

The Association between Prenatal Maternal Mental Health and Infant Memory and Language
Outcomes

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ABSTRACT

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Prenatal maternal depression and anxiety are associated with poor infant health, behavioral and achievement outcomes. The impacts of prenatal maternal mental health on the development of particular brain-based neurocognitive systems in children are less clear. This dissertation examines the association between prenatal maternal depression and anxiety and infant memory and language outcomes. 179 infant mother dyads were recruited in South Dakota. Ninety infants were followed at 9- and 15-months, and 89 were followed at 15- and 21-months of age. These data were used to understand more clearly the association between prenatal maternal depression and anxiety and changes in infant memory and language over the first two years of life. Additionally, by measuring the interaction between prenatal mental health and parenting and the direct association of parenting on changes in infant memory and language, we can better understand if the pathway between prenatal maternal mental health and infant memory and language is biological, social or both. Results demonstrated no significant direct association between prenatal maternal depression and anxiety symptoms and changes in infant memory or language from 9 to 21 months. The HOME language and literacy subscale was associated with changes in memory and language from 9 to 21 months; the HOME parental warmth subscale was associated with changes in language from 9 to 21 months. These results were independent of prenatal maternal social risk. Implications for additional screening measures, interventions, and considerations for future research are discussed.

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CHAPTER 1

INTRODUCTION

Overview

During pregnancy depression afflicts 10-15% of women and anxiety disorders afflict 8.5% of women (Sutter-Dallay, Giaccone-Marcosche, Glatigny-Dallay, & Verdoux, 2004), representing an important public health concern (Giardinelli et al., 2012; Vaid et al., 1997). There is a significant body of research that examines the impact of prenatal mental health on young children's cognitive development, including lower IQ, difficulties with self-regulation, and lower scores on early developmental indexes, including the Brazelton and Bayley's Mental Development Index (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; Maccari & Morley-Fletcher, 2007; Weinstock, 2008). These studies, however, use standardized measures of children's achievement and development (i.e. IQ, achievement tests, and behavior rating scales) that tend to measure combined functioning of many neurological systems (Buitelaar, Huizink, Mulder, de Medina, & Visser, 2003; Elysia Poggi Davis et al., 2007; Talge et al., 2007). The impacts of prenatal maternal mental health on the development of particular brain-based neurocognitive systems in children are less clear (Yang et al., 2007). With the use of more specific measures, researchers will be able to understand more clearly if there is an explicit association between prenatal maternal mental health and infant cognitive outcomes.

This study examines the association between prenatal mental health and infant memory and language outcomes, two fundamentally independent cognitive systems. Memory relies primarily on the function of the hippocampus while language is a complex cognitive process that

depends primarily on left hemispheric functioning and the perisylvian cortex (Koenigs et al., 2011). Depression and Anxiety during the prenatal period may be particularly harmful to infant memory development. This association can be explained through a biological pathway. Exposures to depression and anxiety during gestation are associated with epigenetic alterations in the glucocorticoid receptor (GC) sites in the hippocampus which disrupt normal cortisol response and Hypothalamic Pituitary Adrenal (HPA) reactivity in infants (Oberlander et al., 2008). HPA reactivity and cortisol production in animal and human studies is associated with memory dysfunction (Wolf, 2003). Because increases in depression and anxiety are associated with these changes in the hippocampal region, it is anticipated that higher levels of depression and anxiety will be more directly associated with changes in memory verses language.

If maternal depression and anxiety problems persist into the postnatal period they have the potential to influence both infant language and memory development through parenting. Mothers that have depression and anxiety during the prenatal period are at greater risk of postpartum depression and anxiety (Pungello, Iruka, Dotterer, Mills-Koonce, & Reznick, 2009). Postpartum anxiety and depression are associated with disruptions in parenting that interfere with the “serve and return” interactions between mother and child that are critical to cognitive development in early infancy. Mothers that are depressed and anxious can exhibit more erratic engagement patterns and demonstrate increased negative affect and tone (ibid, 2009). Maternal depression and anxiety problems during the post-partum period are negatively associated with maternal warmth and sensitivity. Parental warmth has been positively associated with both language and memory development during infancy (Farah et al., 2008; Feldman et al., 2009), its association is, however, explained differently for memory and language. Parental warmth is associated with changes in infant memory via a biological pathway. Greater parental warmth is

linked with a more regulated stress response in infants, which is in turn associated positively with memory development (L. Murray, Halligan, Goodyer, & Herbert, 2010). Greater parental warmth is, also associated with increased verbal interactions between parents and children, and gains in infant language (Pungello et al., 2009). Verbally engaged, responsive parenting is particularly critical to language development during infancy, making children of parents with postnatal mental health issues more vulnerable to language delays (ibid, 2009). Disengaged, unstructured parenting has the potential to influence many aspects of learning including both memory and language (Cleveland & Reese, 2005) .

This study aims to test whether a biological pathway, social pathway, or both are responsible for a link between prenatal mental health and changes in infant memory and language in the first 2 years of life. Because of the important association between increases in depressive and anxious symptomology and fluctuations of the neurotransmitter cortisol with hippocampal variation and memory loss, infant memory outcomes may be more sensitive to increases in maternal depression and anxiety during the prenatal period. Because of the importance of early verbal interactions between parent and child during infancy, language development may be more sensitive to parenting. Although, there are no epigenetic or biological measurements in this study and prenatal maternal mental health measures were not available, the analysis should demonstrate the extent to which prenatal mental health in a nonclinical sample is directly associated with changes in infant memory and language from 9 to 21 months and how much parenting interacts with mental health or is associated directly with these infant cognitive outcomes.

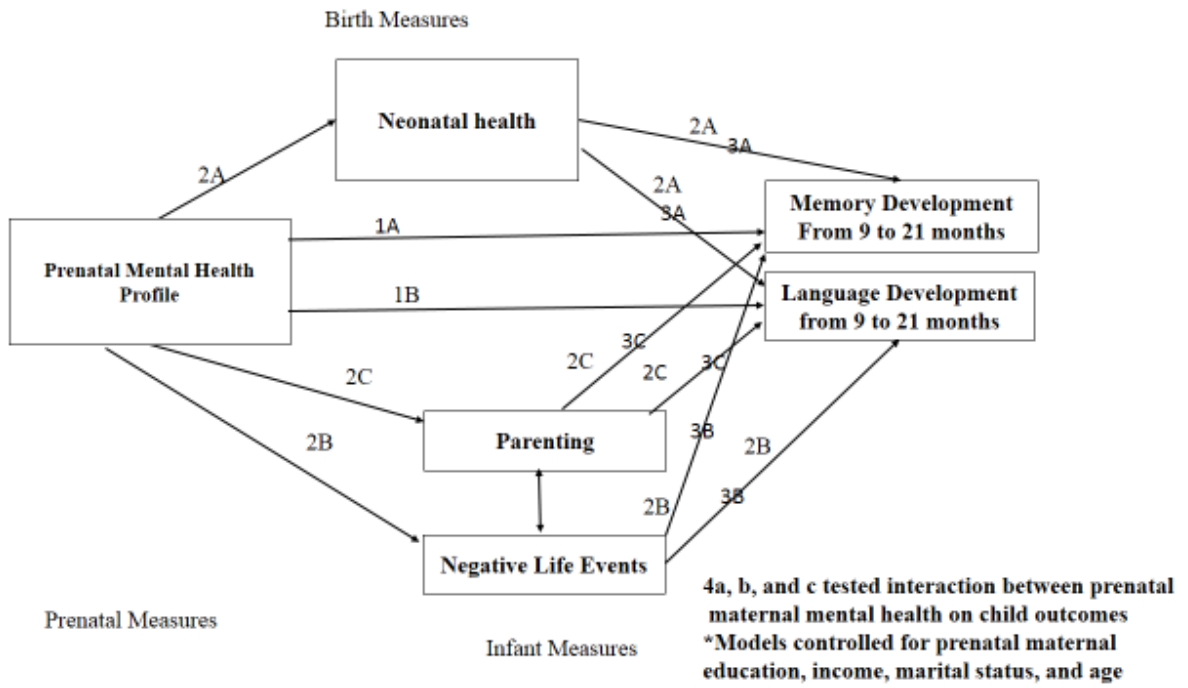
This chapter provides an overview of the theories that have informed my research questions. The summary evaluates the literature on prenatal maternal mental health risk and its

association with infant cognitive outcomes from three main time points: gestation, at birth, and during infancy. This review builds support for the overall aim of my study which is to test whether prenatal maternal mental health has a unique association with changes in infant memory. I begin with an explanation of the social factors that influence the prevalence of mental health problems among women during gestation and the postnatal period. While this study was limited by restricted access to specific maternal prenatal health data and neonatal health data, maternal and infant health are explained and aspects of maternal risk (mental health, income, education, and marital status) and birth outcomes (gestational age and birth-weight) were measured. The review then provides an overview of the research linking prenatal mental health to biological processes associated with infant cognitive outcomes, including recent theories related to DNA methylation, serotonin signaling, and Hypothalamic Pituitary Adrenal (HPA) reactivity, particularly as they influence hippocampal dependent memory function. The second part of the review focuses on the neonatal risks associated with prenatal mental health problems and poor infant cognitive development. The third part of the review will focus on parenting and psychosocial risk factors during infancy associated infant cognitive outcomes.

I begin by reviewing literature that explains the social risks associated with increased incidence of mental health problems during pregnancy. I review past epigenetic literature that provides evidence for the link between prenatal maternal mental health and infant stress reactivity and then describe the association between irregular patterns of stress reactivity and cognitive outcomes in general and then more specifically in relation to memory. I go on to review the literature linking prenatal maternal mental health to postnatal maternal mental health, postnatal mental health to parenting, and parenting to infant memory and language.

My dissertation study will answer the following 4 main questions outlined in the theoretical model in **Figure 1**.

Figure 1. Theoretical Model for Dissertation



1. Research Question 1a: Is prenatal maternal mental health associated with changes in infant memory from 9 to 21 months?

Research Question 1b: Is prenatal mental health associated with changes in infant language from 9 to 21 months?

2. Research Question 2a: Are birth outcomes directly associated with changes in infant memory and language from 9 to 21 months?

Research Question 2b: Are maternal negative life events associated with changes in infant memory and language from 9 to 21 months?

Research Question 2c: Are aspects of parenting and the home environment associated with changes in infant memory from 9 to 21 months?

3. Question 3a: Do birth outcomes mediate the association between prenatal maternal mental health and changes in infant memory and language?

Research Question 3b: Do negative life events mediate the association between prenatal mental health and changes in infant memory and language from 9 to 21 months?

Research Question 3c: Does parenting mediate the association between prenatal mental health and changes in infant memory and language from 9 to 21 months?

4. Research Question 4a: Is there a significant interaction between prenatal maternal mental health and birth outcomes that is associated with changes in infant memory and language from 9 to 21 months?

Research Question 4b: Is there a significant interaction between prenatal maternal mental health and birth outcomes that is associated with changes in infant memory and language from 9 to 21 months?

Research question 4c: Is there a significant interaction between prenatal maternal mental health and infant memory and language from 9 to 21 months?

CHAPTER II

REVIEW OF THE LITERATURE

Overview of Prenatal Mental Health as a Complex Stressor on Infant Development

Prenatal mental health is understood in this paper as a potential stressor on fetal development. Stress, however, is complex phenomenon as it relates to human development and embodies both biological and social risk factors. Dunkel-Schetter and colleagues (2103), in a recent longitudinal study provide support for the use of more sophisticated instruments in measuring stress pathways to explain developmental disparities. From this research and from similar studies exploring stress mechanisms that explain health, cognitive and achievement disparities (Boyd et al., 2009; Bredy et al., 2003; Brooks-Gunn et al., 1994; McLoyd et al., 1991; Noble et al., 2012), it is clear that stress and its impact on human development is multidimensional and relates to many aspects of the environment: including variations in aspects of human biology, culture, socioeconomics, and even gender.

Biological and social stressors when evaluated from a risk perspective are often tested by measuring the dosage and chronicity of stress and their association with developmental outcomes. Just as an increases in chronicity of biological stressors has been associated with poor developmental outcomes, like memory (McEwan et al., 2011; Roozendaal, 2002; Sandi, 2007), chronic exposure to social stressors like financial strain, poverty, and racism are also associated with developmental risks like poor academic achievement and health (Chase-Lansdale et al., 2007; Grant et al., 2004; Kiernan et al., 2008).

Most stressors are complex and include a combination of biological and social risk factors associated with them. Many of the more sophisticated instruments created to explore these types of complex association between stress and human development grew from research

that aimed to disentangle risk factors like poverty and its association with developmental outcomes (Burchinal et al., 2005; Sameroff et al., 2011). Fewer material resources, for example, can influence child development via parenting style and access to quality education (Chase-Lansdale, 1997; Kiernan, 2011; McLoyd, 1991; Smith, 1997), and simultaneously challenge the coping mechanisms and biological stress response of parents and their children, further influencing developmental outcomes (Boyd et al., 2009; Bredy et al., 2003; Lupien et al., 2009).

This study focuses on the stress trajectory between the prenatal maternal mental health and infant cognitive development. Prenatal maternal stressors and their impact on infant development have been tested using varying measurement tools: those that measure pregnancy specific stress (i.e. stress related to abnormalities of the development of the fetus; body changes; lifestyle changes after birth) (DaCosta et al., 1999; Lobel et al., 2008); psychosocial stress (i.e. Spielberger Trait and State Anxiety Scale) (Davis et al., 2010; O'Connor et al., 2001); and biological stress (i.e. maternal cortisol; fetal heart rate) (Allister et al., 2001; Maccari et al., 2007). Despite the prenatal environment appearing to be a finite pathway to explore biological associations (of prenatal anxiety and depression) with infant development (memory), it is still a complex process. There are both biological and social risk factors associated with the prevalence of prenatal maternal mental health and its association with infant health and development.

The next section reviews research relevant to the research questions posited in this study.

1. Research Question 1a: Is **prenatal maternal mental health** associated with changes in infant memory from 9 to 21 months?

Research Question 1b: Is prenatal mental health associated with changes in infant language from 9 to 21 months?

Psychobiological Risks Associated with Prenatal Maternal Mental Health Problems

Anxiety and depression can alter the physiology and behaviors of mothers during pregnancy. These genetic, biological and behavioral modifications have the potential to put pregnant mothers' health and that of their children's at risk. Anxious and depressive symptomology are often reviewed together because they are often comorbid and elicited similar and related neurobiological reactions in the body. I will start by reviewing the literature that describes how prenatal maternal anxiety and depression exposures are associated with biological and genetic changes during pregnancy, then how these changes have the potential to influence infant cognitive development. The biological association between prenatal mental health and memory is referred to as stress reactivity, cortisol reactivity and HPA reactivity in the literature. It will be referenced using these terms throughout the literature review.

In the last section of I will review what is known in the literature about prenatal exposures to anxiety and depression and their specific associations with cognitive outcomes during infancy.

Although anxiety and depression can be activated by specific stressors in the environment or by life events, like pregnancy, there is growing evidence that there is a biological basis for the disorder which may also have an impact on a mother's physiology and that of their developing fetus. The link between maternal anxiety and depression during gestation and fetal and infant physiology and learning is commonly reviewed in the literature as a function of HPA activation and over-arousal, which has a documented association with specific behavioral and learning outcomes in infancy. In Lundy and colleagues 1999 study of 36 pregnant women (36 with depressive symptoms) they found that depressed and anxious mothers had higher levels of

cortisol, and that mothers' cortisol levels positively correlated with their infants'. Hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis in major depression and anxiety disorders is one of the most prominent findings in psycho-neuroendocrinology (See Review by Platsky, 1995). Cortisol production in humans is regulated through the hypothalamic pituitary adrenal (HPA) axis (Sapolsky, 1992) and irregularities in HPA regulation and cortisol production are commonly found in individuals with depression and anxiety (Carroll, 1980; Kitouet, 1984; Field, Diego, Dieter, Hernandez-Reif, Schanberg, Kuhun, Yando, & Bendel, 2004). Maternal cortisol crosses the placenta during gestation (Glover & Sandler, 1996) making the fetus susceptible to her fluctuating cortisol levels. Maternal cortisol is positively correlated with fetal (Gitau, Cameron, Fisk, & Glover, 1998) and newborn cortisol levels and is associated with alterations in the HPA and immune functioning of the infant (Mattes et al., 2009). Some gestational “stress” and cortisol production is essential for optimal fetal growth. However, incidences of high levels of depression and anxiety are both associated with risk in their capacity to alter normal fetal development (Review, Capri et al., 2013).

Cortisol as a function of HPA reactivity is measured several ways in research which can make it difficult to compare findings between studies. There are two primary ways in which cortisol levels are measured: diurnally or as a function of cortisol reactivity. Diurnal measurements are done in the morning and in the evening. Morning is when cortisol is typically higher and in the evening it is typically lowest. Cortisol reactivity is a measurement of cortisol levels in response to specific stressor and/or the time taken for cortisol level to return to resting rate after a stressor was introduced. Both measurements serve as indicators of regulated HPA functioning. The research that uses prenatal maternal stress and mental health indexes to explain

infant variations in cortisol levels is somewhat variable as indicated in the review of the studies below.

