for heightened stress reactivity and abnormal glucose metabolism (Halfon & Hochstein, 2002).

Thus the risks for T2DM are complex, are likely to be influenced by the child's social context and cumulate as the child ages. It is increasingly clear that an understanding of the risk and etiology for T2DM limited to the conditions at diagnosis is incomplete. To understand which children are at highest risk for the development of T2DM a comprehensive life course model that not only accounts for proximal risks, but can also account for risks in prior periods is necessary. Halfon and Hochstein propose such a framework that combines physiological regulations and environmental influences to explain individual health trajectories (Halfon, Russ, & Regalado, 2005). According to the Life Course Health Development (LCHD) framework, an individual's health follows a unique trajectory that is determined by the interactions among surrounding contexts, early life experiences, and his or her biological regulatory mechanisms (Halfon et al.,

2005). The LCHD framework depicts health as "a dynamic, multifactor, and biopsychosocial phenomenon" (Halfon & Hochstein, 2002, p.434) and is based on several assumptions (Halfon & Hochstein, 2002). First, this model assumes the existence of multiple determinants for any disease entity. Second, health is seen as an adaptive process over the life course. Third, cumulative effects of risk and protective factors determine different health trajectories with the timing and sequence of exposure key to health development. Thus, early life events and exposures are important processes that form the foundation from which later risks exert their influence.

The purpose of this paper is to apply Halfon and Hochstein's LCHD framework to what is known about the risk factors associated with the development of T2DM in children. These risks are linked to the developmental stage in which they occur, and traced out through adolescence, highlighting the critical periods and risk accumulation components of the LCHD framework. Four developmental stages of childhood are used for this analysis: the prenatal period, infancy, childhood, and adolescence. The underlying mechanisms posited to explain these risks are reviewed. A cross-sectional summary of these risks by developmental stage is presented in Table 1. Figure 1 lays out the life course model, presenting the factors as a connected chain that accumulates during childhood and either increases or decreases the likelihood that an individual child will develop T2DM by mid-adolescence. The life course framework provides a more comprehensive view of the development of T2DM than a simple cross-sectional approach that considers only risks at the time of diagnosis (e.g., obesity at mid-adolescence). This

life course perspective should prove invaluable for identifying critical periods for prevention, treatment, and research.

2.3. Life Course Stages and Risk for T2DM

2.3.1. Prenatal environment and fetal programming

The idea that the health of an individual is affected by the intrauterine environment has gained increased acceptance among researchers in recent years (Gluckman, Hanson, Cooper, & Thornburg, 2008; Swanson, Entringer, Buss, & Wadhwa, 2009). Birth weight has become a key marker for the intrauterine environment and disease in later life with current epidemiological evidence suggesting that the association of birth weight withT2DM is U-shaped (Boney et al., 2005; Fernandez-Twinn & Ozanne, 2006; Mayer-Davis, 2008). Children born at either end of the weight continuum have been found to be at greater risk for T2DM in later life. Low birth weights have been associated with maternal undernutrition, which has been related to child obesity and T2DM through the "thrifty phenotype hypothesis" (Hales & Barker, 1992). According to this hypothesis, insulin resistance and obesity as well as T2DM in later life are related to undernutrition in fetal life. Evidence supporting this association originated with a study of men in Hertfordshire, England. This study found an inverse relationship between weights both at birth and at one year of age and adult mortality rates from coronary heart disease (Barker, 1995).

During mid to late pregnancy, various tissues and organs continue to grow and develop in the fetus. When undernutrition occurs during this critical period of development, the fetus is likely to develop physiological and metabolic adaptations in

order to increase glucose availability to nourish its developing brain. As a consequence, overall growth of the fetus's body slows down, and these babies are likely to be born small for gestational age. To adjust to the low glucose environment during fetal development, the fetus becomes "thrifty" in its use of glucose. During infancy if nutrients continue to be scarce, this adaptive change may lead to permanent changes in structures or functions.

At the other end of the continuum, high birth weight has been associated with later obesity and T2DM. Maternal gestational diabetes and maternal overweight status, with borderline hyperglycemia, are strongly implicated as possible causes (Boney et al., 2005; Mayer-Davis, 2008; Salsberry & Reagan, 2005). Thus, altered nutrition during the fetal period poses a significant risk for the development of T2DM through either an increase in adipose tissue mass, a reduction of pancreatic function, or both (Cottrell & Ozanne, 2008).

Maternal psychosocial stress during pregnancy has also been linked to altered fetal growth and development (Valsamakis, Kanaka-Gantenbein, Malamitsi-Puchner, & Mastorakos, 2006), possibly through pathways facilitated by increases in maternal glucocorticoid levels coupled with dysregulation of materno-placento-fetal barrier. A placental enzyme, 11beta-hydroxysteroid dehaydrogenase 2, is known to regulate fetal cortisol concentrations by converting cortisol to inactive cortisone. It is postulated that reduced activity and the expression of this enzyme results in increased fetal exposure to glucocorticoid, causing deleterious effects on fetal development (Bertram & Hanson, 2002; Kajantie, 2008). Both acute and chronic stress in the mother may play a role.

Severe and acute life stress during pregnancy, such as an exposure to death or severe illnesses in a close relative, has been associated with a reduced birth weight (Khashan et al., 2008; Precht, Andersen, & Olsen, 2007). Exposure to diffuse and chronic maternal stress, mediated by adverse social environments such as minority status, lower-middle SES, and lower maternal age, has been associated with elevated maternal serum cortisol levels and slow fetal development (Diego et al., 2006). Further, the increased risk for low birth weight may be mediated through maternal behaviors, including cigarette smoking during pregnancy, more frequent in women who experience increased contextual levels of stress (Lobel et al., 2008). Maternal cigarette smoking during pregnancy, in turn, has been shown to result in an increased risk of later childhood obesity (Salsberry & Reagan, 2005) in a dose-dependent fashion (Sharma, Cogswell, & Li, 2008).

Animal studies provide important evidence that is often not possible to obtain in human studies. Animal studies designed to examine the effects of maternal stress on fetal development and later adult disease development are completed in one of two ways; either through the administration of exogenous corticosteroids mimicking the physiological stress response, or through "restraint stress" administered to pregnant animals. For example, exposure of pregnant dams to dexamethasone in late gestation is associated with a lower birth weight in both male and female offspring, and the development of metabolic syndrome in male offspring (O'Regan, Kenyon, Seckl, & Holmes, 2004). Stress through physical restraint on pregnant dams is associated with reduced body weight in both male and female offspring, reduced adrenal and pancreas

size, and decreased serum glucose and cortisol levels at birth in rats (Lesage et al., 2004). In addition, adult offspring of stressed dams show higher levels of leptin and glucose with significantly higher food intake after animals undergo a period of fasting (Lasage et al., 2004). These animal studies are important as they provide evidence to support the observational findings in human that increased prenatal exposure to stress can induce intrauterine growth retardation and insulin resistance, both factors associated with development of T2DM.

Other animal studies reveal that alterations in gene expression or gene products in signaling pathways may contribute to the association between intrauterine environment and birth size. Maternal nutrient deficiency may mediate epigenetic modulation during fetal development, which ultimately alters gene expression of the fetus (Devaskar & Thamotharan, 2007). Within animal models, several epigenetic changes have been found among offspring that experience intrauterine stress (Lillycrop, Phillips, Jackson, Hanson, & Burdge, 2005; Park, Stoffers, Nicholls, & Simmons, 2008; Sinclair et al., 2007). Maternal insults (e.g. psychosocial stress, undernutrition, and smoking) may result in alteration in the hypothalamic-pituitary-adrenal (HPA) axis, leading to dysregulation of neuroendocrine activity and homeostasis mechanisms (Cottrell & Ozanne, 2008; Fernandez-Twinn & Ozanne, 2006; Kajantie, 2008; Osmond & Barker, 2000). Further research is needed to test these relationships.

Thus the risks for T2DM begin within the intrauterine environment when maternal under nutrition and higher stress levels may influence or program the fetus to be more likely to develop obesity and T2DM. This is the beginning point for the health trajectory

illustrated in Figure 1 that unfolds during childhood. Whether these programming effects are reversible is currently unknown and under intense investigation. Animal studies have shown inconsistent results (Cottrell & Ozanne, 2008; de Boo & Harding, 2006) and the child's growth patterns immediately following birth are of particular interest. The children who are thin at birth but have a period of rapid weight gain during childhood are at the greatest risk for developing T2DM. Children who have restricted growth during the fetal period have a reduced muscle mass that cannot utilize an abundant supply of glucose. Subsequently becoming overweight with existing insulin resistance may result in T2DM as early as in mid childhood (Cottrell & Ozanne, 2008; de Boo & Harding, 2006; Valsamakis et al., 2006).

2.3.2. Infancy

Feeding practices during infancy and subsequent child health outcomes, especially child obesity, have received significant attention over the last decade. Although exact mechanisms of how early feeding practices may affect future weight states are unknown, breastfeeding is believed to be protective against developing future obesity (Armstrong & Reilly, 2002; Taveras et al., 2004; Weyermann, Brenner, & Rothenbacher, 2007). Evidence from epidemiological studies indicates that breastfeeding moderately decreases the risk for developing obesity after controlling for sex, birth weight, and low income (Armstrong & Reilly, 2002). Growth is likely to follow a different pattern in an infant exclusively breastfed for greater than nine months from that of a bottle-fed infant or that of an infant switched to bottle-feeding after six months (van Dijk & Innis, 2009). While breastfeeding duration is associated with maternal age, marital status, education, and

smoking during pregnancy (Li et al., 2008), various mechanisms to explain a breastfeeding effect have been suggested. These mechanisms include: (1) biological paths related to leptin; and (2) behavioral paths related to the establishment of healthy eating patterns.

It has been speculated that the hormone leptin in breast milk may be associated with decreased risk for future obesity. In a rodent model, a permanent reversal of an intrauterine programming effect among the offspring of a food-restricted dam was achieved by leptin administration in early infancy (Vickers et al., 2005). Human studies, however, examining the relationship between breast milk, leptin level and risk of obesity are inconclusive (Miralles, Sanchez, Palou, & Pico, 2006; Weyermann et al., 2007). But breastfeeding has been associated with lower blood glucose and serum insulin levels in infancy, as well as a reduced risk of T2DM in later life (Owen, Martin, Whincup, Smith, & Cook, 2006). Whether this protection is mediated by a decreased obesity risk or is an independent result remains an open question.

The acquisition of healthy feeding behaviors during infancy and early childhood may be key to the prevention of or delaying of the development of T2DM. Breastfeeding may be important in achieving these behaviors as studies suggest that breastfeeding may help the infant develop healthier life-long eating patterns, including a self-regulation pattern that reduces the likelihood of overeating. Moreover, breastfeeding, has been suggested, to result in less maternal control of the infant's eating patterns (Harshaw, 2008). A longer breastfeeding period is associated with a less restrictive feeding style in mothers (Taveras et al., 2004). In one-year old children, mothers who breastfed at least

six months were less likely to be disturbed with the child's food intake, though it is unclear as to whether this is because of a self-selection regarding the decision to breast feed or something inherent in the breastfeeding process. Maternal demographic factors such as race, low educational level, and low household income are associated with restrictive feeding style (Taveras et al., 2004). The breastfeeding/feeding behavior path laid down in infancy may contribute to health differences seen in children from these households in later childhood (Mayer-Davis et al., 2008; Woo, Dolan, Morrow, Geraghty, & Goodman, 2008). Improvement in social support system may be necessary to increase the duration of breastfeeding among mothers with low income (Li et al., 2008).