Both prenatal maternal depression and anxiety measured late in pregnancy are associated with higher infant basal cortisol levels at birth (Diego et al., 2004; Oberlander et al., 2008), indicating that variations in prenatal depression and anxiety exposures may have the capacity to alter the HPA pathway during gestation. Brennan and colleagues 2008 study evaluating 189 mother infant dyads found when higher prenatal maternal depression was comorbid with higher prenatal maternal anxiety infants had both higher baseline cortisol levels and higher cortisol reactivity when exposed to a stressor. Grant and colleagues 2009 study found that infants of mothers with greater depressive and anxious symptoms also had higher cortisol levels forty minutes post-stress procedure. Van den Bergh and colleagues 2008, results were somewhat different but likewise indicative of dysregulated infant cortisol reactivity as a result of prenatal exposures to higher levels of maternal anxiety. They found that infants of mothers with higher prenatal anxiety had flattened morning cortisol production and heightened evening cortisol levels.

Epigenetic Understandings of Prenatal Maternal Depression and Anxiety and Maternal and Infant Stress Response

These variations in cortisol reactivity as they pertain to hippocampal function in mothers and infants have been explained in some epigenetic research by changes in the neuron-specific glucocorticoid receptor, the NR3C1 F1 promoter gene. Many of the prenatal mental health studies exploring DNA methylation (suppression) or demethylation (activation) of this gene were built off of the findings of McGowan and colleagues 2009 study of children exposed to abuse.

This study was one of the first to examine epigenetic variations of the neuron-specific glucocorticoid receptor gene in humans. Epigenetic modifications of the receptor NR3C1 as a result of poor maternal care and early life stress had already been well established in adult rodent populations exposed to maternal abuse and early environmental stress (Meany, 2001; Plotsky, 2005), but results had not been replicated in human studies. Mc Gowan and colleagues replicated this study in a posthumous human sample that had been exposed to abuse. When comparing the total glucocorticoid (GC) receptor and receptor 1F expression in the hippocampus of suicide completers (n=12) exposed to abuse versus controls (n= 12); they found a significant association of expression of the NR3C1 promoter in participants exposed to abuse. Post hoc analysis also revealed that GC expression in the hippocampus was significantly lower in victims exposed to abuse.

Oberlander and colleagues in 2008 developed a prospective longitudinal study to evaluate how levels of prenatal depression and anxiety may be associated with epigenetic variations in the same NR3C1 region in the infant hippocampus. All infants in the study were born at term and with no neurodevelopmental difficulties measured by APGAR scores at birth. They compared the DNA from cord blood of infants of depressed mothers treated with serotonin reuptake inhibitors (SRIS) (n=33), infants of non-treated depressed mothers (n=13) infants on non-treated non-depressed mothers. They found that prenatal exposure to increased third trimester maternal depressed/anxious mood was associated with increased methylation of infants' NR3C1 site as predicted. Increased NR3C1 methylation at this site was also associated with increased salivary cortisol stress responses at 3 months, even when controlling for prenatal SRI exposure, postnatal age and pre and postnatal maternal mood. A direct pathway between prenatal maternal mood was not found, indicating the methylation status may be what mediates the relationship between

prenatal mood and infant development variations of the HPA functioning in the hippocampal region.

Prenatal Maternal Depression and Anxiety, Stress Reactivity, and Fetal Health

Maternal depression and anxiety during pregnancy (Glover, O'Connor, & O'Donnell, 2010) may indirectly affect children's risk for later cognitive difficulties through these irregularities in HPA functioning (Quas, Bauer, & Boyce, 2004). High doses of synthetic cortisol administered during pregnancy have been associated with uneven stress response in utero, emotional disturbance in early childhood, deregulated stress response in early infancy (i.e. blunted cortisol in response to stress; disproportionate fear response), and neurodevelopmental delays in toddlers (measured through the Bayley MDI) (E. Davis et al., 2006; Elysia Poggi Davis et al., 2004; French, Hagan, Evans, Godfrey, & Newnham, 1999; Wapner et al., 2007). Elevated prenatal cortisol has also been associated with increased fussiness, negative behavior, and fearfulness in infancy (Elysia Poggi Davis et al., 2007).

Timing of increased cortisol production is relevant for fetal development outcomes but research is mixed. Elevated cortisol may be more harmful to the developing fetus later in gestation. For example, in a seminal study by Huizink and colleagues (2003) elevated maternal cortisol during the third trimester was associated with delays in MDI scores at three months and a reduction in motor development at 8 months (Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003). Davis and colleagues 2010 study found after monitoring prenatal cortisol throughout gestation that elevated cortisol early in gestation was associated with slower rate of development over the first postnatal periods and lower scores on the Bayley's Mental Development Index (MDI) at 12 months. In the same study, elevated levels of maternal cortisol

later in gestation were associated with accelerated development over the first year and higher scores on the MDI at 12 months. Associations were not explained by postnatal maternal psychological stress related to parenting, prenatal medical history, SES factors, child race, sex, or birth order. Results from Davis's study suggest that maternal cortisol and pregnancy specific anxiety may have "programming" influences on the developing fetus that depending on the time of exposure to elevated stress and increased cortisol can result in varying outcomes on development.

Stress Reactivity and Changes in Brain Morphology Associated with Infant Cognitive Outcomes

Prenatal depression and anxiety are, in fact, commonly comorbid (O'Connor, Heron, & Glover, 2002) and both are associated with over-activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis and increased cortisol production during gestation. Since both are related to psychosocial states, evidence from the associations of mood on cognitive outcomes is found for the most part exclusively in human studies. HPA reactivity is associated with changes in brain morphology. Chronic activation of infant HPA may be associated with poor memory and executive functioning- because of their involvement in the hippocampal region and frontal cortical region and how this may influence memory consolidation and executive control. The hippocampus is a limbic structure in the brain that is central to memory processing and involved in the regulation of the stress response in both humans and animals (Uno, Tarara, Else, Suleman, & Sapolsky, 1989). The high frequency of glucocorticoid (GC) receptors in the hippocampal region makes it particularly vulnerable to elevated GC and cortisol during a stress response. Because the hippocampus is implicated in the HPA axis during stress, increases in acute and chronic stress are commonly negatively associated with declarative memory outcomes

(Sapolsky, Uno, Rebert, & Finch, 1990). From adult and child animal studies, there is evidence that exposure to intense or chronic stress is associated with hippocampal morphological changes such as irregularities in hippocampal size (Lupien, McEwen, Gunnar, & Heim, 2009; Sapolsky et al., 1990), changes in dendritic density (Liston et al., 2006; Magariños, McEwen, Flügge, & Fuchs, 1996), and disrupted neurogenesis (Dranovsky & Hen, 2006). However, this the literature on morphological variation in the hippocampus associated with fluctuations in HPA activity and environmental exposures are mixed. Tottenham and Sheridan's 2010 review of neuroimaging literature that explores the association between psychosocial adversity and hippocampal variation reveals these inconsistencies. While in in animal studies the association between increased early adversity and hippocampal size is consistently negative, the association between early adversity and hippocampal size (Vyas et al. 2004; Anderson et al. 2004) in human studies has a lot more inconsistencies; some results indicating adversity having an association with larger human hippocampi and others reporting an association with smaller hippocampi. These variations could be attributed to a variety of factors: methods of MRI measurement and age dependent normal variations are some hypothesized understandings of these differences.

Prenatal maternal anxiety and depression have been associated with a decrease in grey matter in young children (Buss, Davis, Muftuler, Head, & Sandman, 2010). However, these variations were found more in the prefrontal cortical region of the brain, which would interfere with executive function outcomes more than declarative memory. However, because of the robust research that exists which identifies a clear association between HPA reactivity and memory function (see review above) and the developing body of research that demonstrates an association between mental health and increased HPA reactivity it is likely that there is an

association between increases in maternal depressive and anxious symptomology and infant memory dysfunction.

A lot of the research that examines the association between prenatal mood and infant brain variations has evaluated maternal mood through the use of stress measures. There is abundant evidence in the animal literature that maternal stress is associated with alterations in the hippocampus of offspring (Rocher, Spedding, Munoz, & Jay, 2004; Sapolsky et al., 1990; Trejo, Cuchillo, Machín, & Rúa, 2000; Uno et al., 1994; Uno et al., 1989). For example, in rodents maternal stressors (physical restraint three times a day) during the last trimester of pregnancy was associated with reductions in cell proliferation and absence of hippocampal neurogenesis and also associated with significant alterations in the hippocampus (Vaid et al., 1997). Similarly, experiments injecting non-human primate mothers with stress hormones before delivery led to reductions in neurogenesis, cortical thickness, and volume of the hippocampus (Lemaire, Koehl, Le Moal, & Abrous, 2000). Lastly, there is some evidence that prenatal stress influences males and female rodents differently. Learning deficits, reductions in hippocampal neurogenesis, LTP and dendritic spine density in the prefrontal cortex are more readily seen in prenatally-stressed males, while anxiety, depression and increased response of the HPA axis to stress are more prevalent in females (Weinstock, 2007). The association between maternal prenatal stress and hippocampal variation would suggest that declarative memory may also be impacted by maternal prenatal stress.

Hippocampal variation and its association with prenatal maternal mood have not been well studied in humans. The evidence taken from animal studies (Sapolsky et al., 1990; Uno et al., 1989) and human studies that have evaluated stress associations with hippocampal development (Andersen & Teicher, 2008; Bremner et al., 1997; Gianaros et al., 2007; Gilbertson

et al., 2002; McEwen & Gianaros, 2011) would suggest that there is a potential for neonatal stress exposure to influence the volume, synaptic density, and cortical thickness of the hippocampus. In humans there is significant evidence that stress influences declarative memory outcomes in general (Lupien et al., 2009; Noble, Houston, Kan, & Sowell, 2012; Roozendaal, 2002; Sandi & Pinelo-Nava, 2007). Moderate stress and cortisol production enhances memory function (Roesch, Schetter, Woo, & Hobel, 2004; Roozendaal, 2002; Sandi & Pinelo-Nava, 2007) and extreme stress and higher cortisol dosage is associated with memory impairment (Kuhlmann, Piel, & Wolf, 2005; Lupien et al., 2009; McEwen & Magarinos, 2001). However, less is known about prenatal maternal stress levels and how they influence memory outcomes for children. There is some evidence that elevated prenatal cortisol is associated with memory dysfunction in six year olds (MacArthur, Howie, Dezoete, & Elkins, 1982) from unique studies that have administered synthetic cortisol to mothers who were at risk of preterm labor.

Prenatal Mental Health and Infant Cognitive Outcomes

Research has found associations between prenatal maternal depression and anxiety and similar delays in infant mental development (Field et al, 2004). Field and colleagues' 2004 research showed that maternal depression and anxiety were negatively associated with lower subscales on the Brazelton Neonatal Assessment Scale, which measures infant neurodevelopmental outcomes like habituation, orientation, and autonomic stability (Diego et al., 2004; Field et al., 2004). Hanley, Brain, and Oberlander's 2004 study found similar motor delays associated with prenatal depression levels being high at 21 weeks gestation. In studies that have tested the association between prenatal maternal anxiety and its association with infant behavioral and cognitive development results demonstrate a range of outcomes. Van den Bergh and colleagues' 2004 study (Van den Bergh & Marcoen, 2004) measured the association

between maternal anxiety in a non-clinical sample of pregnant women at two time points during gestation (21 weeks and 28 weeks) to determine if higher prenatal anxiety symptomology was associated with children's attention and behavior. They found, even when controlling for parental education, smoking during pregnancy, gender, birth weight, and postnatal anxiety that prenatal anxiety at 21 weeks gestation was significantly associated with CBCL reported attention hyperactivity and externalizing behavior problems in children at age 8. Van den Burgh et al. also conducted follow-up studies (2005; 2008) which demonstrated a significant association with prenatal state anxiety at 21 weeks and persistent difficulties with impulsivity at 14 years of age and lower scores in the WISC-R Intelligence tests. Their results show that negative maternal mood, even at non-clinical levels, during pregnancy could be associated with behavioral risks for infant offspring. O'Connor and colleagues 2002 study showed similarly that higher depression and anxiety at 18 and 21 weeks gestation was associated with attention problems at 24 months

Prenatal Mental Health and Infant Memory

Gutteling and colleagues (2006) were one of the few to investigate prenatal mental health and its association with child memory. In their study they evaluated maternal prenatal stress through self-report questionnaires and collected maternal salivary cortisol samples at three time points (18, 21, and 38 weeks) during gestation. No association was found between prenatal cortisol or prenatal stress and infant memory. Recent epigenetic studies (See Review above) have shown a significant associations between increases in maternal depression and anxiety during gestation and methylation of infant NR3C1 brain regions, located in the hippocampus, the brain region critical for memory function and higher cortisol reactivity in children of mothers with higher pregnancy related anxiety and depression levels (Oberlander et al., 2008; Claes et al., 2013). Both higher prenatal depression and anxiety have been associated with higher

responsivity to novelty (Davis et al., 2004) which could have some indication of early memory differences for children exposed to prenatal maternal mental health problems. Di Pietro and colleagues' 2004 study demonstrated benefits of exposure to moderate levels of depression and anxiety. Higher prenatal and depression scores were associated positively with scores on the Baily's MDI, which include measures of memory in combined tasks.

Prenatal Mental Health and Infant Language

A lot of the research exploring the association between maternal mental health and infant language has been done evaluating the association parenting on child outcomes. Brennan and colleagues 2004 study did demonstrate an association between chronic and severe prenatal depression that was negatively associated with language in 5 years olds. However, results did not hold unless postnatal depression was included in the model. La Plante and colleagues' 2004 study examining the association between moderate prenatal stressors and infant development, did find a significant association between prenatal stress and language. Women that were exposed to stressor of the ice storm of 1984 in Canada were evaluated against controls in the same region. Levels of pregnancy specific anxiety in the last trimester explained 12% of the variation in infant language outcomes measured by the McCarthy language scale at 5.5 years of age. Hanley and colleagues' 2013 study tested the association between prenatal depression at 21 weeks and infant language at 10 months. They found that increased depression during pregnancy was associated with infant behavior at 10 months but not language.

Table 1

Prenatal Depression and Anxiety and Infant Cognitive Outcomes

Article	N	SES	Mental Health Measure	Infant Cognitive Outcomes
Hanley, Brain, Oberlander (2013),	31 (Exposed to SSRI) 51 Non-exposed mom-child dyads	Controlled for Maternal Education,	EDPDS, 36 weeks and 10 months Depression	BSID-III, 10 months Results: Sig lower, gross-motor, social emotional and adaptive behavior in SSRI exposure group- No association with communication or cognitive measures (Controlled for Depressed Mood)
Talge, Neal, and Glover, 2007 (A Review: Prenatal Stress and Infant Cognitive Outcomes)			Anxiety	Mothers with higher prenatal anxiety, higher HPA reactivity and Increases in ADHD and language problems at age 8.

<p>Claes et al., 2013</p> <p>Emotional State/ Cortisol in Pregnancy</p> <p>Methylation of NRC31, GC receptor gene</p>	<p>83 pregnant women- analyze cortisol during pregnancy and blood chord genes of infants at birth</p>	<p>Controlled for Income and maternal education</p>	<p>STAI (40 or more), EDPS (10 or more)</p> <p>Measures infant cortisol at three months, Mothers throughout pregnancy.</p> <p>NR3C1 gene was evaluated 3 months.</p>	<p>These data indicate that prenatal maternal emotional state, particularly pregnancy related anxiety, are associated with the methylation state of the NR3C1 gene (human GC receptor), particularly F1 Site in hippocampus in the child.</p> <p>Increased HPA activity was also associated with NR3C1 methylations, controlling for prenatal and postnatal mood and SSRI</p> <p>Maternal Anxiety during the first and second trimesters has an influence on the methylation state of important NGFI- binding sites of 1f NR3C1</p> <p>Depressive state associated with f9 at all stages of pregnancy</p> <p>Association with depressive state disappeared by t3 in this study.</p> <p>Cortisol explained most variance in terms of methylation in this study.</p> <p>Not depressive, anxious or attachment symptoms were related to cortisol measurements. Therefore, can be concluded that cortisol is not likely to directly mediate the effects of these psychological measures on epigenetic</p>
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Oberlander, 2008.
Emotional State and
Methylation

N=31 dyads depressed
moms treated with
SSRIs and N=13
dyads of depressed
non-treated mothers,
N=35 dyads of non-
depressed non-treated
mothers,

Infant cortisol at 3
months collected
before and after a
noxious and non-
noxious stressor, at a
late afternoon basal
time.

2nd Trim- mean
EPDS 10, SSRI -
Treated. Non-treated
14.0

3rd: 7.5 EPDS; non-
treated: 10.7.

Non-Depressed, 4,
4.; 2.7

Depression & Anxiety

Methylation status of the human
NR3C1 gene in newborns is sensitive
to prenatal maternal mood and may
offer a potential epigenetic process
that links antenatal maternal mood
and altered HPA stress reactivity
during infancy.

Prenatal exposures to depression and
anxiety in the 3rd trimester associated
with increased methylation of the
NR3C1 gene and higher cortisol
stress response at 3 months,
controlling for prenatal SRI exposure,
postnatal age, and postnatal maternal
mood.

**First paper to show association
between prenatal mood and
methylation of receptors associated
with hippocampus**

**Methylation explained cortisol
reactivity even when controlling for
maternal mood.**

**Taking SSRI's was not associated
with these patterns. Prenatal
exposure to maternal mood was key
predictor of infant DNA
methylation, even at low levels.**

Devlin et al. 2010.
Prenatal exposure to
depressed mood and
the MTHFR C677T
Variant Affect
SLC6A4
Methylation in
Infants at Birth

Women with MTHFR C677T
genotype had higher EPDS scores
compared to women with other
Genotypes (CT and TT).

Also, **methylation higher** in general
with mothers who had higher
depressed mood at 33 weeks
gestation.

Brennan et al, 2000 N=4953, Prospective

Mom: Maternal
Delusions;
Symptoms States
Inventory (Self-
Report); BDI

Child: CBCL,
PPPVT-R

Vocabulary scores related to
**chronicity and severity of
depression**. Postpartum depression
did not relate to child behavior. Only
moderate levels of maternal
depressive symptoms at 6 months or 5
years were related to child behavior at
5 years. Severity and chronicity of
depressive symptoms was related to
child behavior

O'Connor et al.,
2002 N=7448
18, 32 weeks gestation

Controlled for
postnatal Anxiety,
SES, and Depression

**Anxiety and
Depression
measured (EPDS
and Crown-Crips**

Anxiety and depression was
associated with increased **behavioral
problems** at 47 months. Boys more
likely to display hyperactivity.

Gutteling et al., 2006 N=112
12, 21, 38 weeks

Controlled for
Income and
Education and
Postnatal Stress

Stress and Cortisol

There was no association between
prenatal maternal cortisol infant
memory at 6 years.

Davis et al., 2004	N=22, Third trimester	Controlled for postnatal depression and anxiety	Depression and Anxiety Used CES-D and STAI	Higher depression and anxiety associated with higher responsivity to novelty.
Van den Bergh & Marcoen (2004)	N=72	Controlled for Postnatal Anxiety, Gender and SES	Anxiety: STAI	Higher levels of anxiety were associated with higher externalizing problems (CBCL) at 8-9 years.
Van den Berge et al, 2005	N=57	Controlled for postnatal anxiety	Anxiety: STAI	Higher anxiety (21-24 weeks gest) predicted higher impulsivity and lower scores n WISC 14-15 years.
Huizink et al. 2003	N=170	Controlled for postnatal anxiety, SES and birth complications	Pregnant Specific Anxiety and Daily Hassles	Daily hassle (prenatally) predicted lower MDI scores at 8 months.
La Plante et al. 2004	N=58 Prospective	Controlled for postnatal depression and birth complications	Specific Stress, Quebec ice storm, IES-R created maternal anxiety scale	Maternal prenatal anxiety last trimester predicted 11% and 12% variation in the MDI and MacArthur vocabulary measured in infants at 5.5 years of age.

DiPietro et al., 2006	N=94 Prospective Highly Educated; Older Mom sample, >30 years.	Controlled for maternal education and fetal sex	Depression and Anxiety , Pregnancy Specific Stress (POMS; STAI; DSI PES; Life Events	Higher levels of prenatal anxiety positively related to Baileys' MDI and PDI scores *mild to moderate levels of psychological stress may enhance development for fetus?
Beversdorf, et al., 2005	N=188 retrospective	Income, Education, MS	Life Events (SRSS)	Life Events , particularly between 25-28 weeks was associated with increased incidence of autism

Table 2

Mental Health and Parenting in Infancy and their Association with Infant Cognitive Development

Article	N	SES	Mental Health Measure	Infant Cognitive Outcomes
Murray, 1992	N=113 mother child dyads 111 assessed at 8 months, random subsample seen at 2 to 3 months intervals	Marital Friction, Maternal IQ, Total Income	EPDS Infant: Piaget: Object Concept Task (9months) Bayley and Reynell Scales at 18 months	Infants of mothers with PPD more likely to fail object concept task at 9 months. Infants of mothers with PPD or previous history of depression were more likely to fail at 18 months (more than controls). Maternal Education and Marital Friction moderated outcomes. No association of depression on Bayley's or Reynell-but social class significant predictor. Low SES negative association with language and mental development. Duration and severity had no association with cognitive outcomes.
Murray et al., 1993	N=29 PDD, 10 mothers prenatal depression not pre	Marital Friction, Maternal IQ, Total Income	Bayley, MDI, Piaget's object concept task at 9 and 18 months 5 minute infant mother observed play (recorded complexity of maternal speech)	Infant- focused speech most significant association with 9-month cognitive outcomes (Bayley and concept tasks). 9 months significantly predicted 18 months' performance; Girls showing more improvement than boys. Speech of PPD mothers who had male infants was significantly less infant-focused than the mothers in other groups and displayed more negative

Murray et al., 1996b. N=100 mother child dyads. 98 dyads assessed at 18 months; 95 dyads at 5 years. Longitudinal, 5 year follow-up

Income, Education, marital friction

PDD: EPDS, SPI, RDC

SADS-L, McCarthy Scale of Children's Abilities, Video interaction mother child

Home Environment : Stimulation

Sinclair, 1998 N= 58 PDD mothers and 42 well mothers at 18 months and 5

Income, Education

SPI with RDC;

affect.

Higher **infant focused maternal speech** at 2 years significantly associated with higher scores on Bayley at 18 months.

Maternal depression not significantly associated with object concept at 9 months; significance was found at 18 months.

Infants of Non PDD mothers had significantly better success rate on tasks overall. Girls performed better overall on object concept tasks irrespective of maternal depression status.

No relationship found between any measure of maternal depression (duration, recency, or levels) and children's performance on cognitive tasks.

Early experiences of sensitive maternal interaction, stimulation at home, social class, and for boys, number of months in school, predicted higher cognitive outcomes.

Interaction between PDD with infant sex and SES on temperament, distractibility and behavioral

years

SADS-L 18 months
and 5 years; LEDS;
DAS

Teacher Ratings: ASQ;
PBQ; TABC; PBCL

disturbance.

Boys: PDD associated with higher scores on
activity scale and behavioral disturbance.

Girls: PDD **behavior** associated with controls

Distractibility: Boys, from **LOW SES, and PDD**
highest

**PDD not related to readiness of school, personal
maturity, pro-social behavior, adaptability,
emotional intensity or persistence.**

34

Hay et al.,
1995 N=60 PDD; 75
controls 4 years

Group was
socially
disadvantaged
(mean)

RDC: Pre (12wks)/post
natal (52wks post)

WAIS-R, GHQ,
GRIMS, CBCL

Child: McCarthy scale
of Children's Abilities,
video of **mother child
interaction**

Children of mothers depressed in first year post-
partum, lower significant GCI scores.

Neither depression during pregnancy or at 4 year
assessment **significantly affected child's cognitive
performance.**

Boys of PDD mothers' scored sig. more poorly on
perceptual, motor and **verbal subscales.** (Specific
to mom's with PDD in first year postpartum)

**When controlling for, Maternal IQ, SES,
HOME, and mother child attunement, PDD,
mother child attunement, and home
environment still a significant predictor of child**

HOME Inventory

cognitive outcomes.

Kurstjens
et al.,
2001

N=1329 mother
child dyads,
Longitudinal 7-years

Income, maternal
education,
neonatal health

SADS, RDC, DSM-IV
Griffiths Scale of Baby
Abilities (20 months),
CMM (4 years); K-
ABC (6 years), MPC,
AS

No association between PPD on cognitive
outcomes at 20 months, 4 years or 6 years. No
significant interactions by gender, SES, neonatal
health risk.

Three way interaction PPD, gender and SES
association between cognitive outcomes,
Kauffmann Assessment Battery for Children (K-
ABC) – Achievement Test (learning score) for 6
year olds. Boys from of chronically depressed
mothers in the Lowest SES category did
significantly worse than controls. Limitations:
drop out, missing data.

Summary

In sum, research demonstrates that prenatal maternal depression and anxiety are associated with, health, behavioral and achievement risks (Field et al., 2004; NI Dieter, 2001) for children. These risks can exist even when maternal depressive and anxious symptoms are slightly below clinical threshold (Kessler, R.C, 2003). While explicit associations between prenatal depression, anxiety and neurodevelopmental outcomes are less clear, it has been established that prenatal depression and anxiety symptomology is associated with variations in fetal and infant development, and that these changes are understood through variations in DNA methylation, fluctuations in maternal cortisol production (Diego et al., 2004; Field et al., 2004; Gitau, Fisk, & Glover, 2004; Glover et al., 2010) maternal behavior (Zuckerman, Bauchner, Parker, & Cabral, 1990) and the associated health risks for child development (Brooks-Gunn et al., 1994; Dieter, Emory, Johnson, & Raynor, 2008; Emory & Dieter, 2006; Field et al., 2004; Klebanov, Brooks-Gunn, & McCormick, 1994). These studies establish a link between prenatal depression and anxiety and specific physical (i.e. birth weight, vagal tone), cognitive (i.e. mental development and infant I.Q.); and temperamental; and behavioral (i.e. responsiveness and irritability) outcomes. More needs to be understood in order to isolate the associations of prenatal maternal mental health and specific infant cognitive outcomes, like memory.

The risks of prenatal maternal depression and anxiety appear to be propagated postnatally, as during infancy there is evidence of higher cortisol reactivity in children of depressive and anxious mothers (Elysia Poggi Davis et al., 2007; Quas, Bauer, & Boyce, 2004). Human and animal studies suggest that deregulated stress reactivity interferes with hippocampal dependent declarative memory (de Quervain, Roozendaal, & McGaugh, 1998). However, little

research has directly evaluated the associations of maternal mental health on infant memory development.

This study's aim is to test the pathway between prenatal depression and anxiety and infant memory outcomes by measuring the association between prenatal depression and anxiety symptomology between 20-24 weeks gestation and declarative memory and language outcomes at 9, 15, and 21 months. Testing will be done to recognize potential confounds including, infant birth weight, socioeconomic status and post-natal maternal behaviors such as nurturing and harsh parenting that often mediate the association between mental health disturbances and cognitive outcomes (Belsky & de Haan, 2011; Buss et al., 2007; Field, 2010; Kiernan & Huerta, 2008; L. Murray et al., 2010). These data will be used to investigate whether differences in infant memory throughout early infancy are associated with prenatal maternal depression and anxiety even when accounting for a variety of factors. This is an area of research that is not well understood and has implications for early pediatric intervention models that consider more seriously how the prenatal environment influences child development.

Aside from maternal mental health, a host of factors are important for infant cognitive development, including birth outcomes, socioeconomic status, parenting and maternal life events. It is likely that some of these factors will partially explain or mediate any associations between maternal mental health and infant memory in early infancy (Vaid et al., 1997). The main objective of my study is to understand via multiple analyses the extent to which prenatal maternal depression and anxiety are associated with changes infant memory. Further, because of the unique dataset and measures used to address these questions, described in detail below, we will be able to assess the *specificity* of this association. That is, by measuring simultaneously memory and language, we will be able to determine the extent to which mental health has a

unique influence on infant memory and language. I hypothesize that prenatal mental health, will have particularly important associations on the development of memory and not language during infancy because of the role prenatal anxiety and depression have in influencing maternal and infant stress physiology and the hippocampus, the brain region associated with memory function. Aspects of parenting related to learning and stimulation (i.e. parental learning subscale) will be important in their association to both memory and language. Aspects of parenting related to nurturance and warmth (parental warmth and parental lack of hostility) will be important for both memory and language outcomes but will have a more powerful association with memory outcomes.

CHAPTER III

METHOD

This chapter will describe the data that will be used to examine my research questions, the variables used in the study, the measures that will be used to operationalize and evaluate the variables, and the proposed analysis for using this data to empirically answer the research questions. To recap briefly, this study examines the predictive associations of prenatal mental health on infant cognition, with a focus on memory and a secondary analysis of language. The study begins by testing the specific risks of prenatal anxiety and depression and their association with infant memory and language during infancy. Birth outcomes and aspects of parenting will be examined to determine the extent to which the relationship between prenatal anxiety and depression and infant memory and language are mediated by these additional risks. A diagram of the dissertation logic model is displayed in Figure 1 and Table 3 is a variable reference sheet that will be useful in understanding the components of the study.

Table 3

<i>Variables</i>		
Variables	Description	Time Point
(Mother) Main Predictor <ul style="list-style-type: none"> Prenatal Maternal Mental Health Profile 	Prenatal Depression and Anxiety Profile. Latent class variable created via cluster analysis <ul style="list-style-type: none"> Profile 1: Lowest Levels of Prenatal Depression & Anxiety Profile 2: Mild Levels of Prenatal Depression & Anxiety Profile 3: Highest Levels of Prenatal Depression and Anxiety 	20-24 weeks gestation
(Infant) Birth Outcomes	2 continuous variables: <ul style="list-style-type: none"> Birth Weight (in grams) Gestational Age (in weeks) 	At Birth
(Mother) <ul style="list-style-type: none"> Parenting 	3 continuous variables HOME Subscales <ol style="list-style-type: none"> Parental Warmth Parental Lack of Hostility Parental Learning and Literacy 	During Infancy (15 months)
(Mother) <ul style="list-style-type: none"> Negative Life Events 	1 continuous variable	During Infancy (15 months)
(Infant) Main Outcomes <ul style="list-style-type: none"> Infant Memory and Language 	2 continuous measurements of language and memory taken at 3 times points, 9, 15, and 21 months. <ul style="list-style-type: none"> Language: PLSA;PLSE Memory: VPC and DI 	During Infancy 9, 15, and 21 months
Controls: <ul style="list-style-type: none"> Prenatal Maternal SES: income, maternal education, marital status and maternal age 	Prenatal Maternal SES: 2 Latent class variables created using cluster analysis. Profile 1: Low SES Profile 2: High SES	SES variables: 20-24 weeks gestation

Sample

Hypotheses will be examined empirically using data collected from a cohort of 179 children (80 males) and their mothers from the second trimester until 21 months of age. Families were recruited from the Northern Plains region centered around Sioux Falls, South Dakota. Ninety children were enrolled at 9 months ($M = 9.45$), and an additional 90 children were enrolled at 15 months ($M = 15.43$). Demographic information for the sample is presented in Table 4. Children were initially recruited as part of a larger study (Boyd et al., 2009) investigating the relations between prenatal exposures and birth outcomes (Boyd et al., 2009). All child assessments were done in South Dakota. Neurocognitive measures were developed by Kim Noble at Columbia University College of Physicians and Surgeons. Coding of infant cognitive measures was done by Dr. Noble and her research assistants at Columbia University Medical College.

The families for the larger study were randomly selected from the pool of patients receiving prenatal care at the clinic site. Approximately 7 in 10 pregnant women at the clinic were randomly approached for recruitment in the larger study (<http://safepassagestudy.org/>). All children selected for the current study were typically developing per parent report. Participants were excluded on the basis of major neurological or developmental deficits, birth before 37 weeks gestation, multiple pregnancies, or maternal age under 18 years. 86 (95.6%) of the participants enrolled at 9 months returned for the second lab visit at 15 months, and 88 (97.8%) completed the home visit at 15 months., 80 (89.9%) of the participants enrolled at 15 months returned for the second lab visit at 21 months, and 85 (95.5%) completed a home visit at 15 months. All parents provided written informed consent for their family's participation in this

Table 4

Demographics of sample

Demographic Variable	<i>M</i>	<i>(SD)</i>	%
Infant Gender			
	Male		44.7
	Female		55.3
Gestational Age (weeks)	39.16	(1.14)	
Birth Weight (in grams)	3364	(606)	
Maternal Age	29	(4.5)	
Maternal Education	15.3	(1.5)	
Maternal Income	46,625.70	(15,540.44)	
Marital Status	Percent Married		80.0

Note: N = 179.

study. Participants were given \$75 and a pack of diapers during each visit. Research procedures were approved by the Columbia University Medical Center IRB and the Sanford Health IRB.

Maternal prenatal assessments took place between 20-24 weeks gestation, birth outcomes were assessed at 1 month, postnatal maternal characteristics were assessed at 15 months and infant cognition was assessed at 9, 15, and 21 months [see variable list in Table 1 for variable descriptions].

Measures

Prenatal.

Depression. The Edinburgh Postnatal Depression Scale (EPDS) was used to evaluate depressive symptomology in mothers at 20-24 weeks gestation. The EPDS is a well validated depression measure that is used both prenatally and postnatally to assess depression symptomology (J. Cox, Holden, & Sagovsky). It is a 10 item scale that asks women to respond to statements that assess how they have felt in the past seven days. Responses range from feeling that way all of the time to not at all. Participants can receive a maximum score of 30. Cut off scores for assessing antenatal risk vary in the literature (Adewuya, Ola, Aloba, Dada, & Fasoto, 2007; Benvenuti, Ferrara, Niccolai, Valoriani, & Cox, 1999; John L. Cox, Chapman, Murray, & Jones, 1996; John L. Cox, Holden, & Sagovsky, 1987; D. Murray & Cox, 1990) and range from 9 to 17.