Thus, an infant's future risk for T2DM is influenced by the maternal decision on breastfeeding and its duration. During infancy eating preferences and behaviors are established and influence the growth, development and health path taken through this developmental phase. Infancy builds upon the set of risks and protective factors laid down in utero. Figure 1 illustrates protective factors increasing the child's health capital, while health risks result in its loss.

2.3.3. Childhood

Children do not live alone. Their health behaviors and physical health are directly influenced by how their immediate caregivers perceive and practice eating rituals. Increased parental BMI is a strong indicator for childhood obesity (Danielzik, Czerwinski-Mast, Langnase, Dilba, & Muller, 2004; Davison, Francis, & Birch, 2005; Gibson et al., 2007; Zeller et al., 2007). Children of single mothers who have a high BMI

and low income are likely to become obese because of decreased accessibility to less energy dense and nutritional food (Gibson et al., 2007). Girls from obesogenic family environments and those from non-obesogenic families have very different weight trajectories (Davison et al., 2005). That is, girls who live with parents with high energy dietary intake and low physical activity are more likely to have consistently higher BMIs than girls from non-obesogenic families. In addition, negative mealtime family interactions and conflicted family environments are significantly associated with overweight among children ages six to 18 years old (Zeller et al., 2007). Regular family mealtime as opposed to disorganized meal patterns has a positive effect on child's food preference and feeding patterns, resulting in reduced risk of becoming overweight (Zeller et al., 2007).

Shortened sleep duration is linked to altered hormonal regulations of food intake, energy balance, and weight maintenance (Lumeng et al., 2007). Chronic sleep disturbances may shift the hormonal control toward weight gain, and altered regulation of leptin and ghrelin may be responsible for the weight gain (Lumeng et al., 2007). Average sleep duration less than 12 hours per day before two years of age may be associated with child's overweight status at age three years old (Taveras et al., 2008). When combined with hours of television viewing greater than two hours per day, the risk of overweight at 3 years of age will be significantly higher than shortened sleep hours alone. A similar finding is reported among preadolescent children (Lumeng et al., 2007) with more apparent effects among boys than girls (Ievers-Landis, Storfer-Isser, Rosen, Johnson, & Redline, 2008). However, the difference in gender may be attributed to other

confounding factors and hormonal effects (Ievers-Landis et al., 2008). Unhealthy family routines can set up an individual's health behavior, which is manifested as undesirable food preference, eating habits, shortened sleep duration, and physical inactivity. This, in turn, negatively affects one's biology through hormonal disturbances toward development of T2DM.

The physical environment of a community may also influence choices of health behaviors (Gordon-Larsen, Nelson, Page, & Popkin, 2006). Low SES neighborhoods are likely to have greater access to fast food restaurants (Hemphill, Raine, Spence, & Smoyer-Tomic, 2008; Li, Harmer, Cardinal, Bosworth, & Johnson-Shelton, 2009) and lower accessibility to healthy food (Baker, Schootman, Barnidge, & Kelly, 2006; Franco, Diez Roux, Glass, Caballero, & Brancati, 2008). Physical activity among children and adolescents is promoted as a sense of safety is increased, such as increased neighborhood greenness (Bell, Wilson, & Liu, 2008) and neighborhood walkability in terms of intersection design (Spence, Cutumisu, Edwards, & Evans, 2008). Shorter distance between intersections seems to promote caregivers to take young children for walks. Although younger children from low-income communities may be no less active there are fewer physical activity facilities available (Voss, Hosking, Metcalf, Jeffery, & Wilkin, 2008), with physical activity level and BMI likely to be impacted by the access to these physical activity facilities (Gordon-Larsen et al., 2006).

In childhood the health trajectory is influenced by the context surrounding the child—exercise, food preferences, food availability, sleeping patterns, and time use all influence the unfolding of the child's health, most visibly measured by the weight status

of the child. These contexts unfold upon a child whose biological and behavioral foundations were laid down in utero and during the infancy period. The curved arrows in Figure 1 illustrate these cumulating relationships.

2.3.4. Adolescence

Adolescents experience dramatic body composition changes during puberty. This occurs in a sex specific fashion. Girls tend to increase fat and lean mass gradually and in equal ratio, whereas boys have a dramatic increase in lean body mass (Brufani et al., 2009; Moran et al., 2008). Total body fat percentage decreases in normal weight boys during this period (Moran et al., 2008). Similarly, overweight and obese boys reduce their total fat percentage but with central adiposity (Brufani et al., 2009), increasing their risk for decreased insulin sensitivity (Maffeis et al., 2008; Taksali et al., 2008).

Pubertal insulin resistance may play an important role in the onset of T2DM among overweight adolescents. Studies have examined the changes in biochemical markers during puberty, with a common finding related to pancreatic beta-cell function and a surge in insulin resistance during puberty; however, the latter is usually transient and recovers by the end of puberty (Brufani et al., 2009). Worsened insulin resistance despite increased lean mass in boys is somewhat puzzling. Attempts to explain this surge of insulin resistance by pubertal hormonal changes has produced inconclusive results (Goran & Gower, 2001). Further study is indicated to explain the relationship between body composition changes and pubertal insulin resistance.

Weight gain during the pubertal period may have detrimental effects as the risk of developing T2DM increases if beta-cell function does not recover during puberty.

Because overweight children do experience earlier puberty and a longer period of maturation with various hormonal changes, they have an added risk for developing T2DM (Goran & Gower, 2001; Goran, Shaibi, Weigensberg, Davis, & Cruz, 2006; Weiss et al., 2005; Xekouki et al., 2007). Comparison of biochemical markers in different Tanner stages is often used to find predictors for T2DM in adolescents. For example, changes in insulin sensitivity are apparent among children in different Tanner stages. A significant decrease in insulin sensitivity has been found among children who progressed to Tanner stage III and IV from stage I (Goran & Gower, 2001). A rise in acute insulin reaction (AIR), which may not be fully compensated for by a fall of insulin sensitivity, suggests that a decrease in insulin sensitivity is related to either compensation in beta-cell function or inadequate beta-cell response (Goran & Gower, 2001). Similarly, a decrease in insulin sensitivity and beta-cell function is especially apparent with weight gain during progression through Tanner stages IV and V (Goran et al., 2006).

Furthermore, psychological stress or depressed mood may lead to maladaptive behavior especially when individuals are not equipped with the appropriate coping resources: social support, optimism, mastery and self-esteem (Taylor & Stanton, 2007). Increased preference for energy dense food under stressful situation is demonstrated in animal models (Teegarden & Bale, 2008). In humans, stress sensitive individuals may be especially prone to binge eating behaviors under stressful situation. Adolescent boys and children from low SES minority groups may be more likely to eat unhealthy food and use eating as a coping mechanism (Jenkins, Rew, & Sternglanz, 2005). Adolescents who are overweight are more likely than normal weight counterparts to use eating as a coping

strategy (Martyn-Nemeth, Penckofer, Gulanick, Velsor-Friedrich, & Bryant, 2009). Conversely, being overweight is associated with psychological stress, depressed mood, and maladaptive behavior (Bender, Fuhlbrigge, Walders, & Zhang, 2007; Doyle, le Grange, Goldschmidt, & Wilfley, 2007; Gray & Leyland, 2008). In addition, overweight adolescents who experience frequent teasing by peers and family members are more likely to practice unhealthy eating (Libbey, Story, Neumark-Sztainer, & Boutelle, 2008). Although these associations may be especially prevalent among younger adolescents (Swallen, Reither, Haas, & Meier, 2005), stress level and coping strategies may very well influence weight status. Combined with the trend in earlier onset of puberty among girls over the past 30 years, correlated with the amount of body fat (Kaplowitz, 2008), there may be a relation among increased obesity, early puberty, maladaptive coping behaviors, and development of T2DM.

Finally, during adolescence significant biological changes occur in the child, which may be influenced by the child's weight status, the individual's contextual stress, their response to this stress, and the child's psychological states during this highly volatile time. It is clear from the above review that the presentation of health during adolescence has a long tail that began in utero. Figure 1 again details how this health trajectory builds across childhood.

2.4. Summary and Conclusions

As detailed within each stage, Figure 1 illustrates how Halfon and Hochstein's framework can be used to better understand a child's individual risk for T2DM. The arrows pointing up indicate protective factors, which increase or improve the health

trajectory across time; the downward pointing arrows indicate risk factors, which decrease or worsen the health trajectory across time. The curved arrows indicate a cumulative effect in that health in a future state (e.g., adolescence) is dependent upon sum of the risk and protective factors in the previous states. For example, as drawn in Figure 1, the health trajectory of child A is below that of child B throughout childhood. From the above review of literature, assume the following scenario. Child A experiences greater health risks in each of development periods: for example, maternal obesity and gestational diabetes during fetal life, followed by bottle-feeding, a childhood with little activity, increased screen time, and a diet high in energy dense foods. By age 11 or so, the child is overweight. By age 15 years this child is experiencing glucose intolerance and is diagnosed with T2DM. The health of child B is always greater than child A and this child's health capital increases at a greater rate than child A, resulting in a child at the end of adolescence with not only greater health capital, but the difference between the two has widened considerably. Child B's scenario may be the following: intrauterine life without exposure to maternal increased stressors and/or increased glucose, breastfed for 15 months, physical activities throughout childhood, enters adolescence at a healthy weight and at the end of adolescence is poised to enter adulthood with strong health reserves.

So the key question is always how do we successfully improve the health of child A (and child B)? The strength of this model is that the points of intervention occur *throughout* childhood. It is not isolated to intervening at mid-childhood when the child is diagnosed as overweight. On this understanding of risk factors, prevention begins during

prenatal life and continues during each developmental stage. Likewise, researchers interested in understanding the development of T2DM should keep in mind the "programming" for T2DM that likely occurs during earlier life. Only with this long view will prevention and interventions be successful in stemming the tide of the 'twin epidemic' threatening children worldwide.

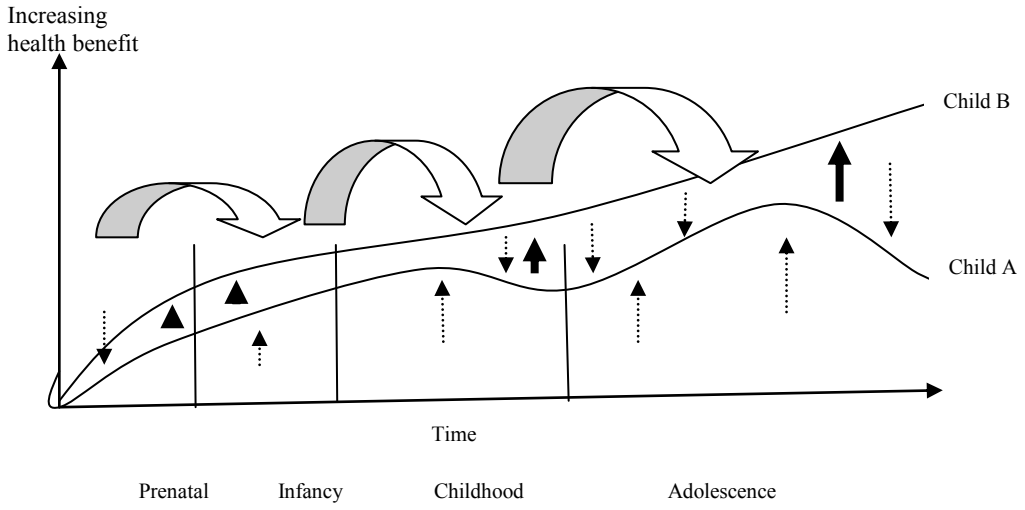

Figure 1. Chain of Risks for T2DM for Two Children (child A and child B)

Note: Upward arrows indicate protective health factors, and downward arrows indicate risk factors. Curved arrows indicate cumulative effect of protective/risk factors.