Anxiety. Anxiety was measured with the STAI (Spielberger, 2010), which consists of two 20-item scales measuring the intensity of anxiety as an emotional state (S-Anxiety) and individual differences in anxiety proneness as a personality trait (T-Anxiety). In responding to the S-Anxiety items, subjects report the intensity of their feelings of anxiety “*right now*, at this moment” by rating themselves on the following 4-point scale: (1) Not at all, (2) Somewhat, (3) Moderately so, (4) Very much so. Responses to the T-Anxiety items require subjects to indicate

how they generally feel by reporting how often they have experienced anxiety-related feelings and cognitions on a 4-point scale: (1) Almost never, (1) Sometimes, (2) Often, and (3) Almost always. The maximum score for both subscales is 80. Trait anxiety gets at more stable conditions of anxiety over time while state anxiety assesses current feelings of anxiety at the time of the assessment (Brouwers, van Baar, & Pop, 2001). Cut off scores for assessing risk vary in the literature (Kabacoff, Segal, Hersen, & Van Hasselt, 1997; Monk et al., 2000; Welberg, Seckl, & Holmes, 2001) ranging from 38-68.

Demographic Characteristics. At 20-24 weeks gestation participants completed a demographic questionnaire which covered maternal race/ethnicity (Asian, Native American, Pacific Islander, Black, Hispanic, and White), total years of education for both parents, marital status and estimated total income in bins (\leq \$500, \$501-1000, \$1001-2000, \$2001-3000, \$3001-4000, \$4001-5000, \geq \$5001).

Neonatal.

Infant Demographics Questionnaire. At birth infant birth weight and gestational age were reported as part of an infant demographics questionnaire by parents. Birth weight and gestational age will be used to measure birth outcomes. Infant weight was measured in pounds and gestational age is measured in weeks.

Postnatal.

Negative Life Events. When infants were 15 months, the Life Events Survey was administered to parents. The Life Events Survey is a 44-item self-report questionnaire used by adults to assess the number and quality of life events that occurred for each individual in the past year (Sarason, Johnson, & Siegel, 1978). Participants report the extent to which events had a negative and positive impact on the person's life. Scores range from 0 (no negative events) to 29

(maximum score for negative life events). Use of the negative life events scale as measure of stressful life events has been validated in studies that have compared the survey to other measures of stress (Bailey, Koepsell, & Belcher, 1984; Bergman et al., 2007; Rahman, Iqbal, & Harrington, 2003)

Parenting. Parenting was assessed during the home visit at 15 months by a trained experimenter who administered the Infant-Toddler Home Observation for Measurement of the Environment (IT-HOME; (Caldwell & Bradley, 1984). The IT-HOME is a structured interview and observational checklist designed to measure the quality of home life for children from birth to age 3. From this 45-item measures 3 subscales were used based on Fuligni, Han, and Brooks-Gunn (Fuligni, Han, & Brooks-Gunn, 2004). The HOME Parental Warmth subscale is a composite measure of supportive interactions and warm behavior from mother to child (e.g. parent spontaneously praises the child; parent kisses or cuddles the child). It is assessed through direct observation of the parent and child. Scores range from 0-7. Alpha is .64 for seven items. The Maternal Lack of Hostility subscale is a measure of the mother's acceptance of her child misbehaving or engaging in undesired behavior and her use of harsh punishment in response (e.g. spanking; scolding). Alpha is .54 for seven items. Scores range from 0-7. The Learning subscale is a composite measure of learning, academic, language stimulation and variety in experience (e.g. child has toys which teach color, size, shape, child is encouraged to learn the alphabet and numbers). Scores range from 0-13. Alpha is .87 for the 32 items.

Infant outcomes.

Memory. There were two measures of infant memory collected at 9, 15 and 21 months. The first, the Visual Paired Comparison task (VPC), is used to assess infant memory through the evaluation of novelty preference by following infant gaze. (Morgan & Hayne, 2006; Richmond,

Colombo, & Hayne, 2007). During the procedure infants sat on their parents lap, 40 inches away from the monitor where the stimulus was presented. Parents closed their eyes or directed them in between monitors to not influence the infant's gaze. First, for 13 seconds each participant was presented with a spinning ball to orient themselves to the monitor. Then, during the familiarization phase, the stimulus (a blue mailbox shaped face on each monitor screen) was presented for 10 seconds followed by a 10 second novelty preference phase in one of the blue faces was presented by a circular yellow face. In the second novelty preference task the yellow face was replaced by the familiar blue face, and a square red face was displayed on the second screen. Scores were omitted or not collected in the following cases: child was too fussy to complete task ($n = 2$ at 15mo), child did not attend to stimuli ($n = 3$ at 9mo, $n = 7$ at 15mo), computer error ($n = 2$ at 15mo), other ($n = 1$ at 15 and 21mo).

Coders reviewed total looking time for each of each phase. At every 200 ms interval, the coder determined whether the child was attending to the left monitor, right monitor, or neither. From this, we established whether the child was attending to familiar stimuli or novel stimuli during the novelty preference blocks. The ratio of novel looking time (i.e., attending to red or yellow faces) to total looking time (i.e., attending to any face) is reported. Ratios above 0.5 indicate greater looking time for novel stimuli relative to the familiar stimulus. Reliability checks were run on 20% of the scores. Scores were considered reliable at the 0.95 level.

The second measure, deferred imitation (DI), assesses infant memory by having infants replicate a series of observed actions after a period of delay. In the puppet tasks infants were shown how to take off the removable mitten with jingle bell attached off the right arm of the puppet and return it. This demonstration was done three times. After the demonstration there was a 35-45 minutes delay. Then, after orienting to the puppet the child was given 120 seconds to

replicate the actions: remove the mitten from the puppet's hand, shake the mitten 3 times in the air to ring the bell inside, and then replaced the mitten on the puppet's right hand. Scores were omitted in the instance: child did not attend to demonstration (N=1).

There are 2 rattles constructed for the Deferred Imitation rattle task: green and red. For the green rattle tasks infants were asked to imitate putting a circular bead into a round opening in the rattle. For the red rattle task, infants were asked to fit a blue plastic ball in a circular opening at the base of the rattle. 9 month old participants were only given the rattle task. It was conducted with the same 35-45 minute delay as the DI task and the task was modeled twice before infants were given 120 seconds to replicate each modeled behavior.

At the end of this test portion, the experimenter set up the pieces out of the child's reach and demonstrated the rattle construction one more time. The experimenter then gave the child access to the pieces and allowed him or her 60 s more to imitate the target actions. Scores were omitted or not collected in the following cases: child was too fussy to complete task ($n = 11$), child did not attend to demonstration ($n = 3$), child did not touch toy during test ($n = 4$), experimenter error ($n = 1$), other ($n = 2$).

Twenty-one-month-old participants also completed a puppet and rattle task. Administration of the tasks was identical to administration at 15 months; only the stimuli differed. A cow puppet was used for the demonstration portion of the puppet task, and a duck puppet was used during the test portions. For the rattle task, the green rattle was used during the demonstration, and the red rattle was used during the test portions. By using different stimuli for the demonstration and test, the coders were able to assess the degree to which participants generalized their memory of the actions to a novel but perceptually similar stimulus. Scores were

omitted or not collected in the following cases: child was too fussy to complete task ($n = 10$), child did not touch toy during test ($n = 2$), experimenter error ($n = 2$), other ($n = 1$).

Deferred imitation administration was recorded digitally. Coders reviewed the videos frame-by-frame to score participants' attention to the demonstration and performance during testing. For both the puppet and the rattle tests, the time it took for the participant to touch the stimulus and the time it took for the child to imitate a target action after touching the stimulus was recorded. Memory was evaluated by determining the number of target items the child imitated during the first test portion. For the puppet task, participants were awarded 1 point for exhibiting each of the following target actions: removing the mitten from the puppet's hand, shaking the mitten up-and-down or side-to-side, attempting to replace the mitten on either hand. For the rattle task, participants were awarded 1 point for each of the following target actions: placing the ball in the cup, attaching the lid to the cup, shaking the rattle with the ball inside. 9-month-olds could score between 0 and 3 points for their performance on the puppet task. Scores at 15 and 21 months were summed across the puppet and rattle tasks; participants could score between 0 and 6 points for their imitation of the target actions. Reliability checks were run on 20% of the scores to ensure the target actions had been counted properly.

Language. Infant auditory and expressive language at 9, 15, and 21 months was assessed using the Preschool Language Scale-4 (PLS). The PLS is a standardized language measure that has been normed from birth through age 6 (Zimmerman & Castilleja, 2005). Language tasks were recorded digitally. Tasks gradually increase in difficulty as the participant moves through tasks. The Auditory Comprehension subscale evaluates infants' ability to understand and respond to language (i.e. following directions, appropriate response to aural commands and spatial recognition tasks). The Expressive Communication subscale evaluates the infants' ability to

verbally respond to questions and general accuracy in language production. Both subtests were discontinued after 7 consecutive incorrect responses. For the present study, the Auditory Comprehension subscale was always administered first, and the complete task took between 30 and 40 min. Missing scores are due to experimenter error ($n = 1$ at 9mo) and child fussiness/refusal to answer ($n = 2$ at 15mo, $n = 4$ at 21mo). Scores were standardized according to child's age. The sum of the standard subtest was used to determine Total Language Standard Score for each child at each age. A single coder reviewed 20% of the videos to establish reliability with the original experimenter's scoring.

Theoretical Rational for Research

This proposed study asks four primary research questions in order to understand more clearly the association between prenatal maternal mental health and declarative memory outcomes in young children. Memory is the main outcome variable of interest in this study, however, language will be tested in each analysis to establish specificity between predictors and memory outcomes. Hypothesis 1a and 1b will test prenatal mental health its association with memory and language. Hypothesis 2 through 4 will evaluate the other risk factors associated with changes in infant memory and language in both the neonatal and postnatal environment. These hypotheses will direct research that aims to understand better the pathway between the prenatal environment and changes in early memory and language in young children.

Theoretical Rationale and Hypothesis

The first research question asks, "Is prenatal health associated with changes in infant memory and language in the first two years of life?"

It is hypothesized that there will be a direct negative association between high prenatal maternal anxiety and depression and changes in infant memory and language in the first two years and results will be more robust for memory.

There is research that demonstrates that presence of maternal *depression and anxiety* during the prenatal period may directly influence health and cognitive outcomes for children including lower birth weight, difficulties with self-regulation, difficulties with sensory/perceptual acuities, discriminations, and response; acquisition of object constancy; problem solving; and vocalization (Bergman et al., 2007; Brouwers et al., 2001; Kaplan, Bachorowski, Smoski, & Zinser, 2001; Peterson, Vohr, Staib, & et al., 2000). The research that does demonstrate unique associations between prenatal mental health and child cognitive outcomes is somewhat non-specific and evaluates cognition through the use of general behavior scales (i.e. the Neonatal Behavioral Assessment Scale) and cognitive measures (i.e. Bayley's MDI) (Elysia P. Davis & Sandman, 2010; Elysia Poggi Davis et al., 2004; Quas et al., 2004). It is less clear if maternal prenatal depression (Elysia P. Davis & Sandman, 2010) and anxiety (Buss et al., 2010) have a unique association with children's memory. Because prenatal maternal anxiety and depression are associated with epigenetic variations related to greater activation of the HPA axis and increased cortisol reactivity in the hippocampus, and because of the association between increased HPA reactivity and hippocampal dependent memory decline, we hypothesize that increases in maternal depressive and anxious symptomology will be negatively associated with changes in infant memory from 9 to 21 months.

The next set of questions relates to how birth outcomes, negative life events, and parenting may mediate the association between prenatal mental health and infant neurodevelopmental outcomes.

Birth outcomes will be measured 2 ways (*gestational age (weeks) and birth weight (grams)*). *Birth weight and gestational age* have been associated with general cognitive outcomes in children, including IQ and long term achievement (Klebanov et al., 1994; Liaw & Brooks-Gunn, 1994). Prenatal risks like mental health, stress, poor nutrition and low SES are associated with health risks for children including premature birth (deWeerth, van Hees, & Buitelaar, 1984) and slower fetal growth (Gitau, Cameron, Fisk & Glover, 1998; Trainer, 2002). The risks of preterm birth and lower birth weight include lower IQ (Brooks-Gunn, Mc Carton, Casey et al., 1994) and sustained school achievement failures (Klebanov, Brooks-Gunn, & McCormick, 1994). Premature birth has also been associated with variations in infant brain morphology including enlarged hippocampi at 24 months (Peterson et al., 2000). This analysis will test how much prenatal mental health is associated with changes in infant memory and language as a result of birth outcomes. All babies that weren't born at term were not included in this sample, so the range for gestational age and birth weight is truncated, which may affect results. However, given that links between infant development and birth outcomes, even for children born at term and of healthy birth weight, has been demonstrated in prior research (Noble, Fifer, et al., 2012; Shenkin, Starr, & Deary, 2004), it is hypothesized that birth outcomes will partially mediate the association between prenatal mental health and both infant memory and language from 9 to 21 months.

Negative life events and social stress have specific associations with memory outcomes in particular, because of the implication of the HPA axis during the stress response (Sapolsky et al., 1990; Uno et al., 1989) and its influence on hippocampal based memory function. Prior research has demonstrated that prenatal mental health has specific associations with quality of parenting (K.-A. Grant et al., 2008; Whiffen & Gotlib, 1993). Persistent postnatal depression is

associated with more severe, less engaged parenting that upsets the “serve–and–return” interactions between mother and child and exhibit more negative affect and engage less verbally with their newborns (Forman et al., 2007). Persistent postnatal anxiety has been similarly associated with more negative parental affect and tone and more severe, controlling interaction style with newborn which discourage infant engagement with mothers. A major limitation of the study is that there is no measure of maternal depression and anxiety during infancy. However, by controlling for postnatal negative life events and parenting it will be clearer whether the pathways between prenatal mental health and infant memory are more related to the prenatal biological environment or postnatal psychosocial risks. I hypothesize that parenting will partially mediate the association between prenatal mental health and infant memory and language outcomes from 9, 15, to 21 months. I also expect that negative life events and parenting will be negatively correlated. As a result, I expect that an increase in negative life events will mediate both language and memory outcomes during infancy. However, given the association between negative life events and social stress with memory outcomes, I anticipate that negative life events will explain more variation in memory than in language.

The last set of questions relates to potential interaction between prenatal mental health and birth outcomes, negative life events, parenting that is associated with changes in infant memory and language.

Persistent postnatal depression is associated with more severe, less engaged parenting that upsets the “serve–and–return” interactions between mother and child and exhibit more negative affect and engage less verbally with their newborns (Forman et al., 2007). Persistent postnatal anxiety has been similarly associated with more negative parental affect and tone and more severe, controlling interaction style with newborn which discourage infant engagement

with mothers. A major limitation of the study is that there is no measure of maternal depression and anxiety during infancy. However, by controlling for postnatal negative life events and parenting it will be clearer whether the pathways between prenatal mental health and infant memory are more related to the prenatal biological environment or postnatal psychosocial risks. I hypothesize that parenting will partially moderate the association between prenatal mental health and infant memory and language outcomes from 9, 15, to 21 months.

In summary, the association between prenatal maternal anxiety and depression and changes in infant memory and language in the first two years will be studied by testing the specific main association between prenatal mental health and infant memory and language and through mediation and interaction analysis with covariates at three different time points between birth and infancy. Because of what the literature suggests about the association between depressive and anxiety symptomology and increased HPA reactivity during gestation and because of what is known about the negative association with heightened HPA reactivity and memory function (Dranovsky & Hen, 2006; Gianaros et al., 2007; Roozendaal, 2002; Schmitz et al., 2002), it is expected that prenatal maternal depressive and anxious symptomology will have a stronger association with changes in infant memory than language in the first two years of infancy. It is expected that birth outcomes and negative life events may partially mediate the association between prenatal mental health and infant memory, and that parenting will fully mediate any association between prenatal mental health and changes in infant language. It also hypothesized that prenatal mental health may interact with birth outcomes, negative life events, and parenting in its association with both changes in infant memory and language.

Analytic Strategy

Statistical approaches were used that account for infant cognitive development over time (Linear Mixed Modeling) that are associated with prenatal maternal mental health class. The next section, explains how *missing data* was managed, the use of *derived variables*, and the last section describes the *analytical approach* detailing the statistical methods that were used to answer each research question.

Missing Data

Rates of missingness on predictors and controls ranged from 0 to 9%, with most variables missing in less than 2% of the cases. 17 out of 179 mothers did not complete the Edinburgh Postnatal Depression Scale. All other prenatal maternal measures were missing 2 or fewer cases and no birth outcome data was missing. For parenting and life event outcomes at 15 months, 2 to 4% of data was missing due to attrition. For infant outcomes, rates of missingness varied by cognitive task. For Deferred Imitation (DI) scores were omitted or excluded at 15 months for the following cases: child was too fussy to complete task ($n = 11$), child did not attend to demonstration ($N=3$), child did not touch toy during test ($n = 4$), experimenter error ($n = 1$), other ($n = 2$). At 21 months scores were not collected or omitted in the following cases: child was too fussy to complete task ($n = 10$), child did not touch toy during test ($n = 2$), experimenter error ($n = 2$), other ($n = 1$). In the Visual Paired Comparison task (VPC) scores were not collected or omitted in the following cases: child was too fussy to complete task ($n = 2$ at 15mo), child did not attend to stimuli ($n = 3$ at 9mo, $n = 7$ at 15mo), computer error ($n = 2$ at 15mo), other ($n = 1$ at 15 and 21mo). For the Preschool Language Scale scores were not collected or omitted in the

following cases ($n = 1$ at 9mo) and child fussiness/refusal to answer ($n = 2$ at 15mo, $n = 4$ at 21mo).