Risk Factors	Maternal smoking Maternal nutritional stores, e.g., undernutrition Maternal stress levels Gestational Diabetes	Formula fed Duration of breast feeding Early life (first 6 months) growth patterns	Family structure and stability Parental diet and exercise history Food and activity environment Neighborhoods Schools Shortened sleep cycles	Health behaviors, including decreasing amounts of exercise, especially in girls Increased food choice independence
	PRENATAL	**INFANCY**	**CHILDHOOD**	**ADOLESCENCE**
Potential Mechanisms	Adipocyte development Size and number of pancreatic beta cells Maternal hyperinsulinemia and glycemia Epigenetic modulation as result of maternal nutrition Increased maternal glucocortiocoids Dysregulation of materno-placento-fetal barrier	Reduced lean body mass and increased fat mass laid down Feeding patterns set Nutritional differences in breast vs. formula—leptin, protein content	Increased caloric intake Decreased energy expenditure Hormonal changes with altered sleep patterns	Increased caloric intake Decreased energy expenditure Hormonal changes with altered sleep patterns Insulin resistance of puberty

Table 1. Summary of Risk Factors and Potential mMechanisms for Developing T2DM during Childhood.

Risk factors for type 2 diabetes are present throughout childhood. Awareness of these risk factors allows practitioners to identify high risk children and to provide them with appropriate interventions.

Chapter 3: The Impact of Prepregnancy Obesity on Children's Cognitive Test Scores[2]

3.1. Introduction

There is growing concern about the potential ill effects of maternal obesity on offspring health. In the United States, more than 30% of reproductive aged women are obese (body mass index ≥ 30 kg/m^2) (Flegal et al., 2010), and the impact of maternal obesity on fetal brain development is unclear. The brain undergoes rapid development during the fetal period and early childhood. Any insult during this critical period of brain development may be detrimental for individuals' central nervous system development. Animal studies have shown that maternal prepregnancy obesity induced by high-fat-diet consumption is associated with alterations in maze performance among the offspring (Bilbo & Tsang, 2010; Tozuka et al., 2010; White, Purpera, & Morrison, 2009). Those studies have also revealed marked elevations in inflammatory markers in the brain (Bilbo & Tsang, 2010; White et al., 2009), and morphological changes in hippocampal neurons

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with shorter and decreased number of dendrites (Tozuka et al., 2010). In humans, influences from post-natal environment and heterogeneity of individual characteristics often complicate the examination of the association between maternal obesity and offspring's cognitive skills. A few studies examining these associations have produced mixed results (Brion et al., 2011; Neggers, Goldenberg, Ramey, & Cliver, 2003). Brion and colleagues (Brion et al., 2011) have found inconsistent evidence for the intrauterine effects of maternal prepregnancy overweight/obesity on a child's cognitive skill using two European cohorts. In contrast, Neggers and colleagues (Neggers et al., 2003) have shown the association between maternal prepregnancy obesity and reduction in child IQ scores among low-income African American population.

Numerous studies examined factors associated with children's cognitive development. For example, using mother-child intergenerational data, Batty and colleagues (Batty, Der, & Deary, 2006) showed a complete attenuation in the association between maternal smoking during pregnancy and a child's cognitive skill after adjusting for maternal Armed Force Qualification Test (AFQT) scores and education using samples from the National Longitudinal Survey of Youth (NLSY). The same authors (Der, Batty, & Deary, 2006) found no independent association between breast feeding on child cognitive ability. Yang and colleagues (Yang, Lynch, Susser, & Lawlor, 2008), comparing within- and between-family associations, found that family characteristics, rather than birth weight, largely accounted for child cognitive test scores. Economic researchers utilized the rich information on postnatal social environment, and demonstrated the robust effects of income, home environment, home structure, and

postnatal growth on child cognitive development (Blau, 1999; Case & Paxson, 2008; Crane, 1996). However, no other studies have examined the association between maternal prepregnancy obesity and a child's cognitive skill.

The aim of this study was to examine the association between maternal prepregnancy weight status and child cognitive skills at primary school age using a life-course approach. There are two major benefits of using the life-course approach for research: (1) the emphasis on early life experiences and cumulative risk exposure, and (2) the ability to examine interaction between experience and risk with biological regulatory mechanisms and environmental context across the lifespan (Halfon & Hochstein, 2002). We hypothesized that maternal high BMI prior to conception lowers a child's cognitive test score after controlling for other intrauterine factors, family background, maternal and child factors.

3.2. Methods and Procedures

3.2.1. Data Source

We used data from the National Longitudinal Survey of Youth (NLSY) Mother and Child Survey. The NLSY has been widely used for social and health research. The NLSY original cohort (NLSY79) included a nationally representative sample of 12,686 men and women who were 14 to 21 years of age on December 31, 1978. Annual interviews have been completed with these respondents from 1979 until 1994, and biennial interviews thereafter. In 1986, the U.S. Bureau of Labor Statistics established a biennial survey to assess all biological children (NLSY-Children) born to female respondents of NLSY79 cohort on a variety of subjects.

3.2.2. Study Samples

Our study sample consisted of NLSY-Children who were term birth (37≤gestational age≤42 weeks), aged between 60 and 83 months at the time of their biennial interview, and whose Peabody Picture Vocabulary Test (PPVT) age was greater than 60 months. All age-eligible children from survey years between 1986 and 2008 (n=6638) were pooled. The analysis was limited to full-term birth children (n=5236) to avoid any influence from prematurity or post-maturity on brain development. Exclusion criteria included: (1) mother-reported health conditions such as seizure disorder (n=12), mental retardation (n=12), and "heart problem" (n=9); (2) implausible birth weight (<500 grams; n=221); (3) missing information on Peabody individual Achievement Test (PIAT) reading recognition and mathematics scores (n=604 missing reading scores, n=378 missing mathematics scores, n=6 missing both due to missed interviews), Home Observation for the Measurement of the Environment-short form (HOME-SF) cognitive stimulation subset scores (n=148), per-capita income (n=50), mother's AFQT scores (n=179), maternal prepregnancy BMI (n=79), maternal pregnancy weight gain (n=106), child BMI z-score at testing (n=717); or (4) invalid BMI percentile for age and gender using the Center for Disease Control and Prevention (CDC) growth charts program (n=123). The final study sample consisted of 3412 (65.2%) children who had complete data on cognitive test scores, maternal prenatal information, family background, and maternal and child's information.

3.2.3. Measures

All variables used in the analysis are presented in Table 2. We reviewed children's cognitive development studies to guide covariate selection. We organized variables into four broad areas of influence using Halfon and Hochstein's Life Course Health Development framework (Halfon & Hochstein, 2002). These areas are intrauterine factors, family background, prenatal and postnatal maternal factors, and child factors. Selected variables are described below.

The PIAT mathematics and reading recognition scores were used to assess children's cognitive skills. The PIAT has been widely used in research, and has shown relatively high validity and reliability (KR-20 >0.90) (Luther, 1992). In addition, the PIAT demonstrates a moderate to high correlation with the Wechsler Intelligent Scale for Children-Revised (WISC-R; e.g. PIAT mathematics and WISC-R performance IQ, r=0.76 and PIAT reading recognition and WISC-R verbal IQ, r=0.71) (White, 1979). The NLSY provided standardized scores were used, with a mean of 100 and a standard deviation (SD) of 15.

Mother's prepregnancy body mass index (BMI) was calculated from reported height and prepregnancy weight. Subsequently, mothers' BMI was categorized into four groups according to the World Health Organization classification: underweight (BMI<18.5), normal weight (18.5≤BMI<25), overweight (25≤BMI<30), and obese (30≤BMI). Mother-reported weight changes for each pregnancy was used to categorize gestational weight gain according to the 2009 Institute of Medicine (IOM) recommendation (Rasmussen & Yaktine, 2009). Child's birth weight and gestational age were obtained from the mother's report.

HOME-SF is a shorter version of the HOME inventory developed by Caldwell and Bradley (Caldwell & Bradley, 1984), and a unique observational measure of the quality of the cognitive stimulation and emotional support by a child's family (Mott, 2004). The NLSY provided age-based standardized HOME-SF cognitive stimulation scores were used, which has a mean of 100 and an SD of 15. An average HOME-SF cognitive stimulation score for a child's entire observation window was calculated and used as a permanent measure of cognitive stimulation at home. For household income, an average per-capita income deflated to 2008 US dollars for a child's entire observation window was used. For maternal genetic endowment or maternal cognitive skills, the NLSY provided age-adjusted AFQT percentile scores were used.

Child height z-score was derived from mother-reported and interviewer-measured height using the CDC growth charts program. Child BMI z-score and BMI percentile were derived from mother-reported and interviewer-measured height and weight. Of the study sample's height and weight data, 71.6% of height and 65.2% of weight were interviewer-measured.

3.2.4. Statistical Analysis

Dependent variables were PIAT reading recognition and mathematics scores. The primary independent variable was maternal prepregnancy obesity. Ordinary least squares (OLS) regression was used to estimate the association between PIAT scores and maternal prepregnancy BMI categories, adjusting for intrauterine factors, family background, maternal and child factors. We adjusted for PIAT assessment year due to a secular trend in increasing test scores over time. Because siblings were present in the sample, standard

errors were corrected for clustering by family level using the Huber-White sandwich method. We assessed for multicollinearity in the OLS regressions. A variance inflation of greater than 10 indicates serious multicollinearity (O'Brien, 2007); however, our diagnostics did not indicate serious multicollinearity in our models. All analyses were performed using SAS (SAS Institute Inc., Cary, NC) version 9.2.

3.3. Results

Table 3 shows characteristics of the study sample. The mean PIAT reading recognition score was 106.1 (SD=13.5), and the mean PIAT mathematics score was 99.9 (SD=13.6). More than half of children were of Hispanic (20.4%) or African American (30.2%) origins. Children were equal in gender ratio, and 42% were first born. The mean real per-capita income was $15,840 (SD= 20,510) measured in constant 2008 US dollars. A majority of mothers (75.7%) had 12 – 15 years of education, 4.9% with less than high school, and 19.4% with at least 16 years of education. More than half (65.6%) of mothers had normal BMI before pregnancy, and only 9.6% were obese. Nearly half (44.6%) of mothers gained above the 2009 IOM recommended weight gain during pregnancy. The mean weight gains among overweight and obese women were 14.0kg (SD=6.8) and 12.4kg (SD=7.7) respectively. Of mothers who gained above the IOM recommendation, 12.3% were obese, 25.4% overweight, 57.9% normal BMI, and 4.4% underweight.