Expectation-Maximization with Bootstrapping (EMB) algorithm devised by King and Honaker (Honaker & King, 2010; Honaker, King, & Blackwell, 2006) was used to manage missing data collected during infancy. EMB is a common method for managing missing data in time series studies. EMB is an algorithm that integrates imputation and bootstrapping approaches in order to manage missing data in time series cross by integrating new values from complete-data parameters (Honaker et al., 2006). LMM in R automatically draws of the posterior (bootstrapping) of the complete-data parameters; imputations are then made using a linear regression with parameters that can be calculated directly from θ . These methods assume data missing be missing at random. Limitations discussed later.

Derived Variables

Prenatal Maternal Mental Health Profile. The prenatal mental health profile groups were created using cluster analysis based on prenatal maternal depression and anxiety levels within this sample. Recommendations for clinical cut-offs for prenatal depression (Buss et al., 2010; Elysia Poggi Davis et al., 2007; Matthey, Henshaw, Elliott, & Barnett, 2006; Sandman, Davis, Buss, & Glynn, 2011) and prenatal anxiety (K.-A. Grant et al., 2008) are highly variable in the literature within non-clinical samples. Three profile groups were created. Profile 1 participants have the lowest levels of depression and anxiety (Low); Profile 2 participants have mild levels of depression and anxiety (Mild), and Profile 3 participants have the highest levels of depression and anxiety (High). High profile scores mirrored clinical cut-off in the literature, 9 or higher was designated for picking up on higher depression symptomology, which represents

roughly 12% of our sample, which is similar to the prevalence of prenatal depression in the normal population (D. Murray & Cox, 1990) and high profile anxiety scores, 40 or higher for both state and trait anxiety represented roughly 9% of our sample which is similar to the prevalence of maternal prenatal generalized anxiety disorders in the normal population (B. F. Grant et al., 2004).

Prenatal Maternal Risk. The prenatal maternal risk variable (Soc_Risk) was derived from the work of developmental theorists who have identified cumulative risks in the parent child environment and their associations with delayed cognitive development (Burchinal, Roberts, Hooper, & Zeisel, 2000; Sameroff, Seifer, Baldwin, & Baldwin, 1993; Sameroff, Seifer, Barocas, Zax, & Greenspan, 1987). Given what is known about the complexity of factors that are related to prenatal depression and anxiety and the risks associated with mental health and infant cognitive outcomes, multiple risks will be tested to assess the pathway between prenatal maternal depression and anxiety and infant cognition in general. The specific risk variables used in this part of the analysis will be taken from research that has isolated maternal and infant factors that are associated with infant neurodevelopmental outcomes and trajectories for cognitive development and achievement over time (Brooks-Gunn et al., 1994; Chase-Lansdale, Gordon, Brooks-Gunn, & Klebanov, 1997; Fuligni et al., 2004; Gutteling et al., 2006; Klebanov et al., 1994; Liaw & Brooks-Gunn, 1994; Mennes, Stiers, Lagae, & Van den Bergh, 2006; Noble, Houston, et al., 2012; Smith, Brooks-Gunn, & Klebanov, 1997). Three prenatal risk factors were included in the profile of prenatal risk: marital status, family income, and maternal education. Participants were classified by which prenatal risk profile group dependent on how cluster analysis defined high and low SES within the sample.

Maternal social characteristics that are known to be associated with infant development were measured as part of the prenatal risk variable include marital status, maternal education and family income because of their association with child development (Duncan et al., 2008; Sameroff et al., 1987; 1993) outcomes. Not being married was considered a risk factor because of the association between single parenting and lack of social support with poor child outcomes (Conger et al, 1996; Furstenbug et al., 1989). Maternal education was also used as a factor in calculating prenatal maternal risk. Maternal education can be a buffer and risk factor in relation to infant development. Maternal education is associated with several measures of child development (including IQ and long-term school achievement) (Furstenburg et al., 1989) particularly for children from low-income families (Burchinal et al, 1997; Sameroff et al., 1993). Fewer material resources, for example, can influence child development via parenting style and access to quality education (Chase-Lansdale, 1997; Kiernan, 2011; McLoyd, 1991; Smith, 1997), and simultaneously challenge the coping mechanisms and biological stress response of parents and their children, further influencing developmental outcomes (Boyd et al. 2009; Bredy et al., 2003; Lupien et al., 2009). In research that has measured maternal education as a social risk factor in predicting infant outcomes, less than high school education is typically the criteria for identifying risk (ibid).

Birth Outcomes. Birth weight (in grams) and gestational age (in weeks) were used in order to assess birth outcomes. All infants selected for the study were born at term, so birth outcome risks will be truncated; however, gestation age will still be taken into consideration as evidence suggests that, even within the term range, gestational age and birth weight may be important predictors of subsequent cognitive development and academic achievement (Noble, Fifer, et al., 2012; Shenkin et al., 2004).

Memory and Language. Outcomes were measured using composite of z transformed scores for memory (VPC and DI) and language (PLSA and PLSE) at each age. To place the memory and language tests on a single common scale, scores were converted to z scores relative to the distribution of children within each age group (Noble, et al., 2007; Noble et al. 2005). Then z scores were averaged together to create a Memory and Language composite score for each age.

Proposed Analysis

Correlation. Correlation in SPSS version 21 was used to test bivariate associations between variables.

Cluster Analysis. Cluster analysis in Mplus was used to identify two profiles within this sample: one group based on levels of maternal prenatal depression and anxiety symptoms and another group based on prenatal risk characteristics including education level, total income, and marital status. Cluster analysis is commonly used to evaluate mental health symptomology and public health factors in non-clinical samples (Pascalis et al., 2003) and their association with longitudinal outcomes (Fiori, Antonucci, & Cortina, 2006). Groupings help to determine profiles by characteristics within a group, in this case mental health symptoms and prenatal social risk characteristics. Parameters that define groups in cluster analysis are based on differences specific to the sample and are not-predefined (Fleury et al., 2013).

K-means procedure for clustering was used to identify maternal mental health and social risk profile groups. This process began by separating profiles into two groups based on the sample characteristics included in the model. Characteristics considered for creating a prenatal maternal mental health profile group were based on measurements of depression and anxiety

(EPDS and STAI scores). Characteristics considered for creating the prenatal social risk profile were maternal education level, total income, and marital status. As a first step in finding a sensible initial partition, k-means analysis was used to establish profile grouping by taking the values of the two individuals furthest apart in terms of k characteristics that were introduced in the model (using the Euclidean distance measure). Specifically, a centroid based on Euclidean means of mental health symptoms or prenatal risk factors was selected. Then, the distance from each of the other observations was calculated for each of the k clusters and observations were put into the clusters to which they were closest. Each individual's distance to its own cluster mean was smaller than the distance to the other cluster's mean. Bootstrapping Least Likelihood Test Ratio (LRT) determined the power or p-value by holding a k +1 model against a k model (a best fit model that adjusted for individual's and their specific mental health or social risk traits) and evaluated the differences in parameters among groups (Pledger, 2000). Best fit and ideal groups were determined by using the Bayesian Information Criteria (BIC) (Ding & He, 2004). The lowest BIC score indicated the ideal number of groups. Clustering procedures were replicated in R and group characteristics were very similar.

Linear Mixed Modeling. Linear Mixed Modeling (LMM) in R (<http://cran.r-project.org/web/packages/lme4/lme4.pdf>) was conducted to assess how levels of prenatal anxiety and depression and related postnatal covariates may influence changes infant language and memory from 9 to 21 month. LMM is particularly useful in settings where observations are measured repeatedly. It can accommodate an unbalanced design; not all individuals need to have the same number of observations and not all individuals need to be measured at the exact time point. LMM allows for random effects in addition to fixed effects and is flexible enough to allow for residuals to be correlated or independent (Jenson, Birch, Woodall, 2007). LMM is a

preferred model to Repeated Measures design in this analysis because it can accommodate categorical predictors and continuous outcomes and can manage multiple missing data points when conducting longitudinal analysis. LMM allows for the natural correlation that may occur among predictors and pools information from multiple profiles in order to improve estimates and subsequent inference (Jensen et al., 2007) and allows for non-linear changes over time.

LMM procedures allowed for an identification of whether a) prenatal maternal mental health is associated with changes in infant memory and language in the first 2 years ; b) postnatal covariates related to mental health are independently associated with changes in infant memory or language from 9 to 21 months; c) postnatal covariates mediate an association between prenatal maternal mental health and changes in infant memory and language from 9 to 21 months or d) postnatal covariates interact with mental health in their association with changes in infant memory or language from 9 to 21 months.

Data was first restructured in long format (cases in rows of variables across time points (9, 15, and 21 months)) in order to be able to conduct longitudinal analysis in LMM. Subject variables were entered in order to identify blocks of repeated measures by participant. Age was entered as the repeated measure variable. The dependent variable was then be defined for each model (Z transformed memory composite score for either language or memory). Predictor variables were either entered into the model as factors or covariates. The categorical variables prenatal maternal mental health profile, maternal social risk profile and age were always entered into the model as factors. By specifying age as a factor, estimated means for the distance at each age level was calculated. The continuous variables for birth outcomes, negative life events and the measurements of parenting and the home environment were entered into the model as

covariates. Fixed effects for each model were then be specified. Fixed effects are the constant, unknown regressions coefficient associated with either continuous covariates or categorical predictors. Within fixed effects the main effects and interaction terms were entered. Between subjects differences (between infants) were accounted for as random effects. These “random” conditional means will, as result, were shrunken toward the fixed effects estimates. LMM analyzed the association of predictors on dependent outcomes from 9 to 21 months by first evaluating the different changes in intercepts using type 3 fixed effects modeling and then differences in slopes using estimated slope modeling (Verbeke & Lesaffre, 1996; Vermunt & Van Dijk, 2001). The estimated slopes indicate total change over time (from 9 to 21months) and the y-intercept indicates overall differences in neurodevelopmental measures. This analysis identified estimated patterns of changes in memory and language associated with the specific predictors and/or covariates that were selected to answer each research question.

In order to validate findings Growth Mixed Modeling was also used (GMM) in Mplus 6.1. GMM in Mplus also allows for the possibility of analysis of categorical and continuous data in addition to the differences test run in GMM which assesses the fit of categorical predictors on continuous outcomes. GMM in Mplus varies from LMM in that it also allowed for a longitudinal analysis of the latent class mental health predictors’ association with changes in infant neurological outcomes while simultaneously measuring the association of covariates in the same model. GMM was useful in determining if any predictors (parenting in particular) in the model varied by prenatal maternal mental health class in their association with changes in infant memory and language over time.

Testing the Model

Four main analyses were run to test our model. First, a test was conducted to determine if there was an association between the main predictor, prenatal maternal mental health, and changes in infant memory and language from 9 to 21 months. Second, an analysis was run to test the direct association between birth outcomes, negative life events, and parenting with changes in infant memory or language from 9 to 21 months. Third, an analysis was run to test if birth outcomes, negative life events, or parenting mediate an association between prenatal maternal mental health and any changes in infant memory from 9 to 21 months. Fourth, an interaction test will be conducted to determine if prenatal maternal mental health interacts with any of the postnatal covariates: birth outcomes, negative life events and parenting in their association with changes in infant memory and language from 9 to 21 months.

Research Question 1a: Is prenatal maternal mental health associated with changes in infant memory from 9 to 21 months?

Research Question 1b: Is prenatal maternal mental health associated with changes in infant language from 9 to 21 months?

Linear Mixed Modeling will be used to determine if levels of prenatal maternal depression and anxiety symptomology are associated with changes in infant memory and language from 9 to 21 months. First a test for an interaction between prenatal mental health and age on changes in infant memory and language from 9 to 21 months will be conducted. If the results of the interaction test are not significant a test for the main association between prenatal maternal mental health on infant outcomes will be conducted. Each analysis will control for prenatal maternal social risk. Prenatal maternal mental health, social risk categories, and age

will be held fixed. Participant/subject variables will be entered as random effects for each analysis. All cognitive outcomes will be z-transformed composite scores in order to be able to make comparisons between measures. Therefore, results will demonstrate if prenatal mental health is associated with changes in infant relative rank from 9 to 21 months. Results will be reported using Type III Fixed Effects. Cognitive measures for memory and language were z-transformed by age group in order to be able to make comparisons between neurocognitive systems; this method has been used in similar studies (McCall & Carriger, 1993; Noble, McCandliss, Farah, 2007). Results thus indicate how predictors are associated with changes in the relative rank of infants' memory and language scores and are not related to infants' individual trajectories of development over time. LMM also utilizes modeling procedures that deliberately control for individual differences between infants.

Interactions and main effects tests will be reported using an F statistics and a significance score using a Pearson coefficient, p value ($<.05$). Robustness checks will be done on continuous variables for depression (See Appendix A) to further validate results.

It is hypothesized that there will be a direct negative association between high prenatal maternal anxiety and depression and changes in infant memory and language from 9 to 21 months and results will be more robust for memory.

Research Question 2a: Are birth outcomes associated with changes in infant memory and language from 9 to 21 months?

Birth outcomes will be measured using infant measures of birth of weight (in grams) and gestational age (measured in weeks). Preliminary analysis was conducted to test for bivariate associations between prenatal maternal mental health and birth outcome covariates.

LMM will be used to test if there is an association between birth outcomes and changes in infant memory and language from 9 to 21 months. Separate predictor by age interaction tests will be conducted in LMM for birth weight and gestational age on changes in infant memory and language from 9 to 21 months. If results are not significant separate main effects tests of birth weight and gestational age on infant outcomes will be conducted. Birth weight and gestational age will be included in each model as “covariates” and prenatal social risk and time (Age) will be entered as “factors” and measured as fixed effects. Participant/subject variables will be entered into the model as random effects. Results will be reported using Type III Fixed Effects. Interactions and main effects tests will be reported using an F statistics and a Pearson coefficient, p value (<.05) will be used to report significance. Regression coefficients (estimated β 's) will be used to plot any significant results. High and low values for any significant plotted adjusted means will be calculated using median splits. Each analysis will account for time, social risk and birth outcomes.

$$\text{Predicted value} = \alpha\text{Intercept} + \beta_1 * \text{SocRisk} + \beta_3 * \text{Neo} + \beta_4 * \text{time} + \epsilon$$

Research Question 2c: Are negative life events associated with changes in infant memory and language from 9 to 21 months?

LMM will be used to test if there is an association between maternal negative life events at 15 months and changes in infant memory and language from 9 to 21 months. First a negative life events by age interaction test will be conducted to determine if negative life events have an age dependent association with changes in infant memory and language from 9 to 21 months. If the results of the interaction test are not significant a test for the main association of negative life events on infant outcomes will be conducted. Each analysis will control for

prenatal maternal social risk. A negative life events continuous score will be entered into the model as a covariate; social risk and age will each be entered in the model as factors. Negative life events, social risk, and age will be measured as fixed effects. Participant/subject variables will be measured as random effects for each analysis. All cognitive outcomes will be z-transformed composite scores in order to be able to make comparisons between measures. Therefore, results will demonstrate if negative life events are associated with changes in infants' relative rank from 9 to 21 months. Results will be reported using Type III Fixed Effects. Interactions and main effects tests will be reported using an F statistics and a significance score using a Pearson coefficient, p value (<.05). For any significant results, regression coefficients (estimated betas) will also be reported using a Pearson coefficient; p values <.05 in order to graph main results. Median splits will be used to designate high and low scores for negative life events. Each analysis will account for social risk, age and negative life events.

Predicted value = α Intercept + β_1 * SocRisk + β_2 * Neg_Events + β_3 * time + ϵ

Research Question 2d: Are aspects of parenting and the home environment associated with changes in infant memory and language from 9 to 21 months?

Parenting and aspects of the home environment will be evaluated using measures of the HOME parental warmth, HOME parental lack of hostility, and HOME learning and literacy subscales. Preliminary analysis was conducted to test for bivariate associations between prenatal maternal mental health and parenting and the home environment.

LMM will be used to test if there are associations between aspects of parenting and the home environment and changes in infant memory and language from 9 to 21 months. First a parenting by age interaction test will be conducted to determine if there is an age dependent

association of parenting on changes in infant outcome. If the results of the interaction test are not significant a test for the main effects of all parenting variables on infant outcomes will be conducted. Each analysis will control for prenatal maternal social risk. All parenting and home environment variables will be entered into the model as covariates; social risk and age will be entered into the model as factors. HOME Parental warmth, HOME lack of hostility and HOME learning and literacy on infant outcomes will each be evaluated in separate models. For each analysis, parenting, social risk, and age will be entered into the model as fixed effects and participant/subject variables will be entered into the model as random effects. All cognitive outcomes will be z-transformed composite scores in order to be able to make comparisons between measures. Therefore, results will demonstrate if aspects of parenting and the home environment are associated with changes in infants' relative rank in memory and language from 9 to 21 months. Interaction and main effects tests will be conducted using a Type III Fixed Effects test in LMM; an F statistic and a significance score using a Pearson coefficient, p value (<.05) will be reported. For any significant results, regression coefficients (estimated betas) will also be reported using a Pearson coefficient; p values <.05 in order to graph main results. Median splits will be used to designate high and low scores for HOME measurements. Each analysis will account for social risk, age and parenting.

$$\text{Predicted value} = \alpha\text{Intercept} + \beta_1 * \text{Soc_Risk} + \beta_2 * \text{Parenting_HOME15} + \beta_3 * \text{time} + \epsilon$$

Research Question 3: Do birth outcomes, negative life events and aspects of parenting and the home environment mediate the association between prenatal maternal mental health and changes infant memory and language from 9 to 21 months?