Children in the study sample were not different from those who were excluded in birth weight, gender, birth order, mothers' pregnancy weight gain and prepregnancy BMI categories. However, excluded children were more likely to be older in PPVT-age, but

younger in chronological age, have lower PIAT reading and mathematics scores, and more likely to be of Hispanic origins. Compared to those included, mothers of excluded children were more likely to be older and less educated, have lower AFQT scores, and provide less stimulating home environment.

Table 4 shows the results of OLS regression for PIAT reading and mathematics score. One specification included child height z-score; another specification included child BMI z-score. Overall, our models explained 21-25% of variance for cognitive test scores. Maternal prepregnancy obesity, but not overweight, was negatively associated with cognitive test scores in both specifications. Using height z-score (Table 3 Columns 1 & 3) and holding all other factors constant, children of obese women was associated with 0.23 SD units lower PIAT reading recognition score and 0.16 SD units lower PIAT mathematics score compared to those of normal weight women. Maternal gestational weight gain was not an independent factor for cognitive test scores. A linear term for birth weight was not a significant predictor for PIAT reading score (β=0.67, p=0.13), but a quadratic relation between birth weight and PIAT mathematics score was present. Using height z-score as a covariate, PIAT mathematics score increased with increasing birth weight until approximately 3.58kg, and then decreased with increasing birth weight. For example, an increase in birth weight from 3.75kg to 4kg resulted in 0.2 points (or 0.01 SD units) lower PIAT mathematics score, holding all other factors constant. An increase in birth weight further from 4kg to 4.5kg resulted in 1.0 point (or 0.07 SD units) lower PIAT mathematics score.

Both HOME-SF score and income were positively associated with cognitive test scores after adjusting for all other factors. Maternal education and AFQT scores were also positively associated with cognitive test scores. Maternal age at childbirth was positively associated with mathematics scores only. Female gender and first-born were positively associated with higher test scores. Child height z-score was positively associated with cognitive test scores. Race/ethnicity was also associated with cognitive test score. There was no significant interaction among any of the variables used.

Of note, as shown in Table 4 columns 2 and 4, child BMI z-score was not an independent predictor for PIAT reading recognition scores (β=0.19, p=0.17), and the association between BMI z-score and PIAT mathematics score was significant only at the 5% level (β=0.34, p=0.02). When child BMI percentile was categorized and entered in the model, an association between cognitive test scores and child BMI categories did not emerge. Inclusion of child BMI z-score or BMI categories did not affect the magnitude of the effect of maternal prepregnancy obesity.

3.4. Discussion

Results indicate that among generally healthy primary school aged children of term birth, maternal prepregnancy obesity is associated with reductions in cognitive test scores after adjusting for other intrauterine factors, family background, and maternal and child factors. The association is consistent in both PIAT reading recognition and mathematics scores. We repeated our analyses excluding all children who had any health conditions that limited school attendance, schoolwork, or physical activities, yet found similar estimates. Adjustment for maternal smoking during pregnancy, breastfeeding,

gestational age, and maternal marital status did not change the estimates substantially. Although test scores reductions of 2-3 points sound small, our results indicate that the effect of maternal prepregnancy obesity is equivalent to a decrease of seven years of education for both reading and math scores. The effect on reading (math) scores of a 1-point increase in HOME-SF score was equivalent to a $5,000 ($3,750) increase in income.

Maternal prepregnancy obesity is associated with various congenital anomalies, such as neural tube defects (Stothard, Tennant, Bell, & Rankin, 2009) and congenital heart defects (Mills, Troendle, Conley, Carter, & Druschel, 2010). The alarming increasing prevalence in obesity among women of reproductive age may affect cognition and health of future generations. For example, a recent Finnish study showed an increased incidence of mild intellectual disability among children of obese mothers (Heikura et al., 2008). However, studies examining the association between maternal prepregnancy obesity and cognitive test scores among generally healthy children have produced inconsistent results due to differences in socioeconomic characteristics and prevalence of obesity in study cohorts, as well as methodological differences (Brion et al., 2011; Neggers et al., 2003).

The results on the effects of maternal prepregnancy obesity were consistent with those by Neggers and colleagues (Neggers et al., 2003), who first documented a negative association between IQ and maternal prepregnancy obesity among a low-income African American population. Since maternal prepregnancy obesity did not interact with any of race/ethnicity groups, this indicates that effects of maternal obesity were not confined to

African American populations but remain equally applicable to other racial/ethnic groups. Our results differ from Brion and colleagues (Brion et al., 2011), who found no consistent association between cognitive test scores and maternal overweight and obesity in two European cohorts. Brion and colleagues (2011) combined obesity and overweight categories, which may have masked the effect of maternal prepregnancy obesity on children's cognitive development. Both Neggers' and the current study did not find an independent effect of maternal overweight on children's cognition. We recommend confirmatory studies with different cohorts using similar analytical methodologies.

Pregnancy and birth complications are more common with excessive gestational weight gain (Catalano, 2010), and therefore, weight gain during pregnancy is a significant health concern for both mother and child. Excessive gestational weight gain alone is an independent factor for a number of adverse neonatal outcomes (Stotland, Cheng, Hopkins, & Caughey, 2006), which may lead to delayed child cognitive development. However, results of the current study did not demonstrate an association between maternal gestational weight gain above the IOM recommendation and cognitive test scores in our sample.

Studies examining the relationship between birth weight and children's cognitive test scores have produced mixed results. A few studies have found a quadratic relation (Sorensen et al., 1997) and other studies have found a linear relation (Yang et al., 2008; Yang, Platt, & Kramer, 2010), or no relation at all (Pearce, Deary, Young, & Parker, 2005). Direct comparison of each study is difficult due to the methodological differences, but a systematic review of the studies examining the association between

birth weight and cognitive skills has shown a linear relation with inconsistent results at a higher end of birth weight (Shenkin, Starr, & Deary, 2004). In the current study, we found a linear association between birth weight and reading scores, whereas math scores followed a quadratic association. It is possible that certain biological characteristics unique to obese women influence fetal brain development, but do not necessarily alter fetal growth. If true, the obstetrical standard of early delivery to avoid large birth size would not change the outcome of children's cognitive skills.

Mechanisms for the association between maternal obesity and reduction in children's cognitive skills are not clear. However, it has been speculated that insulin receptors in the brain bind with neurotrophic factors (Chiu & Cline, 2010); hence, restricting neuronal cell growths and synapse formations. Fetal insulin resistance as well as altered metabolic regulations, often found among neonates of obese as well as diabetic women (Catalano et al., 2009; Dyer, Rosenfeld, Rice, Rice, & Hardin, 2007), may work to impede neuronal growth of the fetal brain.

As shown in results of the current study as well as those from many other previous studies, genetic endowment and the postnatal environment have strong influences on development of children's cognitive skills. The postnatal home environment is a powerful factor of child cognitive development in early age (Crane, 1996). In particular, poverty limits parental ability to provide a stimulating early home environment (Blau, 1999). While income and parental genetic endowment are nonetheless important for child cognitive development, these effects are mediated by home environment (Crane, 1996). In addition, racial differences found in scholastic test

scores are largely accounted for by disadvantaged early home environment (Yeung & Pfeiffer, 2009). While maternal age at childbirth *per se* may not be a causal factor, children born to young mothers are more likely to have disadvantaged family background (Lopez Turley, 2003), thus are more likely to have lower cognitive skills.

The extent of recovery from an insult by maternal obesity undoubtedly depends on postnatal environment. These insults may have the greatest impact on children who live in disadvantaged home environments. With risk factors accumulated in childhood, a chance of recovery will likely decrease among children living in disadvantaged environment. In other words, early investment in the health of children before they are born could result in amplifying differences in the cognitive outcomes between children of advantaged and disadvantaged parents.

Strength of our study was that we were able to control for a number of confounding factors shown to have strong influence on development of cognitive skills in children: intrauterine, family background, maternal, and child factors. We also used permanent measures of family functions, which has been demonstrated to be a better predictor for child cognitive outcomes than point-in-time measures (Blau, 1999). Our study also has some limitations. First, we did not have information on paternal cognitive skills and maternal gestational diabetes. We do not know how much gestational diabetes accounts for the association between maternal obesity and children's cognitive test scores. It is possible that there may be other omitted variables. Second, our results are limited to cognitive skills in reading and mathematics; therefore, generalization to other

domains of cognition may be limited. Finally, we may have introduced sampling bias because missing data did not appear to occur at random.

In summary, we found that maternal prepregnancy obesity was associated with a reduction in cognitive test scores among generally healthy children from term birth. The magnitude of the reduction due to prepregnancy obesity is large compared to magnitude of the changes in income or education that would be required to produce a comparable effect. Compounded with an adverse childhood environment, a large and long-term impact on child's future may result. Thus, it is imperative for practitioners and policy makers to encourage young women to maintain a healthy weight prior to conception, promote weight reduction after each child, and provide easy access to an early supportive postnatal environment for children. We recommend study replication with different cohorts using analytic methodologies prior to translating findings into practice.

MEASURES	Description
Children's cognitive skills	
PIAT mathematics score	84 multiple-choice items. Standardized to have mean of 100 and standard deviation of 15
PIAT reading recognition score	84 words for a child to read silently, then say it aloud. Standardized to have a mean of 100 and standard deviation of 15.
Intrauterine factors	
Maternal prepregnancy BMI	Calculated from self-reported adult height and weight just before each pregnancy. Categorized to underweight, normal weight, overweight, and obese according to the World Health Organization BMI categories.
Maternal gestational weight gain	Reported weight changes of mother during each pregnancy: categorized into below, within, and above recommendation using the 2009 IOM Guideline according to prepregnancy BMI categories.
Birth weight	Mother reported birth weight in kilograms.
Family background	
HOME-SF cognitive stimulation score	A permanent measure constructed from HOME-SF cognitive stimulation subscale by averaging all scores of a child over entire observation window. Questions and raw scores differ by age groups (less than 3 years, ages 3 - 5, ages 6 - 9, and ages 10 - 14). Some items of the HOME-SF included: numbers of books or toys child has, how many times child gets out of house, how many times child eats meals with both parents, and if the play environment is safe.
Household income in 2008 US dollars	A permanent measure constructed from household income and number of persons in the household deflated to 2008 US dollars. It is an average of per-capita income from birth of a child to the age of his/her PIAT assessment.
Maternal factors	
Education	Expressed as maximum years of education completed
Cognitive skills	Age adjusted percentile score of Armed Force Qualification Test (AFQT). Developed by the Department of Defense, and a measure of trainability and a primary criterion of enlistment eligibility for the Armed Forces. Four areas of ASVAB, arithmetic reasoning, word knowledge, paragraph comprehension, and mathematics knowledge, make up AFQT scores.
Age of mother at birth of child	Reported in years.
Child factors	
Gender	Male vs. female (female=1)
Height at PIAT assessment	Height percentile for age and gender, calculated from mother reported or measured height using the CDC growth chart program.
PPVT age of child at PIAT assessment	Reported in months. Determined by the Peabody Picture Vocabulary Test score. PPVT> 60mon is the eligibility for the PIAT assessment.
Birth order	Dichotomous measure: first child =1
Race/ethnicity	Mother reported race/ethnicity: Hispanic, African American, White, and Asian.

Table 2. Measures

Characteristic	Mean	(SD)	Median	Range	n	(%)
Child						
PIAT mathematics score	99.9	(13.6)	101	65 - 135		
PIAT reading recognition score	106.1	(13.5)	105	65 - 135		
Birth weight, kg	3.42	(0. 51)	3.4	0.9 – 6.5		
Height z-score at testing	0.24	(1.3)	0.3	-6.4 – 6.4		
Height, cm	116.1	(7.6)	116.8	88.9 – 152.4		
BMI z-score at testing	-0.06	(1.5)	0.09	-5.9 – 3.4		
Age at testing, month	71.5	(6.7)	72	60 - 83		
PPVT age at testing, month	71.8	(7.7)	72	60 - 108		
Female					1688	(49.5)
First born					1416	(41.5)
Race/ethnicity						
Hispanic					697	(20.4)
African American					1030	(30.2)
White					1658	(48.6)
Asian					27	(0.8)
Family Background						
Average Home-SF score	97.6	(13.7)	100	22 - 129		
Average per-capita income (in 2008 US $1000)	15.8	(20.5)	11.2	0 - 293		
Mother						
Education, year	13.3	(2.4)	12	0 – 20		
AFQT percentile score	39.4	(27.9)	35	0 - 100		
Age at child birth, year	25.4	(5.0)	25	15 - 41		
Prepregnancy BMI (kg/m^2)						
BMI<18.5, underweight					247	(7.2)
18.5≤BMI<25, normal weight					2239	(65.6)
25≤ BMI<30, overweight					599	(17.6)
30 ≤ BMI, obese					327	(9.6)
Gestational Weight Gain						
below IOM recommendation					843	(24.7)
within IOM recommendation					1046	(30.7)
above IOM recommendation					1523	(44.6)

Table 3. Characteristics of Study Sample (n=3412)

Note: PIAT mathematics, reading recognition, HOME-SF scores are standardized to a mean of 100 and an SD of 15. Pregnancy weight gain categories were determined by amount of weight gain for each prepregnancy BMI category.

	PIAT Reading Recognition		PIAT Mathematics	
	(1) Included height	(2) Included BMI	(3) Included height	(4) Included BMI
Variable	β(se)	β (se)	β (se)	β (se)
Intrauterine Factors				
Prepregnancy BMI				
Underweight	-0.36(0.80)	-0.34 (0.80)	-0.75(0.87)	-0.70 (0.87)
Overweight	-0.73(0.59)	-0.81 (0.59)	-0.68(0.57)	-0.81 (0.57)
Obese	-3.05(0.79)***	-3.14 (0.80)***	-2.22(0.82)**	-2.37 (0.83)**
Gestational Weight Gain				
Above recommendation	-0.54(0.49)	-0.53 (0.49)	-0.49(0.50)	-0.48 (0.50)
Birth weight in kg	6.47(3.21)*	6.62 (3.18)*	11.11(2.91)***	11.33 (2.87)***
Birth weight squared	-0.85(0.46)	-0.86 (0.46)	-1.55(0.42)***	-1.56 (0.42)***
Family Background				
HOME-SF score	0.15(0.02)***	0.15 (0.02)***	0.15(0.02)***	0.15 (0.02)***
Per-capita income in $1K	0.03(0.01)*	0.03 (0.01)*	0.04(0.01)*	0.04 (0.01)**
Maternal Factors				
Education in years	0.42(0.12)***	0.42 (0.12)***	0.32(0.12)**	0.33 (0.12)**
AFQT score	0.11(0.01)***	0.11 (0.01)***	0.09(0.01)***	0.09 (0.01)***
Age at child birth	0.07(0.10)	0.07 (0.10)	0.22(0.11)*	0.23 (0.11)*
Child Factors				
Female gender	3.07(0.40)***	3.01 (0.41)***	1.41(0.42)*	1.31 (0.42)**
Height z-score	0.32(0.16)*	--	0.41(0.16)***	--
BMI z-score	--	0.19 (0.14)	--	0.34 (0.14)*
First-born child	2.70(0.47)***	2.72 (0.47)***	0.70(0.48)*	0.71 (0.48)
Race/ethnicity				
Hispanic	0.07(0.61)	0.01 (0.61)	-2.21(0.63)***	-2.29 (0.63)***
African American	3.34(0.60)***	3.40 (0.60)***	-2.42(0.63)***	-2.37 (0.63)***
Asian	4.12(1.90)*	4.10 (1.90)*	1.95(1.84)	1.89 (1.87)
R^2	0.25	0.25	0.21	0.21
N	3412	3412	3412	3412

Table 4. Associations between Cognitive Test Scores and Maternal Prepregnancy Weight Status and Gestational Weight Gain among Children ages 60-83 months of the NLSY-C cohort

Note: Significant at *α=0.05, **α=0.01, ***α=0.001 levels. All standard errors were calculated correcting sibling clustering. Estimates were also adjusted for maternal weight gain below IOM recommendation, child's PPVT age in months at cognitive testing, and year of cognitive testing.

Chapter 4: Racial Differences in the Association between Maternal Prepregnancy Obesity and Children's Behavior Problems

4.1. Introduction

Research over the past two decades has established a robust relation between the intrauterine environment and the development of various human biological systems, particularly those important for metabolic and cardiovascular function, i.e., heart, pancreas (Barker, 1995). More recent work has begun to document the effects of the intrauterine environment on the central nervous system (CNS) (Antonow-Schlorke et al., 2011; Georgieff, 2007). Prepregnancy obesity and weight gain during pregnancy are two factors that have been associated with the development of adult chronic disease (Boney et al., 2005), but the CNS effects of maternal obesity are less clear. Because of the high prevalence of obesity (body mass index: BMI $\geq$ 30 kg/m^2) among reproductive-aged women (Flegal, Carroll, Kit, & Ogden, 2012), understanding the possible health effects of maternal prepregnancy obesity on long-term CNS function is a high priority.

Recent work has examined the possible effects of prepregnancy maternal obesity on child cognition and behavioral problems. A handful of studies have demonstrated that maternal prepregnancy obesity is associated with offspring's cognition (Krakowiak et al., 2012; Neggers et al., 2003; Tanda, Salsberry, Reagan, & Fang), but fewer studies examined maternal weight status and the child's psycho-behavior problems.

Traditionally, one's behavior is thought to be shaped in the post-natal environments. Indeed contributions from social scientists have shown strong evidence that economic disadvantage has harmful effects on children's development (Blau, 1999; Brooks-Gunn & Duncan, 1997). The effects of poverty on children's mental and emotional health are often mediated through home environment, parental skills, and maternal depression (Berger, Paxson, & Waldfogel, 2009; Rijlaarsdam et al., 2012). The current study helps to fill the gap by examining the relation between prepregnancy weight status and child behavior problems.

Animal studies have demonstrated that maternal obesity prior to conception, coupled with a high-fat diet (HFD) during pregnancy and lactation, is associated with altered offspring's memory and learning of young mice (Bilbo & Tsang, 2010; Tozuka et al., 2010). Bilbo *et al* found that adult offspring of a HFD-induced obese rodent exhibited anxiety-like behavior and increased inflammatory markers in the brain (Bilbo & Tsang, 2010). In humans, epidemiological studies examining childhood behavior problems and maternal prepregnancy weight status have produced mixed results. Studies using Nordic cohorts have shown that children born to obese women are at a higher risk of having attention deficit hyperactivity disorder (ADHD) symptoms compared to those born to women with normal weight (Rodriguez, 2010; Rodriguez et al., 2008). In another study, Brion *et al.* using two European cohorts found no consistent associations between prepregnancy overweight/obesity and behavior problem scores at preschool age or at primary school age across the cohorts (Brion et al., 2011). No study has examined the

association between prepregnancy BMI and offspring's behavior problems using racial groups other than European White.

The purpose of the current study is twofold: (1) to examine the association between maternal prepregnancy obesity and children's behavior problems using children from the United States (US) and (2) to test the hypothesis that the association is similar across racial differences. A recent study using a mixed racial/ethnic group of children from the US found no evidence for a differential impact of race/ethnicity on the association between maternal prepregnancy BMI and children's cognitive function (Tanda et al.). In the current study, we use the term *race* as a social construct (Caprio et al., 2008). If maternal prepregnancy obesity adversely influences children's behavioral development purely through a pathway involving obesity-related metabolic mechanisms during intrauterine period, one would expect the association between prepregnancy obesity and a measure representing children's behavior to demonstrate a similar trend regardless of racial differences.

4.2. Methods

A descriptive observational study design was employed using longitudinal data. Data were obtained from a longitudinal cohort in the United States, the National Longitudinal Survey of Youth (NLSY), Mother and Child file. The NLSY originally included a nationally representative sample of 12686 men and women who were between 14 and 21 years old when the survey began in 1979. Annual interviews were conducted from 1979 through 1994, then biennially thereafter. Starting in 1986, biennial surveys on

the biological children of the NLSY female respondents began and continued to date on a variety of subjects.

4.2.1. Study Sample

The current study was based on primary school-aged children between 96 and 119 months old (n = 7280), using NLSY surveys from 1986 through 2008. Primary school-aged children were chosen because behavior problems are more recognized during this period than at earlier ages and the results could be compared to previous studies (Brion et al., 2011; Rodriguez, 2010; Rodriguez et al., 2008). All age-eligible children were pooled from different survey years, with birth years of children eligible for the study spanning 1976 to 2000. Inclusion criteria for the current study were: White or African American children, term births (gestational age 37-42 weeks), and birth weight 2500 grams or greater. The last two criteria were used to minimize influences from prematurity and low birth weight on subsequent behavioral problems. This resulted in a total of 4183 children born to 2400 mothers. Final sample included a total of 3395 children born to 2080 mothers (81.2% of the eligible sample: Whites = 2127 or 82.3% eligible sample born to 1307 mothers; African Americans = 1268 or 79.3% or eligible sample born to 773 mothers) with complete data and biologically plausible BMI values according to the Centers for Disease Control and Prevention (CDC) growth chart program.

Characteristics of White children who were included in the current study were not different from those excluded. Among African Americans, children who were excluded differed from those included in the study sample in that they were more likely to have

mothers with lower Armed Forces Qualification Test (AFQT) scores and come from families with lower income.

4.2.2. Measures

Variables were selected through reviews of existing literature. Only those that were statistically significantly correlated with the dependent variable were included in the final models. Selected variables are further described below.

Children's behavior problems. Children's behavior problems were measured using total scores of the Behavior Problems Index (BPI), developed by Zill and Peterson(1986) based on Children's Behavior Checklist (Achenbach & Edelbrock, 1981) and other preexisting children's behavior scales to measure behavior problems of children aged 4 years and older. Numerous studies have shown that the BPI has acceptable reliability (e.g., α-reliability = 0.91 for adolescent data from the 1981 Child Health Supplement (Zill, 1990)). The completion rate for the BPI in this cohort has been above 90%. Mothers rated scores on 28 questions, which were based on their children's behavior exhibited for the past three months. A higher score represents a higher level of behavioral problems. The age-based population-normed standardized scores (mean = 100, standard deviation [SD] = 15) as well as percentile scores were calculated by the NLSY analyst and included in the data set. The standardized score was used as a continuous outcome variable.