Mediation analysis will be conducted using univariate tests in GLM procedures. Prenatal maternal mental health will be placed in models separately with each covariate that was significant from Step2. Difference of R^2 when covariates are included in the same model as prenatal mental health, will be used to assess mediation. Results will be reported using regression coefficients (Standardized Betas) and R^2 change scores and significance will be reported using a Pearson coefficient (p values $< .05$).

Research Question 4a: Is there a significant interaction between prenatal maternal mental health and birth outcomes that is associated with changes in infant memory and language from 9 to 21 months?

Research Question 4b: Is there a significant interaction between prenatal maternal mental health and negative life events that is associated with changes in infant memory and language from 9 to 21 months?

Research question 4c: Is there a significant interaction between prenatal maternal mental health and parenting that is associated with changes in infant memory and language from 9 to 21 months?

The last step of the analysis will test for significant interactions between prenatal mental health and any of the postnatal covariates related to birth outcomes, negative live events, or parenting.

LMM analysis will be conducted to test the association of the interactions between prenatal maternal mental health and each of the covariates on changes in infant memory and language from 9 to 21 months. All continuous predictors will be entered as covariates. Prenatal maternal mental health and prenatal social risk and all covariate interactions will be entered as

fixed effects in each model. Participant/subject variables will be entered as random effects in each model. Each mental health by covariate interaction will be run separately and each analysis will control for prenatal social risk and age.

First a three-way interaction of prenatal maternal mental health by covariate by age interaction on infant outcomes will be conducted to test for an age dependent mental health by covariate interaction on changes in infant memory and language from 9 to 21 months. If the results for the three-way interaction tests are not insignificant a two way interaction test of prenatal mental health by covariate on infant outcomes will be conducted.

Results will be reported using Type III Fixed Effects. Interactions and main effects tests will be reported using an F statistics and a significance score using a Pearson coefficient score, p value ($<.05$).

Summary

The proposed study asks four primary research questions in order to understand more clearly the association between prenatal maternal mental health and changes in infant memory and language in young children. In order to understand better the contextual factors implicated in this process our research questions draw from three time points: the prenatal period between 20-24 weeks gestation, at birth and during infancy. Our first set of hypothesis focus on the relationship between prenatal mental health and infant memory and language in the first two years. Hypothesis 2 through 4 focus on the additional risk factors after birth associated mental health and infant neurodevelopmental outcomes. These hypotheses will direct research that aims to better understand the pathway between the prenatal environment and early cognitive development in young children.

CHAPTER 4

RESULTS

Results

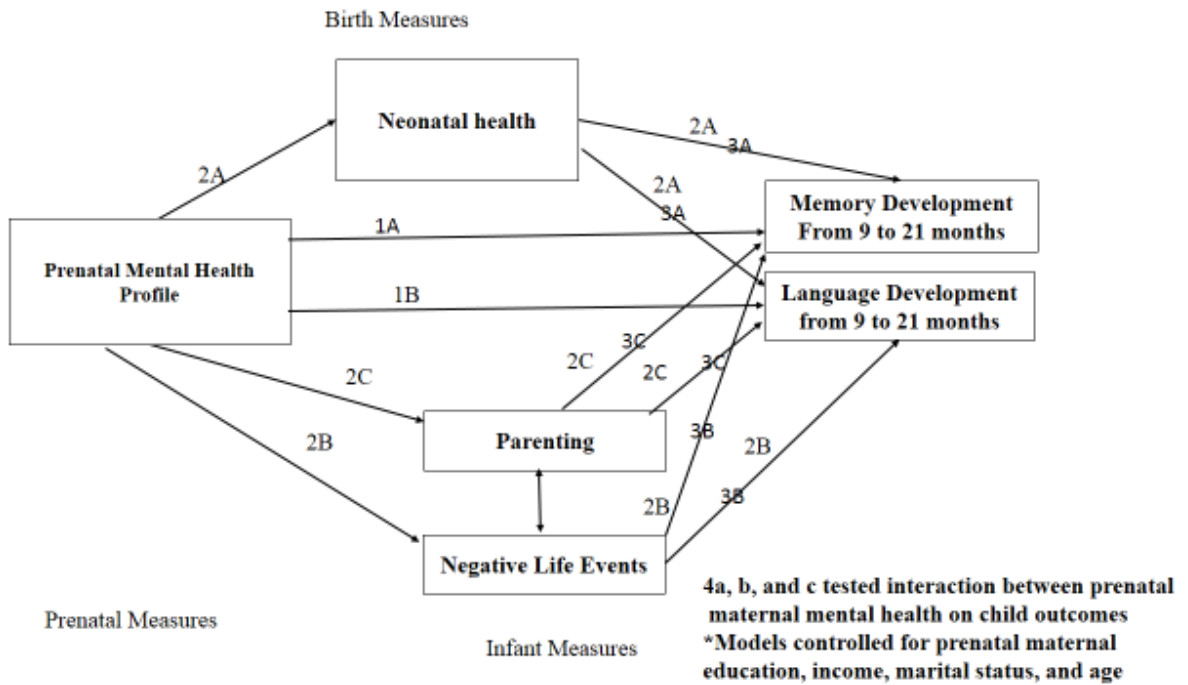
Research questions relate to measurements at three different time points: the prenatal period; at birth, and during infancy. Maternal prenatal mental health was measured at 20-24 weeks gestation, child neonatal measures were taken at birth, and parenting, negative life events, and infant neurodevelopmental outcomes were all measures during infancy between 9 and 21 months. The model being tested is presented in Figure 1.

Research Question 1a: Is prenatal maternal mental health associated with changes in infant memory from 9 to 21 months?

Research Question 1b: Is prenatal mental health associated with changes in infant language from 9 to 21 months?

Research Question 2a: Are birth outcomes directly associated with changes in infant memory and language from 9 to 21 months?

Figure 1. Theoretical Model for Research



Research Question 2b: Are maternal negative life events associated with changes in infant language and memory from 9 to 21 months?

Research Question 2c: Is parenting associated with changes in infant memory from 9 to 21 months?

Research Question 3a: Do birth outcomes mediate the association between prenatal maternal mental health and changes in infant memory and language from 9 to 21 months?

Research Question 3b: Do negative life events mediate the association between prenatal maternal mental health and changes in infant memory and language from 9 to 21 months?

Research Question 3c: Does parenting mediate the association between prenatal maternal mental health and changes in infant memory and language from 9 to 21 months?

Research Question 4a: Is there a significant interaction between prenatal maternal mental health and birth outcomes that is associated with changes in infant memory and language from 9 to 21 months?

Research Question 4b: Is there a significant interaction between prenatal maternal mental health and negative life events that is associated with changes in infant memory and language from 9 to 21 months?

Research question 4c: Is there a significant interaction between prenatal maternal mental health and parenting that is associated with changes in infant memory and language from 9 to 21 months?

Preliminary Analyses

Descriptive statistics were computed on prenatal depression and anxiety scores and prenatal maternal social risk variables (see Table 5). Additionally, descriptive statistics were run for all infant measures (see Table 6). Then Pearson correlations were computed to determine the relationship amongst the depression and anxiety scales. Results found that the correlations between maternal prenatal anxiety and depression scores were quite high (Depression and State Anxiety $r = .574, p < .001$; Depression and Trait Anxiety $r = .723, p < .001$, and State and Trait Anxiety $r = .673, p < .001$) as demonstrated in scatterplot diagram below (See Figure 2). Trait anxiety was slightly more strongly correlated with depression than state anxiety, which was anticipated given that trait anxiety like EPDS evaluates more stable characteristics of mood (over the past week/month), and the STAI state anxiety measure evaluates how the mother is feeling in the moment, at the time of the assessment. Table 7 represents bivariate correlations between covariates and main predictors. These correlations will be discussed further with each research question they pertain to later in the chapter. Covariates were selected a priori based on prior research exploring associations between prenatal mental health and infant neurodevelopmental outcomes (See Literature Review). Predictors were measured at three time points prenatally at 28 weeks; at birth; and during infancy at 15 months.

In order to identify profiles of mothers based on their depression and anxiety scores, a latent cluster analysis was conducted (See Table 8). Three groups were created based on the results from the cluster analysis. The BIC and LRT scores revealed four groups with the fourth group only having four participants, so those four were included in the third group. Figure 3 shows the characteristics of the three groups: Group 1: Low Anxiety, Low Depression (Pre_MHLow); Group 2: Mild Anxiety, Mild Depression (Pre_MHMild); Group 3: High Anxiety, High Depression (Pre_MHHigh).

A second cluster analysis for prenatal maternal risk (Soc_Risk) was run to determine maternal groups based on prenatal risk profile (see Tables 9 and 10). The cluster analysis revealed 2 groups within the sample.

Profile 1 includes mothers from higher prenatal social risk categories (Mat_SocHi); Profile 2 (Mat_SocLo) mothers within our sample are from the lower prenatal social risk categories. We have social risk profiles of the women in our sample based on prenatal demographics apart from mental health. Mothers in cluster 1 were in education categories (Mat_Ed) 2 to 6 whereas mothers in cluster 2 were more likely to be in categories 5 through 7. Prenatal income (Pre_Inc) was more likely lower than 4 in cluster 1 and greater than 3.

Table 5

Descriptive statistics: Prenatal depression and anxiety

	PN Depression	PN State Anxiety	PN Trait Anxiety
9mo/15mo	$M = 5.1$ $SD = 4.38$	$M = 25.6$ $SD = 7.03$	$M = 29.05$ $SD = 7.4$
15mo/21mo	$M = 4.51$ $SD = 2.93$	$M = 24.15$ $SD = 5.4$	$M = 29.74$ $SD = 7.1$

Note: Depression scores were measured using the Edinburgh Postnatal Depression Scale (EPDS). Anxiety Scores were measured using the Spielberger Trait and State Anxiety Scale (STAI).

Table 6

Descriptive statistics for infant measures of memory and language

	VPC	DI	PLS-A	PLS-E
9-months	M = .659 SD = .151 n = 87	M = 1.17 SD = .944 n = 89	M = 19.4 SD = 1.56 n = 89	M = 21.46 SD = 2.08 n = 89
15-months	M = .630 SD = .139 n = 162	M = 3.92 SD = 1.42 n = 157	M = 20.59 SD = 1.37 n = 171	M = 25.5 SD = 1.62 n = 173
21-months	M = .609 SD = .111 n = 79	M = 3.48 SD = 1.32 n = 67	M = 25.66 SD = 3.19 n = 76	M = 29.47 SD = 2.51 n = 79

Note: VPC = Visual Paired Comparison, DI = Deferred Imitation. Range of scores for DI task at 9 months is 0-3; range of scores for DI task at 15 and 21 months is 0-6. PLS-A = Preschool Language Scale–Auditory Comprehension Subscale, PLS-E = Preschool Language Scale–Expressive Communication Subscale.

Figure 2. Scatterplot: Comparing mental health

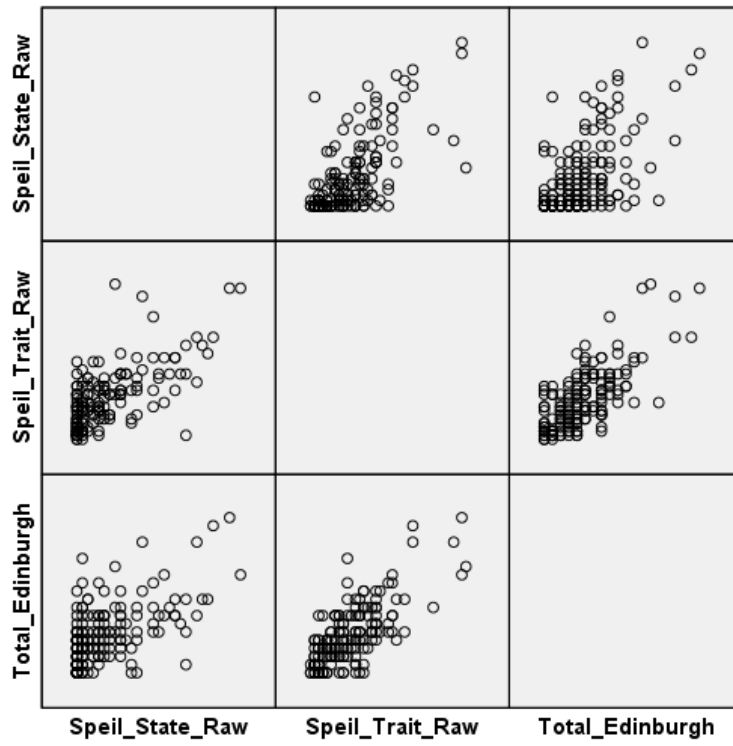


Table 7

Correlations amongst maternal mental health and covariates

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Pre_MH	--	-.087*	-.239**	-.076	-.197**	.027	-.080	.032	.136**
2. Mat_Soc		---	.203**	.315**	.214**	.023	-.055	-.082	-.170**
3. 15Warm			---	.192**	.313**	.002	-.083	.014	-.164**
4. 15Harsh				---	.250**	.026	.064	.113*	-.192**
5. 15Learn					---	-.059	-.131	-.005	-.119**
6. Neo_Bwt						---	.145**	-.056	.018
7. Neo_GA							---	-.047	-.015
8. Sex_F								---	.020
9. 15Neg_E									---

* $p < .05$, ** $p < .001$

Note: Pre_MH= Prenatal Mental Health Profile (HighAnxious/Depressed); Mat_Soc = Prenatal Maternal Social Risk; 15Warm = HOME Parental Warmth at month 15; 15Harsh = Parental Lack of Hostility at month 15; 15Learn = Language and Literacy at 15 months; Neo_Bwt = Birth Weight; Neo_GA = Neonatal Gestational Age; Sex_F = Female; 15Neg_E = Maternal Negative Life Events at 15 months. All correlations with categorical variables were done with Spearman's coefficient and those with continuous were done using Pearson's coefficient.

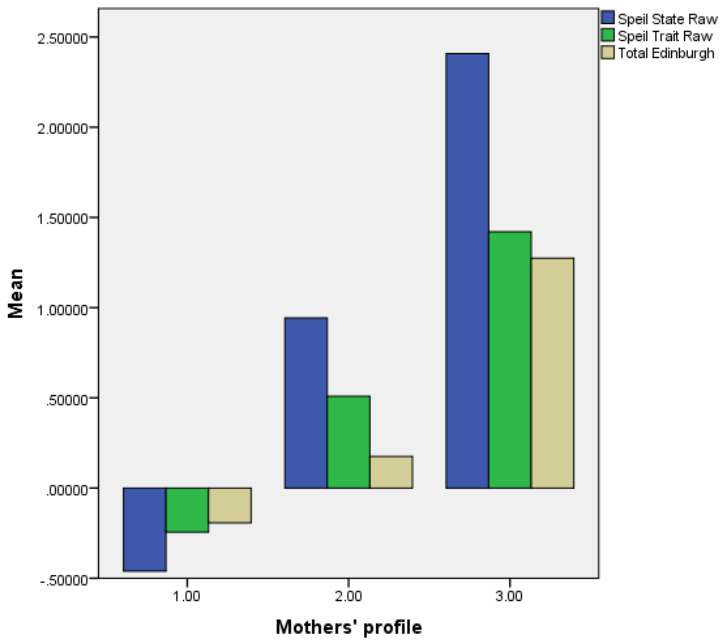
Table 8

Latent cluster analysis for prenatal maternal mental health profile

Mat_MH Profile	BIC	Bootstrapped LRT
Pre_MHLow	3045.367	p < .001
Pre_MHMild	3037.236	p < .001
PreMHHigh	3028.882	p < .001

Note: Mat_MH = Maternal mental health group; BIC= Bayesian Information Criteria; LRT = Likelihood Ratio Test.

Figure 3. Profiles of mothers with low, mild, and high depression symptoms



Note: Mat_MH Profile 1 (Pre_MHLow) has lowest levels of depression and anxiety indexes within the group; Profile 2 (Pre_MHMild) has intermediate levels of mental health indexes and within the group; Profile 3 (Pre_MHHigh) includes mothers in the highest level of every index

Table 9

Descriptive statistics by mother's mental health profile

Mat_MH Group	Scale	N	Min	Max	Mean	SD
Pre_MHLow	PN_Dep	138	0	16	4.03	3.2
	PN_Trait Anxiety	138	20	58	27.81	6.23
	PN_State Anxiety	138	20	32	22.26	2.61
Pre_MHMild	PN_Dep	24	0	12	5.36	3.28
	PN_Trait Anxiety	24	23	50	32.75	6.24
	PN_State Anxiety	24	28	36	31.6	2.55
Pre_MHHigh	PN_Dep	16	1	19	9.5	4.9
	PN_Trait Anxiety	16	21	57	40.88	8.93
	PN_State Anxiety	16	37	50	42.13	4.26

Note: Mat_MH = prenatal maternal mental health (Low, Mild High). Depression scores were measured using the Edinburgh Postnatal Depression Scale (EPDS) and had a possible range of 0 to 30. Anxiety Scores were measured using the Spielberger Trait and State Anxiety Scale (STAI) and had a possible range of 0 to 80.