Prepregnancy weight status. Mothers were asked to report their weight just before pregnancy at their first interview after each birth of their child. Self-reported height for each mother was collected in 1981, 1982 and 1985 interviews. The first

reported height from these interview years and weight just before each pregnancy were used to calculate their prepregnancy BMI. The World Health Organization adult BMI criteria were used to categorize weight status into underweight (BMI < 18.5 kg/m^2), normal weight (18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2), overweight (25 $kg/m^2 \leq$ BMI < 30 kg/m^2), and obese (30 $kg/m^2 \leq$ BMI).

Other covariates. *Emotional support at home* was measured using the Home Observation for the Measurement of Environment Short Form (HOME-SF) emotional support subscale. Developed by Caldwell and Bradley (1984), HOME-SF, a shorter version of HOME, was designed to measure quality of stimulation and support provided by family caregivers, and has shown high correlations with children's cognitive and behavioral development (Totsika & Sylva, 2004). Wording of some items in the scale differs according to developmental age groups. Examples of emotional subscale questions include: "About how many times do you spank your children?" and "If your child got so angry that he/she hit you, what would you do?" Age-based internally normed standardized scores (mean = 100 and SD = 15) were determined by the NLSY analyst. We created a permanent measure of emotional support at home by calculating a mean score of all available HOME-SF emotional support scores of a child from birth to age 119 months.

A permanent *household per capita income* of a child was derived from averaging household per capita incomes from his/her entire observation period. At each interview, mothers reported their family net incomes and the number of people in their families. Per capita income, deflated to 2008 US dollars, was calculated from family net income

divided by the number of family members. Mother's *AFQT scores* (percentile) was used as a general measure of trainability of a mother. The AFQT was administered to original respondents of the NLSY in 1980. Other variables included in the analyses were maternal smoking during pregnancy (dichotomous), birth weight, gestational age, maternal education (maximum years completed), mother's age at birth of each child, child's race by mother-reported racial assignment, and child's age and weight status (determined by the CDC growth chart program) at assessment. Maternal weight status categories when children were aged 96-119 months (thereafter called "maternal contemporaneous weight status") instead of prepregnancy weight status categories were used in the analytical model to assess timing of maternal obesity in relation to children's behavior problem. Maternal marital status (permanent measure), breast-feeding (dichotomous), and birth order (dichotomous) were also considered as covariates. But, these variables showed no independent association with the BPI total score; therefore, they were not included in the final model.

4.2.3. Statistical Analysis

Characteristics of the samples by racial groups were compared using the *t* test (normally distributed variables), Wilcoxon-Mann-Whitney test (non-normally distributed variables), and χ^2 test (categorical variables). We used multivariate linear regression to examine the association between maternal prepregnancy weight status and children's behavior problem scores, adjusting for other specified variables. First, we examined a model that includes both White and African American children. While none of the maternal BMI categories was associated with children's behavior problem scores using

the whole cohort, the interaction for White race by maternal prepregnancy obesity was significant (data not shown). Therefore, we proceeded to examine the association separately by racial groups. We repeated the analyses using maternal contemporaneous weight status in place for prepregnancy BMI categories. Clustering of standard errors by sibling correlation was corrected using the Huber-White sandwich method. Comparisons of characteristics of White and African American children whose mothers were obese before pregnancy were done against those of non-obese mothers using *t* test, Wilcoxon-Mann-Whitney test, and χ^2 test. All analyses were conducted using Stata 11 (StataCorp, College Station, TX).

4.3. Results

Characteristics of the study samples are shown in Table 5. Overall, the mean BPI total score of the study sample was slightly higher than a normative sample. Gender ratio was the same in the whole group and each racial group. Approximately 10% of the children had mothers who were obese before becoming pregnant. The maternal obesity rate increased to 24% when children were primary school-aged. About one half of children (50.9%) had mothers with high school diploma, 27.5% had mothers with some college, and 21.6% had mothers with at least 16 years of education.

There were noticeable differences in characteristics between the two racial groups in all but gender ratios. African American children had approximately a 3-unit higher mean BPI total score ($p < 0.0001$) than White children. Mean birth weight was approximately 200 grams lower among African American children than White children ($p < 0.0001$), but the mean BMI at age 8-9 years was higher among African American

children than among White children ($p < 0.0001$). A greater proportion of African American children had mothers who were overweight and obese before pregnancy than did White children ($\chi^2 = 14.24$, $p = 0.0026$). Maternal smoking prevalence during pregnancy was lower among the African American sample than the White sample ($\chi^2 = 7.55$, $p = 0.0060$). In addition, income, HOME-SF scores, maternal age, education, and AFQT were all lower among the African American sample than the White sample (Table 5).

4.3.1. Association between Maternal Obesity and Children's BPI Total Scores

Table 6 shows the results of the multivariate linear regressions. For the White children, maternal prepregnancy obesity was associated with an average 4.4-unit increase in the BPI total scores compared to having mothers who were normal weight before pregnancy, holding other factors constant. Maternal prepregnancy overweight was marginally associated with the BPI total scores holding other factors constant (p=0.058). In the unadjusted model, maternal prepregnancy underweight showed a positive association with the BPI total scores ($\beta = 3.69$, 95%CI = 1.37 – 6.04). However, inclusion of maternal age and prenatal smoking in the model reduced the magnitude and strength of the association to non-significant level.

On the other hand, among African American children, prepregnancy obesity was not only associated with the BPI total scores in unadjusted models but also the direction of the coefficient was opposite from that of Whites ($\beta = -2.66$, 95%CI = -5.66 – 0.34). Adjustment for other factors reduced the magnitude of the association but remained statistically non-significant ($\beta = -1.74$, 95%CI = -4.82 – 1.34). Neither maternal

prepregnancy overweight nor underweight was associated with children's BPI total scores. Interestingly, only the coefficient for maternal prepregnancy underweight bore positive sign.

We then tested the effects of maternal contemporaneous obesity on children's BPI total scores. We used the same covariates as the models specified before. We found that among Whites, maternal contemporaneous obesity was independently associated with an approximately 2-unit increase in the BPI total scores ($\beta = 2.15$, $p=0.034$) compared to children with normal weight mothers. Removing children whose mothers were obese before pregnant with them resulted in null association between maternal obesity at child's aged 96-119 months and the BPI total scores ($n=1942$, $\beta=0.23$, $p = 0.844$). Among African Americans, on the other hand, maternal contemporaneous obesity was not associated with the BPI total ($\beta = -0.24$, $p = 0.836$). Removing children whose mothers were obese before becoming pregnant with them did not change the results among African Americans.

Across racial groups, the effects of maternal and family background factors on the BPI scores were similar, although the magnitudes and strengths of the associations differed slightly. However, a close examination of some of family background factors showed differences between racial groups by maternal prepregnancy obesity status. For example, un-adjusted associations between HOME-SF scores and the BPI scores showed a systematic increase in the BPI total scores by maternal prepregnancy obesity among White children, while there was a systematic decrease in the BPI scores by maternal

prepregnancy obesity among African American children (Figure 2, Panel A). A similar relation was present between income and the BPI scores (Figure 2, Panel B).

4.3.2. Comparison of Obese vs. Non-obese Characteristics by Racial Groups

Comparison of sample characteristics by maternal prepregnancy obesity status is shown in Table 3. Among Whites, the maternal prepregnancy obese group had lower HOME-SF scores, lower household income, and higher maternal depressive symptom scores than the non-obese group. In contrast, among African Americans, the HOME-SF scores, household income, and maternal depressive symptom scores did not differ between obese and non-obese groups. The gender ratio for the children of obese African American women prompted an examination of gender-separate linear regression models for this racial group. No evidence was found for the gender ratio altering the positive association between maternal prepregnancy obesity and BPI total scores of African American children.

4.4. Discussion

This study was designed to examine the relation between maternal prepregnancy weight status and children's behavior problems, and to examine if the same relationship holds in different racial groups, using African and White U.S. children. We found that the association between children's behavior problem scores and maternal prepregnancy obesity was not consistent across the two racial groups. Maternal prepregnancy obesity was associated with an increase in mother-rated children's behavior problem scores among White primary school-aged children from term-birth. Among African American

children, we found no association between maternal prepregnancy obesity and children's behavior problems. In addition, contemporaneous maternal obesity was not an independent factor for children's BPI scores in either racial group, suggesting that the timing of a White woman's being obese may play an important role in the association. Characteristics of children born to obese women were different from those of non-obese women, although the patterns of difference varied by racial groups in such a way that a wide social gap between obese and non-obese women seemed to exist among Whites but not among African Americans.

With regard to White children, our results are in accordance with those of Rodriguez *et al.* (Rodriguez et al., 2008) and Rodriguez (Rodriguez, 2010) in that maternal prepregnancy obesity was an independent factor for increasing children's behavior problems. However, direct comparisons of these studies may not be possible; the outcome measure in the current study is the mother-rated global behavior problem score, whereas the studies by Rodriguez used the measures to specifically identify ADHD symptoms. Our results are different from those of Brion *et al.* (2011) who examined the same association in two different age groups (preschool and primary school) using a similar instrument to the current study but a different analytic strategy. Their use of an analytical method of estimating the probability of a child being in a higher quintile may have been necessary because of the use of raw scores, but their analysis may have been insensitive to detecting small increases in behavior problem scores, which in our study was about 4.4 units of standardized total score (or a 0.3 SD unit).

With regard to African American children, this was the first study examining the association between children's behavior problem scores and maternal prepregnancy obesity using a large number from a minority racial group. All three of the previous similar studies were conducted in European countries with overwhelming White populations. Our results indicated that maternal prepregnancy obesity in the African American sample was not a factor for their children's developing behavior problems. This was unexpected. Replication of the study using African American children from a different cohort is warranted to verify our findings.

While prevalence of obesity is higher among populations with low socioeconomic status (SES) and minority racial/ethnic standings (Gordon-Larsen, Adair, & Popkin, 2003), obese White women may experience larger social and economic consequences than their African American counterparts. For example, Salsberry and Reagan (2009) found that both childhood and adult low SES were associated with being obese among middle-aged White women, but this relationship did not exist among African American women. Other studies indicated a larger wage difference between obese and non-obese White women than that between obese and non-obese African American women (Cawley, 2004). Using data from the 1981-2000 NLSY79, Cawley (2004) estimated that an obese White woman would earn 11.9% less wages than her normal-weight counterpart. An inverse relationship between BMI and SES was also found among White female adolescents from the early 2000s in the US, whereas high BMI was more prevalent among African American female adolescents from high SES in the same period (Gordon-Larsen et al., 2003; Wang & Zhang, 2006).

The psychological impact of obesity also appeared greater among White women than African American women. For example, low self-esteem was more pronounced among obese White women than obese African American women (Averett & Korenman, 1999). Similarly, quality of life perceived by obese White women was significantly lower than that perceived by obese African American women, though a negative relationship between BMI and perceived quality of life was a general trend in both racial groups (Cox et al.). It is possible that the significant relationship between children's behavior problems and maternal prepregnancy obesity observed in Whites in the current study may be because prepregnancy obesity acts as a marker of persistent social disadvantage or stigma related to obesity that exists among White women. This notion is supported by our results among the White sample showing that children's BMI significantly associated with their own behavior problems. In addition, the null association between children's BPI scores and contemporaneous maternal obesity may demonstrate distinct characteristics of the White women who were obese before becoming pregnant.

Results of the current study may have important health, social, and economic implications. When we estimated the odds of a child having a clinically-significant behavior problems (BPI total score ≥ 90 %ile), children born to obese White women had approximately 1.8 times higher risk of having "high behavior problems" (odds ratio = 1.78; 95% CI: 1.15 – 2.74) compared to those born to normal weight White women. The social and economic burdens of treating these children with behavior problems are high. An annual societal cost for childhood ADHD alone has been estimated over $40 billion in

the US (Pelham, Foster, & Robb, 2007). For young White women who are especially affected by obesity epidemic, providing them with guidance to nurture successful parenting skills and encouraging them to regain healthy weight status may be necessary for reducing the risk of their children developing severe behavior problems. For young African American women, because high weight status carries high costs for their health, innovative approaches to weight maintenance while preserving its protective effect for children's behavior problems are imperative.

The current study has strengths and limitations. One of our major strengths is a large number of African American children in our sample, which allowed us to conduct a separate analysis for each racial group. Panel data design also made it possible to construct permanent measures of HOME-SF scores and household income: more accurate measures for family background than those from point-in-time (Blau, 1999). Our study also has limitations. Most data were from mothers' self-reports, including maternal prepregnancy weight. Individuals at a higher end of weight tend to underestimate and those at a lower end to overestimate their weights (Spencer, Appleby, Davey, & Key, 2002). Therefore, use of self-reported body weight may have resulted in overestimation of the effects by prepregnancy obesity on children's BPI score. In other words, our estimates for prepregnancy obesity may represent for those with much higher BMI than the current cut-off for adult obesity (BMI$\geq$30 kg/m^2). Unfortunately, low frequency of prepregnancy obesity in our sample (9.5%) did not allow us to examine the effects of different obesity classes (e.g. WHO obesity class I, II, or II).

There may be omitted variables that may be correlated to maternal prepregnancy obesity. One of these may be the effect of maternal depression on children's behavior problems, which we were unable to demonstrate due to the limitation in the timing of maternal depressive symptom assessment in the NLSY. The scores of the Center for Epidemiologic Studies Depression scales (CES-D) for the mothers were only available from the interviews in 1992 and 1994. This would mean that the assessment for maternal depressive symptoms may have occurred at varying times for each participant, depending on when she became pregnant: time before childbirth, during pregnancy, or after childbirth. While we were aware of this limitation, we ran our analyses including maternal CES-D score and its interaction term. Inclusion of these variables resulted in strengthening of the positive association between maternal prepregnancy obesity children's BPI scores ($\beta = 5.99$, 95%CI = 2.49 – 9.49) among Whites, and in a statistically significant negative association between prepregnancy obesity and children's BPI score among African Americans ($\beta = -5.6$, 95%CI = -9.40 – -1.81), suggesting that maternal depression may have a distinct effect on the relationship between prepregnancy obesity and children's behavior problems by racial groups.

We may also have introduced sample selection bias. Characteristics of the study sample and those excluded due to missing information were not equally distributed. We realized that disadvantaged African American children were more likely to be excluded, which could have underestimated the effects of income and AFQT scores for this racial group. However, we do not think that it would result in a meaningful change in the association between maternal prepregnancy obesity and children's behavior problem

scores because prepregnancy obesity tends not to bear a signature of social disadvantage among African American women in this sample. Lastly, because of the observational nature of our study design, causal relationship cannot be assumed.

In conclusion, there is little evidence suggesting maternal prepregnancy obesity impact children's behavior problems through intrauterine mechanisms. The association between maternal prepregnancy obesity and children's behavior found in White samples in the current as well as previous studies could not be replicated with the African American sample of the NLSY. Our results indicate that the association between maternal prepregnancy obesity and children's behavior problems may be largely due to disadvantaged social characteristics that are uniquely present among White female population. Culturally sensitive and innovative approaches are needed to reduce the risk of developing childhood behavior problems while encouraging young women of all racial/ethnic backgrounds to maintain healthy weight. The findings of this study add to the growing body of literature documenting the relationship between health outcomes of prepregnancy obesity and racial/ethnic differences. We recommend replication of the study using samples from other racial/ethnic groups.

	Whole Cohort (n = 3 395) mean (SD)	White (n = 2 127) mean (SD)	African American (n = 1 268) mean (SD)	*Sig. p value*
Child				
BPI total standardized score	105.2 (15.0)	104.2 (14.8)	107.0 (15.1)	<0.0001
Gender (female)	49.3%	48.2%	51.0%	0.1160
Birth order (First-born)	44.6%	46.7%	41.1%	0.0014
BMI z-score	0.37 (1.18)	0.30 (1.15)	0.49 (1.2)	<0.0001
Birth weight (kg)	3.46 (0.47)	3.54 (0.46)	3.32 (0.44)	<0.0001
Mother				
Prepregnancy weight status				0.0026
Underweight	7.2%	7.2%	7.2%	
Overweight	17.0%	15.5%	19.3%	
Obese	9.5%	8.7%	10.7%	
Contemporaneous weight status				<0.0001
Underweight	3.0%	3.4%	2.1%	
Overweight	26.8%	25.0%	29.9%	
Obese	23.9%	17.9%	33.9%	
Smoking during pregnancy (Yes)	31.1%	32.9%	28.4%	0.0060
Maternal education (year)	13.5 (2.2)	13.7 (2.3)	13.1 (2.0)	<0.0001
AFQT score	42.6 (28.4)	54.3 (26.1)	23.0 (19.9)	<0.0001
Age at childbirth (year)	25.4 (5.4)	26.3 (5.2)	24.0 (5.4)	<0.0001
Family background				
HOME-SF emotional support	97.9 (12.3)	102.2 (9.5)	90.6 (13.0)	<0.0001
Per capita income (2008 US $1000)	16.5 (19.8)	20.3 (22.3)	10.1 (12.2)	<0.0001

Table 5. Characteristics of study samples from Children of the NLSY at ages 96 and 119 months

Note: The p values shown are from the results of comparisons between White and African American children using t tests, Mann-Whitney-Wilcoxon tests, and χ^2 tests.

	White		African American	
	β	[95% CI]	β	[95% CI]
Prepregnancy weight status				
Obese	4.39***	[1.89,6.90]	-1.74	[-4.82,1.34]
Overweight	1.73	[-0.06,3.53]	-0.46	[-2.92,2.00]
Underweight	1.94	[-0.37,4.25]	0.56	[-2.83,3.95]
Birth weight (kg)	-2.12**	[-3.56,-0.69]	-0.77	[-2.80,1.25]
Gestational age (week)	0.55	[-0.00,1.10]	0.22	[-0.55,0.99]
Maternal prenatal smoking (yes)	2.29**	[0.69,3.89]	2.16*	[0.08,4.25]
Mother's age at childbirth (year)	-0.49***	[-0.63,-0.35]	-0.24*	[-0.43,-0.05]
Maternal Education (year)	0.11	[-0.27,0.49]	-0.40	[-0.99,0.19]
Maternal AFQT score (%ile)	-0.00	[-0.04,0.03]	-0.01	[-0.06,0.04]
HOME-SF emotional support score	-0.29***	[-0.37,-0.22]	-0.18***	[-0.25,-0.10]
Household per capital income (2008 US $1000)	-0.03	[-0.05,0.00]	-0.09**	[-0.16,-0.03]
Child gender (female)	-3.63***	[-4.84,-2.42]	-2.47**	[-4.15,-0.78]
Child BMI z-score	0.71*	[0.15,1.28]	0.54	[-0.19,1.26]
N	2127		1268	
R^2	0.124		0.079	

Table 6. Multivariate Linear Regression Predicting for Children's BPI Total Standardized Score

Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Standard errors shown here were corrected for clustering by sibling correlation.

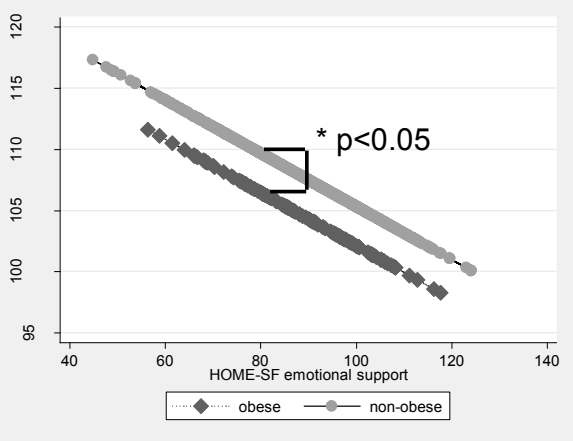
	White				African American			
	Non-obese (n = 1 942)		Obese (n = 185)		Non-obese (n = 1 132)		Obese (n = 136)	
	mean	(SD)	mean	(SD)	p	mean	(SD)	mean	(SD)	p
BPI total standardized score	103.9	(14.7)	107.5	(15.2)	0.0016	107.3	(15.0)	104.6	(15.8)	0.0482
Gender (%)					0.9707					0.1673
Female	48.3%		48.1%			50.4%		56.6%		
BMI z-score	0.24	(1.14)	0.90	(1.13)	<.0001	0.42	(1.19)	1.03	(1.20)	<.0001
Birth weight (kg)	3.53	(0.46)	3.63	(0.49)	0.0070	3.31	(0.44)	3.43	(0.44)	0.0022
Prenatal smoking (%)					0.1967					<.0001
Yes	33.3%		28.7%			30.1%		14.0%		
Mother's education (year)	13.7	(2.33)	13.7	(2.42)	0.9198	13.1	(1.96)	13.5	(2.15)	0.0222
Maternal AFQT score	54.5	(26.2)	52.5	(25.2)	0.3160	22.5	(19.3)	26.8	(23.6)	0.1470
Mother's age at childbirth	26.0	(5.14)	29.0	(4.85)	<.0001	23.5	(5.18)	27.3	(5.62)	<.0001
HOME-SF emotional support score	102.5	(9.43)	99.4	(9.31)	<.0001	90.8	(13.0)	88.5	(12.9)	0.0507
Household per capita income (2008 US $1000)	20.6	(23.1)	16.3	(11.6)	0.0115	10.0	(12.5)	10.6	(8.7)	0.1520

Table 7. Comparison of Sample Characteristics by Racial groups and by Maternal Prepregnancy Obese Status

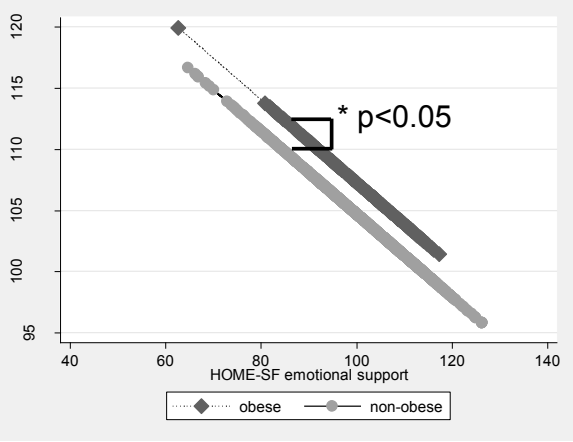
Note: Group differences were assessed using t test, Wilcoxon's non-parametric test, and χ^2 test