Table 10

Latent cluster analysis for prenatal maternal demographics

	BIC	Bootstrapped LRT
1 Mat_SocHi	2377.103	p < .001
2 Mat_SocLo	2430.622	p = .50

Note: BIC= Bayesian Information Criteria; LRT=Likelihood Ratio Test; Mat_Soc = Maternal prenatal social risk factors.

Table 11

Descriptive statistics by mother's prenatal social risk group

Mat_Soc Group	Scale	N	Min	Max	Mean	SD
High	Pre_ED	38	11	16	13.39	1.39
	Pre_Inc	38	9,000	54,000	26,921.05	12,130.78
	Marital Status	38			41%	
Low	Pre_ED	141	12	17	15.84	1.19
	Pre_Inc	141	18,000	66,000	48,127.66	13,115.34
	Marital Status	142			100%	

Note: Mat_Soc = prenatal maternal social risk; Pre_Ed= Mother's prenatal education level. Pre_Inc = mother's prenatal income. Marital Status indicates percent married.

in cluster 2. In cluster 1, mothers were more likely to be single. All the mothers of cluster 2 were married. Mothers in cluster 2 were older than those in cluster 1.

Cluster analysis was rerun in R using K-means clustering, and the means and standard deviations in all profile groups for maternal mental health and social risk profile were the same.

Research Question 1a: Is prenatal maternal mental health associated with changes in infant memory from 9 to 21 months?

Research Question 1b: Is prenatal mental health associated with changes in infant language from 9 to 21 months?

Results (see Table 12) demonstrate there was no significant interaction between age and prenatal maternal mental health class that was associated with changes in infant memory ($F=.56$, $p=.70$) or language ($F=.511$, $p=.73$) from 9 to 21 months. There was also no significant main association of prenatal maternal mental health on infant memory ($F=.992$, $p=.373$) or language ($F=.750$, $p=.288$). It was expected that levels of prenatal depression and anxiety would be associated negatively with changes in memory and language from 9 to 21 months. Results were graphed to confirm results from analysis for memory (See Appendix, A2) and language (Appendix, A3). Robustness checks were included (See Appendix, A1) to determine if results changed when considering mental health as a continuous variable. Results were again not significant for both memory and language.

Research Question 2a: Are birth outcomes directly associated with changes in infant memory and language from 9 to 21 months?

Preliminary analyses showed that Neo_GA was positively associated with Neo_BW ($r = .162, p < .05$) for all infants, as would be expected. The range for all neonatal measures was truncated within this sample because infants were excluded if not born healthy and at term. Preliminary bivariate correlations (see Table 7) were computed to determine if prenatal maternal mental health status was associated with changes in birth outcomes. Neither of these correlations was significant, showing no relationship between prenatal maternal mental health and birth-weight or gestational age.

Infant sex was also included in preliminary analysis. There was no significant association between infant sex and prenatal maternal mental health or any of the postnatal covariates.

Next an analysis will be conducted test if there is a direct association between infant birth weight (Neo_BW), gestational age (Neo_GA), negative life events (15_Neg), HOME parental warmth (15Warm), and HOME parental learning and literacy (15Learn), and changes in infant memory and language from 9 to 21 months.

There was no significant interaction between gestational age and time/age associated with changes in infant memory ($F=1.5, p=.700$) or language ($F=.1.5, p=.227$) from 9 to 21 months and there was no main association of gestational age on infant memory ($F= 1.0, p=.311$) or language outcomes ($F=1.03; p=.383$). There was also no significant interaction between birth weight and age associated with changes in infant memory ($F=1.5, p=.231$) or language ($F=.143, p=.700$) from 9 to 21 months, nor was there a main association of birth weight on infant memory ($F=.143, p=.706$) or language ($F=.143, p=.869$) outcomes. Results did not vary based on Mat_Soc profile (See Table 13.).

Table 12

LMM results: Association between prenatal mental health and changes in infant memory and language in the first 2 years

Measure	N	F	df	<i>p</i>
Memory	179			
Mat_MH*Age		.55	4	.701
Mat_MH		.679	2	.509
Soc_Risk		1.8	1	.314
Age		.04	2	.965
Intercept		1.73	1	.302
Language:	179			
Mat_MH*Age		.51	4	.730
Mat_MH		.992	2	.373
Soc_Risk		.575	1	.449
Age		.055	2	.947
Intercept		.935	1	.335

Note: All results were non-significant, $p > .05$. Mat_MH = maternal prenatal mental health; Soc_Risk = prenatal maternal social risk.

Table 13.

LMM results: Association between covariates and changes infant memory and language in the first 2 years.

	N	Memory			Language		
	179	df	F	<i>p</i>	df	F	<i>P</i>
Neo_BW*age		2	1.5	.231	2	.143	.706
Neo_BW		1	.143	.706	1	.143	.869
Soc_Risk		1	.458	.364	1	.555	.457
Age		2	.049	.953	2	.049	.706
Intercept		1	.006	.939	1	.014	.907
Neo_GA*age		2	1.5	.700	2	1.5	.227
Neo_GA		1	1.0	.311	1	1.03	.383
Soc_Risk		1	.485	.487	1	.485	.487
Age		2	.052	.949	2	.052	.949
Intercept		1	.197	.657	1	.124	.493
15_Neg*age		2	.392	.677	2	.883	.452
15_Neg		1	1.9	.200	1	1.8	.903
Soc_Risk		2	.506	.478	1	.485	.487
Age		2	.102	.903	1	.102	.941
Intercept		1	.084	.772	1	.084	.280
15Learn*age		2	1.44	.243	2	.354	.955
15Learn		1	2.02*	.050	1	5.2*	.025
Soc_Risk		1	.117	.733	1	.523	.471
Age		2	.243	.958	1	.128	.880
Intercept		1	-1.91	.200	1	2.6	.265
15Warm*age		2	1.17	.315	2	.596	.551
15Warm		1	.002	.966	1	7.25*	.008
Soc_Risk		1	.644	.424	1	.601	.439
Age		2	.043	.958	2	.071	.931
Intercept		1	.945	.333	1	6.7	.214

*Note: *Sig. = $p < .05$. Neo_GA= Gestational Age; Neo_BW= Birth-Weight; 15Neg=Negative Life Events; 15Warm=Home Parental Warmth; Soc_Risk=Prenatal Social Risk.*

Research Question 2b: Are maternal negative life events associated with changes in infant language and memory from 9 to 21 months?

Preliminary analysis was conducted to test for bivariate associations between prenatal maternal mental health (Mat_MH) and negative life events.

Since preliminary bivariate correlations (Table 7) determined that there was a significant association between prenatal maternal mental health (Mat_MH) and negative life events ($r = .136, p < .001$), further multivariate tests were performed. It was expected that prenatal maternal depression and anxiety would be correlated with higher postnatal maternal depression and anxiety and that higher levels of prenatal maternal depression and anxiety would be associated with more maternal negative life events during infancy.

LMM procedures demonstrated that there was no significant negative life events by age interaction that was associated with changes in infant memory ($F=.392, p=.700$) or language ($F=.883, p=.452$) from 9 to 21 months, nor was there a main association of negative life events on infant memory ($F=1.9, p=.200$) or language outcomes ($F=1.8, p=.903$) (See Table 13).

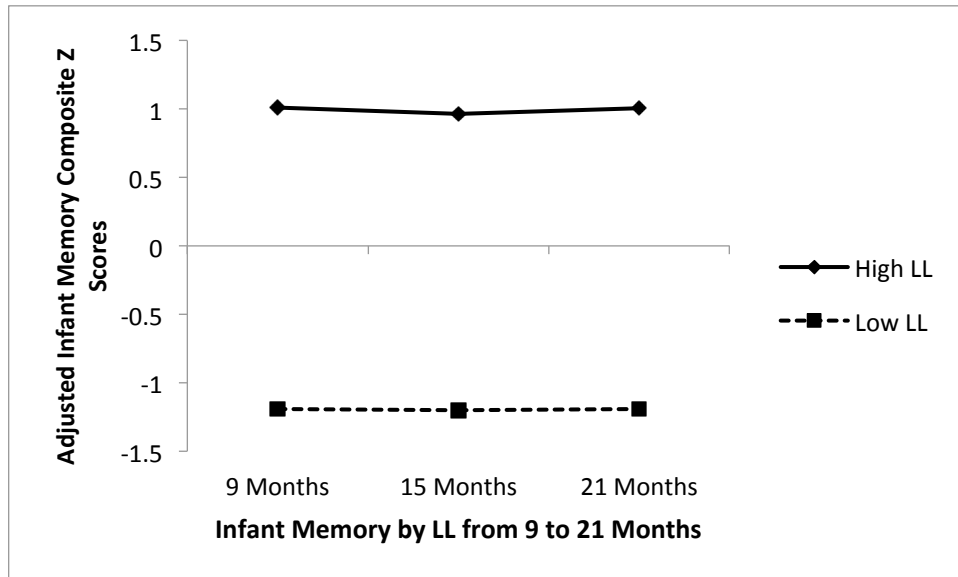
Research Question 2c: Are parenting and the home environment associated with changes in infant memory or language from 9 to 21 months?

In preliminary bivariate correlation procedures, HOME parental warmth (15Warmth) and HOME parental learning and literacy (15Learn) (Table 7) were negatively associated with prenatal maternal mental health (Mat_MH) ($r = -.239, p < .001$; $r = -.197, p < .001$) as was expected. Further, higher depression and anxiety in the postnatal period was expected to be correlated negatively with parenting. As a result, further multivariate tests were performed. Since the parental lack of hostility subscale was not correlated significantly with prenatal maternal mental health no further analysis was conducted using this measure of parenting. For the

parenting variables that were significantly associated with prenatal maternal mental health (HOME parental warmth and HOME parental learning and literacy), further analysis was conducted in Steps 2 through 4.

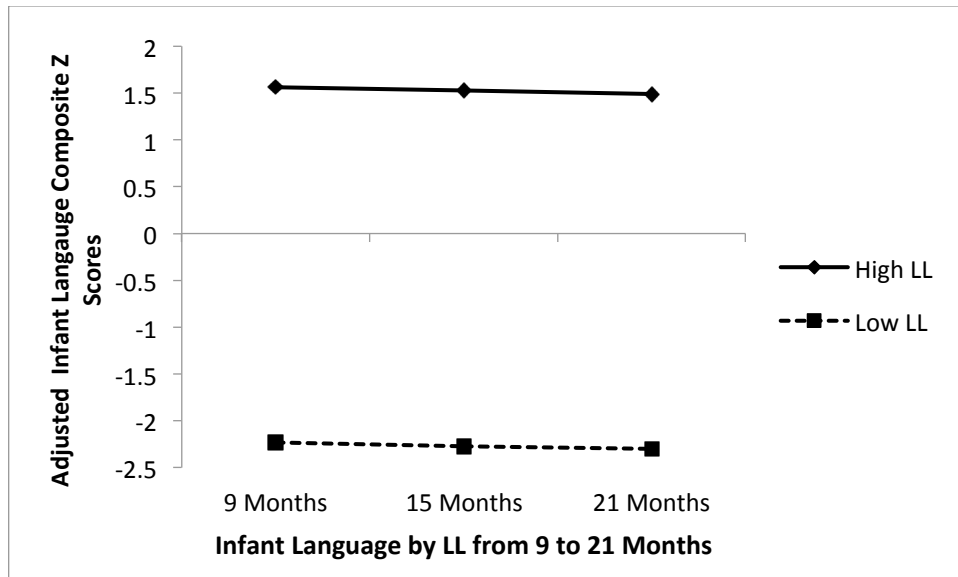
LMM results demonstrated that there was no significant HOME parental warmth by age interaction that was associated with changes in either memory ($F=1.17, p=.315$) or language ($F=.596, p=.551$) from 9 to 21 months. There was a significant main association of the HOME measure of parental warmth on infant language ($F=7.25, p=.008$) but not on memory ($F=.002, p=.966$) outcomes (See Figure 6 and Table 13). There was no significant HOME learning and literacy environment (15Learn) by age interaction that was associated with changes in either memory ($F=1.44, p=.243$) or language ($F=.596, p=.551$) from 9 to 21 months (See Figure 4 and Figure 5 and Table 13). There was a main association of the HOME learning and literacy environment associated with associated with infant memory ($F=2.02, p=.05$) and language ($F=5.2, p<.05$) (see Figure 4 and Table 13). Results did not vary by prenatal social risk (Mat_Soc) profile.

Figure 4. Infant Memory in the First Two Years of Life by HOME Learning and Literacy (15LL)



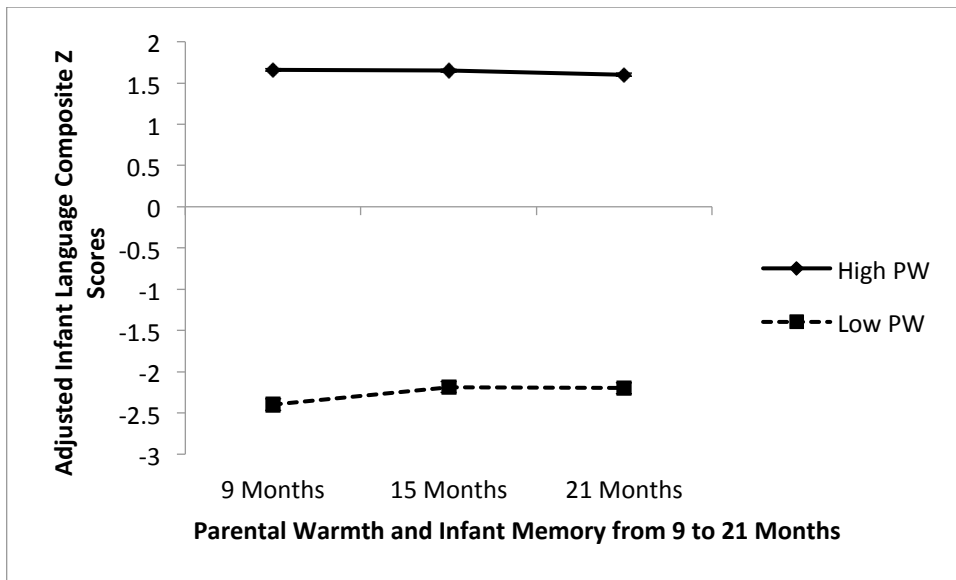
Note: LL=HOME Learning and Literacy Scale. Scores on 15LL range from 0-15. Median splits established low and high groups. From this sample, N=100 mothers are in the High LL category and N=79 mothers are in the Low LL category. Memory outcomes were adjusted by prenatal maternal social risk, age, and LL group.

Figure 5. Infant Language in the First Two Years of Life by HOME Learning and Literacy (15LL)



Note: LL=HOME Learning and Literacy Scale. Scores on 15LL range from 0-15. Median splits established low and high groups. From this sample, N=100 mothers were in the High LL category, and N=79 in the Low LL category. Language outcomes were adjusted by maternal social risk, age, and LL group.

Figure 6. Infant Language in the First Two Years of Life by HOME Parental Warmth (15PW)



Note: PW= HOME Parental Warmth Scale. Scores of 15PW range from 0-8. Median splits established low and high groups. From this sample, N=139 mothers were in the high PW category and N=40 were in the low PW category. Language outcome scores were adjusted by maternal social risk, age, and PW group.

Research Question 3a, b, & ,c.

Do covariates mediate an association between prenatal maternal mental health and infant memory and language from 9 to 21 months?

There were no significant results from Step 1, so mediation analysis was not conducted.

Research Question 4a: Is there a significant interaction between prenatal maternal mental health and birth outcomes that is associated with changes in infant memory and language from 9 to 21 months?

Research Question 4b: Is there a significant interaction between prenatal maternal mental health and birth outcomes that is associated with changes in infant memory and language from 9 to 21 months?

Research question 4c: Is there a significant interaction between prenatal maternal mental health and infant memory and language from 9 to 21 months?

The last step of the analysis will test for significant interactions between prenatal mental health and any of the covariates: birth weight (Neo_BW), gestational age (Neo_GA), negative life events (15Neg_Events), HOME parental warmth (15Warm), or HOME parental learning and literacy (15Learn), which are associated with changes in infant memory and language from 9 to 21 months.

There were no significant interactions between prenatal mental health (Pre_MH) and any of the covariates that was associated with changes in infant memory and in the first 2 years of life. (See Table 14 for results).

Table 14.

Interactions between prenatal maternal mental health and covariates on changes in infant memory and language in the first 2 years.