A. BPI total standardized score vs. HOME-SF score

African American

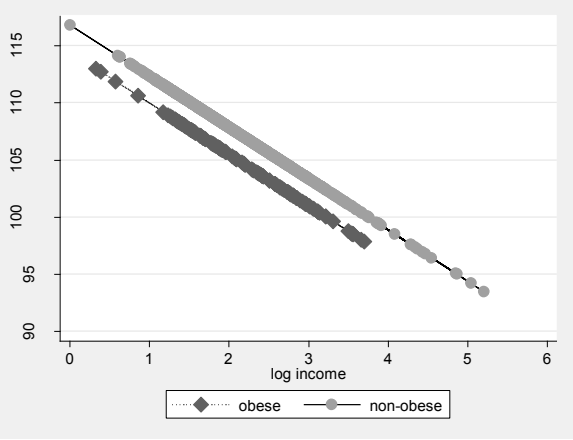


White



B. BPI total standardized score vs. log-transformed household per capita income

African American



White

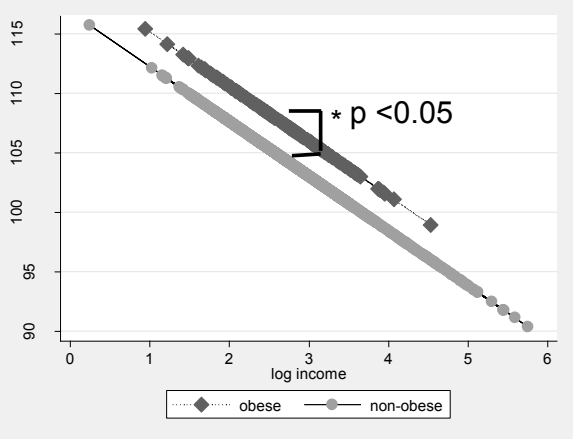


Figure 2. Unadjusted Relations between BPI Total Standardized Score and Selected Family and Maternal Factors Stratified by Maternal Prepregnancy Obese Status.

Panel A shows relationship between HOME-SF emotional score and BPI total score by racial groups: Panel B for the relationship between log-transformed household per capita income and BPI total scores. Dark-shaded lines showing regression lines of the BPI total scores for children of women who were obese before pregnancy; light- shaded lines for those of women who were non-obese before pregnancy.

Chapter 5: Future Research Directions

5.1. Introduction

A child's health is a function of his and her biological systems interacting with multiple contexts. These contextual influences impact his or her health to a different degree depending upon the developmental stage of the child (Halfon & Hochstein, 2002). Identifying critical or sensitive periods of development that are most influential for a particular health development is the key to preventive or treatment intervention. This chapter summarizes overall findings from the studies presented in chapters 2, 3, & 4, and offers directions to future research.

5.2. Summary of Overall Findings

Chapter 2 has demonstrated usefulness of the life-course approach and reviewed risk factors for developing type 2 diabetes (T2DM) during childhood (Tanda & Salsberry, 2012). T2DM risks accumulate from the time of conception through adolescent period. Children from a disadvantaged social background may be especially at a high risk for developing T2DM because they may encounter more adverse events throughout their childhood. The relationship with socioeconomic status (SES) and children's general health outcomes has been empirically tested by Currie and Stabile (Currie & Stabile, 2003) using a longitudinal Canadian cohort. The widened gap in the health status between children from low and high SES is found more prominent as these children age

despite the fact they all have universal health insurance. The reason for the widening gap may be a higher number of new illnesses experienced by low SES children over time than those from high SES (Currie & Stabile, 2003). The question is why disadvantaged social background makes these children encounter more adverse events.

A life course model captures key features in prior periods that are fundamental for altering outcomes. It is no longer adequate to examine behaviors as simply individual action occurring within the current moment. Attention must be paid to the broader context surrounding environments during previous developmental periods. Results from this dissertation study have demonstrated that multiple risk factors for developing ill health are present throughout one's life course. Health of an individual who is exposed to adverse environment in the very early developmental period may be already compromised at the beginning. With subsequent encounters to other adverse conditions, health development trajectory of the individual may further deviate from that of an individual without such early life high risk exposures.

The relationship between maternal prepregnancy obesity and children's central nervous system (CNS) development was examined using samples from the National Longitudinal Surveys of Youth (NLSY). Chapters 3 and 4 demonstrated that the cognitive and behavioral health of a child depends on both intrauterine and postnatal environments. The findings indicated that adverse intrauterine condition evidenced by maternal prepregnancy obesity (BMI $\geq$ 35 kg/m^2) may contribute to lower mathematics and reading skill attainment among children of the NLSY (Tanda et al.). This study served as a confirmation of the finding reported in studies using low-income African

American women and their children (Neggers et al., 2003). Similar study findings were recently noted in samples from the Early Childhood Longitudinal Study—Birth cohort (Hinkle et al., 2012) and the Millennium Cohort Study in the United Kingdom (Basatemur et al., 2013). These study results call for deeper understanding of mechanisms of how maternal prepregnancy obesity influence fetal cognitive development.

This novel finding does not discredit the importance of postnatal environment, such as maternal education, home environment, and poverty, for children's cognitive development. In fact, the results of this study have shown that a large portion of variance in children's reading and mathematics test scores are explained by postnatal environmental factors. The brain's plasticity—experience dependent ability of the brain may play a large role for this despite the fact that substantial changes in the brain development depend on the critical or sensitive periods development that occur during prenatal and early postnatal periods (Cynader, 1994). And this, in fact provides intervention opportunities to help individuals who are already affected by maternal prepregnancy obesity through intrauterine mechanisms.

Unlike the relationship with cognitive skill acquisitions, the results from the study in chapter 4 have shown that the relationship of maternal prepregnancy obesity with childhood behavior problems is different by racial groups. This study assumes that the effects of obesity-related metabolic abnormalities on fetus through placenta are similar regardless of racial difference and that the term race is a socio-cultural construct. The results suggest that childhood behavior problems are primarily shaped by social and

possibly emotional conditions of mothers but not by obesity-related metabolic abnormality during pregnancy. A significant positive association between maternal prepregnancy obesity and childhood behavior problems among White samples in the NLSY could not be replicated with African American samples in the same cohort. In fact, White women, but not African American women, in the sample who are obese prior to pregnancy are found to have disadvantaged socioeconomic characteristics. This is the first study using a large number of African Americans investigating the impact of maternal prepregnancy obesity on childhood behaviors. Other studies used cohorts that were predominantly white European samples (Brion et al., 2011; Rodriguez, 2010; Rodriguez et al., 2008). Replications of the study results with other cohorts with diverse racial/ethnic groups will be necessary to confirm the study findings. The findings also support the notion of racial/ethnic perceptual difference in the relation between health and body composition (Caprio et al., 2008), and make us realize how it may be complicated for some racial/ethnic groups to maintain "healthy" weight status.

5.2. Opportunities for Future Studies

Three major areas for future research are identified that can expand on the work presented here. First, research needs to be directed to unfold the mechanisms that may involve the association between maternal prepregnancy obesity and offspring's cognitive development. Second, there is a need for studies to test conditions that can prevent the original insult during the prenatal period. Third, strategies to mitigate the effects of exposure to maternal obesity during the intrauterine period are needed, and it is

imperative to explore the effective post-exposure interventions to prevent further health declines.

5.2.1. Studies to Examine Mechanisms

Limited discussions will be offered in this area because the research examining mechanisms related to brain development is primarily done with animal models. While human studies may be possible, conducting such research may be costly. Human studies require well-planned longitudinal observations of two generations of samples consisted of expectant mothers and their future offspring. Examinations of biomarkers of mothers before and during pregnancy, their placentas and children may be required. Children also need to undergo series of laboratory examinations including cognitive tests and brain imaging studies.

5.2.2. Studies Examining Modifications in Intrauterine Conditions

The NLSY does not have data on maternal gestational diabetes status or pregnancy oral glucose tolerance test results. This is one of the limitations for the study presented in chapter 3. As a result, contribution of maternal gestational diabetes (GDM) or mild hyperglycemic status to the offspring's cognitive development is unknown. Although adverse pregnancy outcomes of GDM are well established, some questions have been raised regarding the effects of gestational mild hyperglycemia on pregnancy outcomes. The results of the Hyperglycemia and Adverse Pregnancy Outcome study have shown that pregnant women with mild hyperglycemia within normal range of glucose tolerance test results have an increased risk of having adverse pregnancy

outcomes including fetal hyperinsulinemia (Metzger et al., 2008). Many obese pregnant women may experience mild hyperglycemia that is untreated during pregnancy. Therefore, it may be interesting to explore the effects of aggressive glycemic control during pregnancy on the offspring's cognitive outcome.

Studies to examine cognitive outcomes of siblings born to a woman whose weight status changed from obese for one pregnancy to non-obese for subsequent (or vice versa) are also needed. The results of such studies may not only validate the association between maternal prepregnancy obesity and the offspring's cognitive development, but also establish the causal pathway for fetal brain development. However, difficulties in this type of studies are the fact that women's weight change may be modest, and finding a large number of eligible women who already had at least one child before weight loss procedure and who have achieved non-obese status before their subsequent pregnancy. One close example is a cross-sectional study looking at the effect of surgical weight loss procedures on the offspring's cardio-metabolic indicators including weight status, serum levels of lipids, insulin, and a measure of insulin resistance (Smith et al., 2009). The study results are limited because of inadequate controls in the design where children of the pre-surgical mothers are much older (16 ± 0.6 years) than those of the post-surgical mothers (10 ± 0.5 years) and the failure to include children's pubertal stage as a covariate. With weight reduction surgical procedures becoming more accessible at a younger age, the time may be maturing to conduct a well-planned comprehensive multi-centered prospective observational study of the women who have undergone weight

reduction surgical interventions and their children who are born before and after their surgical procedures.

5.2.3. Studies Examining the Effects of Postnatal Environments

For those who are exposed to maternal obesity during intrauterine period, finding the interventions to help best support their cognitive development is priority. In chapter 3, the OLS models show none of postnatal environment modifying the effects of maternal prepregnancy obesity (i.e. no interactions). However, there may be omitted variables that may have moderating effects. Explorations of candidate variables within the NSLY and using other longitudinal cohorts may be warranted. In addition, while the current dissertation study has found independent effect of several postnatal environment, but did not test mediation effects of those on the offspring's cognition. Finding moderating and mediating factors for the relationship between maternal prepregnancy obesity and the offspring's cognitive development will help determine types and timings of interventions best support those children. Close examinations of moderating and mediating effects of early home environment, parenting skills, and early nutritional and educational programs on cognitive outcomes of those affected may bring some very good avenues for interventional studies.

5.3. Summary

Health is a product of not only current but also past contextual exposures interacting with an individual's biological systems. Looking back at the environments where the individual has lived during critical periods of development may provide better

understanding of his or her health development. In this current dissertation study, taking this long view approach has provided an important finding in the relationship between maternal prepregnancy obesity and child's cognitive development. This very same approach can offer several avenues for future research in relation to the current findings.

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