Interaction	N 179	Memory			Language		
		df	F	<i>p</i>	df	F	<i>p</i>
MatMH*NeoBW		3	.985	.376	3	1.10	.455
MatMH		2	1.15	.313	2	1.25	.316
BW		1	.503	.479	1	1.1	.547
Intercept		1	.013	.908	1	1.0	.345
MatMH*NeoGA		3	.746	.478	3	1.48	.248
MatMH		2	.265	.767	2	1.15	.316
GA		1	.522	.471	1	2.00	.200
Intercept		1	.023	.808	1	.875	.351
MatMH*15NegEv		3	.764	.468	3	.002	.989
MatMH		2	.199	.820	2	.072	.931
15NegEv		1	.126	.723	1	.171	.680
Intercept		1	.098	.754	1	.354	.533
MatMH*15PW		3	.602	.549	3	.080	.923
MatMH		2	.591	.555	2	.288	.750
15PW		1	.014	.906	1	6.4	.011
Intercept		1	.072	.789	1	.197	.357
MatMH*15Learn		3	.232	.793	3	.083	.921
MatMH		2	.156	.856	2	.147	.863
15Learn		1	1.41	.015	1	4.2	.042
Intercept		1	1.7	.289	1	.233	.154

Note. MatMH = prenatal maternal mental health profile; NeoBW = neonatal birth-weight; NeoGA = neonatal gestational age; 15Warm = HOME Parental Warmth scale at month 15; 15Harsh = HOME Parental Lack of Hostility scale at month 15; 15Learn = HOME Language and Literacy scale at 15 months. All results were non-significant at .05 level.

Discussion

Through mixed modeling repeated measures design this study tested whether there was a direct pathway between prenatal maternal mental health and changes in infant memory and language within the first two years of life and whether prenatal maternal mental health in conjunction with other social and infant health related predictors was associated with these outcomes. It was hypothesized that prenatal maternal anxiety and depression would be associated with changes in infant cognitive development in the first two years of life and that these findings would be more robust for memory. This hypothesis was derived from prior research that has found an association between prenatal maternal mental health and disparities in infant cognitive development on measurements, such as the Bailey's Mental Development Index (MDI) and the Mac Arthur Language Scale (MLS), even when controlling for postnatal confounds like postpartum mental health problems and socioeconomic risk (See Review by Fields, 2010). The hypothesis that prenatal maternal mental health would have a more robust association with infant memory is derived from research that has demonstrated an association between greater mental health problems and irregularities in methylation of the NR3C1 F1 promoter gene and cortisol reactivity in the hippocampus, the region of the brain associated with memory function (Claes et al., 2013; Hanley et al., 2013; Oberlander, 2008). A direct association between prenatal maternal mental health with infant memory or language would provide some evidence for a potential fetal programming pathway. Advances in research and technology have allowed doctors and researchers to develop a greater understanding of the importance of the prenatal environment in its association with human development. Prenatal stress has also been reviewed to take into consideration its evolutionary adaptive association with

infant development (Glover, 2011); explaining the link between prenatal stress and poor infant mental health and cognitive outcomes as being evolutionarily valid for survival but maladaptive in today's current learning environment. The prenatal environment is vulnerable to fluctuations in maternal mood (Talge et al., 2007), nutrition (deWeerth, van Hees, & Buitelaar, 1984), and stress (Monk, Fifer, Myers, Sloan, Trien, Hurtado, 2000). These risks and their association with fetal development are often moderated by other social factors like marital status, social support, income, and education (Burchinal et al, 1997; Sameroff et al., 1993). Risks to the prenatal environment are thought to have a loading "stress association" on the early cognitive development that takes place during gestation. Because high levels of mental health problems during gestation are associated with specific epigenetic (Claes et al., 2013; Oberlander et al., 2008) and biological changes (Hanley et. al., 2013; Talge et al., 2007) that are in turn are associated with poor cognitive outcomes for children (ibid). Studying the direct association of prenatal maternal mental health on specific infant neurodevelopmental outcomes is important; in order to better understand the scope and specificity of prenatal mental health problems and related risks on infant cognitive development. In sum, the prenatal environment has the potential to interrupt or enhance cognitive outcomes for children.

Links between Prenatal Maternal Mental Health and Young Children's Cognition

In this study, prenatal maternal mental health status was not associated with significant changes in infant memory or language from 9 to 21 months. This is not what was hypothesized, it was expected that higher levels of depression and anxiety would be negatively associated with language and memory outcomes in the first two years of life and the association would be more robust for memory. There are multiple ways to interpret this finding. It could be that more moderate levels of depression and anxiety are not associated with significant changes in infant

memory or language at all. This would correspond with similar results from prior research which found no association between heightened cortisol and stress levels and infant memory (Guettling et al., 2006). There is some research that also demonstrates that moderate stressors and increased cortisol reactivity can have null or positive associations with infant cognitive outcomes, like language (Di Pietro et al., 2006). It is also possible that the way maternal mental health and infant cognition was measured in this study influenced the results.

Mental Health

In this study there was an interest in understanding how prenatal maternal mental health from a symptom level perspective was associated with changes in infant memory and language in the first two years of life. The rationale for this type of study was validated by research showing that depression and anxiety symptoms are 1) commonly comorbid (Field et al., 2002) and 2) are collectively associated with prenatal fetal HPA programming and poor health and infant cognitive related outcomes (Guettling et al., 2006; Oberlander et al., 2008). Robustness checks were done to determine if results differed when mental health variables were evaluated as continuous predictors of infant cognitive outcomes (See Appendix). Results were the same; there was a null association between prenatal maternal mental health and infant memory and language. Indicating the results are most likely not related to how mental health was coded.

Prenatal maternal mental health was measured using well established instruments for assessing clinical risk for depression (Edinburgh Postnatal Depression Scale (EPDS) and anxiety (Spielberger Trait and State Anxiety Scale (STAI). The EPDS and the STAI have also been used in similar studies that have explored prenatal maternal mental health in non-clinical settings and its association with infant outcomes (Murray et al., 1996; Sinclair, 1998). These measures have

also been used to evaluate the association between prenatal mental health symptomology and fetal development (Guetteling et al., 2006) and infant health and cognitive outcomes (Oberlander, 2008) in more at-risk samples. Prenatal maternal mental health measures that are commonly used in addition to the EPDS and STAI are the Crown-Crisps mental health inventory (Evans et al., 2004; Heron et al., 2004; O'Connor et al., 2002), the Center for Epidemiologic Studies Depression Scale (CES-D) (Davis et al., 2004), the Pregnancy Specific Stress Scale (POMS) (Di Pietro et al., 2006), and the Hospital Depression and Anxiety scale (SIR) (Brennan et al., 2002). Additional mental health measures such as these would have been useful in providing further validation of our current findings, which demonstrate that moderate levels of depression and anxiety do not have a significant association with changes in infant memory or language in the first two years. The measures used in this study were not appropriate for establishing a clinical diagnosis. Diagnostic measures similar to, The World Health Organization's Composite Diagnostic Interview Short Form (CIDI-SF), for example which has a high clinical sensitivity for diagnosing Major Depressive Disorder (89.6%, SE=.8) and Generalized Anxiety Disorder (96.6, SE=.9) would have helped to determine if severe maternal mental health problems were linked to infant cognitive outcomes (Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998). It was also difficult to determine if measures of distinct symptoms for depression (hypotonic versus reactive, for example, for example) would have a different association with infant cognitive outcomes. Inclusion of diagnostic measures as well as more symptom specific measures of pregnancy related stress, anxiety and depression would have been useful in making this determination.

Of course, these results should not be generalized to suggest that severe prenatal depression and anxiety are not associated with infant health and cognitive outcomes, since so few women in the present sample fell into the categories for high clinical risk. Severe risk scores for anxiety on the STAI, tend to be greater than 46 (Monk et al., 2000; Teixeira et al., 1999) and for depression on the EPDS, greater than 15 (Murray et al., 1992; Hanley et al., 2013). Mothers' depression and anxiety scores in this sample ranged (Anxiety, Minimum=20; Maximum=58; Depression: Minimum=0, Maximum=19). When using these definitions for severe risk, very few mothers would fall in the severe risk group, 5% and 6% respectively for depression and anxiety, and when looking at the mean scores for depression (M: 9.9; SD: 3.7) and anxiety (M: 40; SD: 7.3) in the highest risk group of the mothers in this sample, they were not in the severe risk range.

While there is evidence that prenatal maternal depression and anxiety symptoms within the range of this sample can be associated with infant developmental risks (Adeyuya et al., 2007; Benvenuti et al., 1999), the majority of studies that have identified an association between prenatal maternal mental health problems and various developmental outcomes, including irregular infant epigenetic methylation (Meany, 2001; Plotsky, 2005), infant health (Gitau et al., 2002; Guetteling et al., 2006), and cognitive development (Field et al, 2010; Talge et al., 2007), typically sample women with depression and anxiety scores that are representative of more severe risk (Oberlander et al., 2008; Field et al, 2010). Even for mothers with a diagnosis of clinical depression during gestation (Kurstjens et al., 2001; DePietro, 2006) there is research that has demonstrated no association between maternal depression and infant cognitive outcomes at 20 months, 4 years and 6 years of age, unless mothers were chronically depressed and from the lowest SES category. Exclusion criteria and the fact that this sample was on average well off,

with only 4% below the poverty line, inevitably truncated the range for maternal mental health risk. It is likely that severe clinical risk is most reliably linked to later child functioning.

Child Outcomes

The infant cognitive measures utilized in this study may also be considered in assessing outcomes. Much of the research that has explored the association between prenatal maternal mental health and infant outcomes have used general intelligence measures, like the Bayley's Mental Development Index (Hanley et al., 2013; Huizink et al., 2003; Di Pietro et al., 2006), as the preferred model. These studies, however, use standardized measures of children's achievement and development (i.e. IQ, achievement tests, and behavior rating scales) that tend to measure combined functioning of many neurological systems (Buitelaar, Huizink, Mulder, de Medina, & Visser, 2003; Elysia Poggi Davis et al., 2007; Talge et al., 2007). The impacts of prenatal maternal mental health on the development of particular brain-based neurocognitive systems in children are less clear (Yang et al., 2007). With the use of more precise measures, like those used in this study, it was possible to see more clearly if there was an association between prenatal maternal mental health and specific infant cognitive outcomes.

The cognitive measures used in this study were chosen because they were reliable measures of infant memory (The Visual Paired Comparison Task (VPC) and the Deferred Imitation Task (DI) and language (Preschool Language Scale (PLS-A; PLS-E)). The VPC and DI tasks are long standing preferred measures of memory in early infancy because of their ability to measure memory through non-verbal measurements (Bauer et al., 1987; 1984; Fagan, et al., 1973; Herbert et al., 2007) and the PLS is a standardized language measure that has been normed from birth through age 6 (Zimmerman & Castilleja, 2005). VPC and DI utilize non-verbal and

play based interactions with delays in order to reliably measure memory skills in early infancy (Meltzoff, 1995; Barr et al., 1996). The Preschool Language Scale utilizes ecologically valid measurements of infant language, meaning that the categories assessed to determine proficiencies in auditory and expressive language are done through the context of play and stimulus based engagement: i.e. attention, play, gesture vocal development and social communication, all of which are critical aspects of early language development that are associated with later language proficiencies in word recognition and communication of ideas (Adams, 1998; Adamson, 1996).

As precise as the measures are there is also some debate how reliably infant memory and language can be captured, in general, as early as 9 months. Classical developmental theory has held that the onset of declarative memory does not occur until 15 to 18 months of age. However, this view was revised when Meltzoff and colleagues in 1985 demonstrated that declarative memory could occur as early as 9 months of age. Heimann and colleagues (2004) also found the memory scores at 9 months were associated with scores at 15 months. There is some evidence that infants have the capacity for declarative memory as early as 6 months with scaffolding and longer pre-exposure regimens (Barr, Marrott, & Rovee-Collier, 2003; Giles & Rovee-Collier, 2011). On the other hand, there is also some evidence with longer delays after being introduced to a stimulus young infants have significantly greater difficulty remembering more complex memory tasks (Barovsky & Rovee-Collier, 2003; Barr et al., 1996) than older infants, providing further support for the potential to obtain greater effect sizes later in development. There is likewise some debate in developmental theory how reliably language can be assessed as early as 9 months of age (Bloom, 1970; Brown et al. 1970). There is evidence of language discrimination as early as between the ages of 6 and 9 months of age (Kuhl et al., 1992;

Lindblom et al., 1992; Werker et al., 1986) and these differences at 9 months are correlated with differences in language at 18 months (Murray et al., 1993). It is therefore likely that differences in memory and language were reliably measured given the reliability of the instruments and that prior research has demonstrated measurable differences in memory and language within the first two years of infancy. However, it is impossible to predict the stability of this finding before 9 months or post 2 years of age.

We may have expected that prenatal maternal mental health would be linked to infant memory and language differently by time point. For example, since the earliest age (9 months) is most proximal to the prenatal period, cognitive scores at 9 months could have been more sensitive to prenatal maternal mental health, this was not the case. Nor, was there a finding that demonstrated that there was a significant link between prenatal maternal mental health and memory or language later in development (at 21 months) when cognitive skills could have been more experientially canalized (shaped by biology and experience to promote specific abilities over others) (Blair et al., 2012). The reliability of the measures may differ by age, however, that is not operating in this study, as there was no significant prenatal maternal mental health by age interaction that was associated with any of the child outcomes. As experiential canalization literature suggests (Blair & Raver, 2012), biological and environmental factors may interact later on to influence infant memory or language at a developmental time point when memory and language skills become more contextually relevant to children's development. This has been true in studies that have demonstrated an association between prenatal maternal mental health and behavior and achievement problems that emerge during later childhood (Van den Berg & Marcoen (2004); Van den Berg et al., 2005; La Plante et al., 2004). It is, nonetheless, promising that moderate levels of depression and anxiety during the prenatal period were not significantly

associated with changes in infant memory or language in the first two years. Mental health in non-clinical samples may be linked to development more significantly through alternate pathways and some levels of heightened depression and anxiety may be normal and safe for the fetus during gestation.

Links between Birth Outcomes, Prenatal Mental Health and Child Cognitive Outcomes

Prenatal Maternal Mental Health and Birth Outcomes

Prenatal maternal mental health was not significantly associated with either birth outcome measure: gestational age or birth-weight. There are a few ways to interpret these results. Due to exclusion criteria, infants in this sample were relatively healthy (i.e. born at term; and without reported neurological deficits at birth); so the range of problems at birth were inevitably truncated. These restrictions also potentially eliminated families of mothers with the most severe mental health problems. Prenatal maternal mental health problems have a well-established association with poor neonatal outcomes, including low birth-weight (Dieter, N.I., 2008), premature birth (deWeerth, van Hees, & Buitelaar, 1984) and slower fetal growth (Gitau, Cameron, Fisk & Glover, 1998; Trainer, 2002). However, prenatal maternal mental health was not in the severe risk range, as discussed. Additionally, while there was some variation in the normal range of gestational age and birth-weight, there were very few infants that were in a high risk category for gestational age (less than 38 weeks) or birth-weight (less than 1500 grams), 4% and 0% respectively. Due to privacy restrictions, it was not possible to access more specific data about maternal prenatal health behaviors that are likewise associated with these neonatal risks. Women experiencing depressive and anxious symptoms during pregnancy are at risk of not seeking adequate prenatal care (Miller, 1992), gaining less weight (Walker, Cooney, & Riggs,

1999), erratic sleep patterns, and engaging in at-risk behaviors like increased smoking, drug use, poor nutrition, and alcohol intake (Zuckerman, Amaro, Bauchner, & Cabral, 1989), which are also associated with premature birth and low weight. Most likely because this is an advantaged sample, nutrition would, however, have been adequate and smoking and drinking would be quite low. Birth outcomes, in the context of this sample, should be understood as restricted within the range of relatively healthy infants. As a result, it was difficult to find an association between prenatal maternal mental health and birth outcomes since this sample does not have severe mental health problems or very poor birth outcomes.

Birth Outcomes and Infant Cognitive Outcomes

Low birth-weight and premature birth have been negatively associated with several measures of children's long-term achievement including lower IQ (Brooks-Gunn, Mc Carton, Casey et al., 1994; Shenkin, Starr, & Dreary, 2004) and sustained school achievement failures over time (Klebanov, Brooks-Gunn, & McCormick, 1994). In this study, this was not the case. Neither birth-weight nor gestational age was independently associated with changes in infant memory or language from 9 to 21 months. This is mainly an artifact of the exclusion criteria. All children in this study were born at term, and premature birth is the biggest predictor of low birth-weight (Barker, 1998; Rasmussen, 2001). Much of the research that has evaluated achievement risks as a result of premature birth, find an association with children that are born before 37 weeks gestation (See Review by Reichman, 2005 & McCormick et al., 1992) and at birth-weights less than 1500 grams (Hack, Wright, Shankaran, Tyson, Horbar, Bauer, & Younes, 1995). None of the children in this study met those criteria for extreme neonatal risk; no children were born before 36 weeks and the lowest birth-weight baby weighed 2200 grams. There is an emergence of research exploring the association of early term birth and healthy birth-weight on

infant outcomes (Review by Shenkin, 2004; Noble et al., 2012). Noble and colleagues' 2012 study found infants born between 37 and 39 weeks gestation performed significantly better than children born between 40 and 42 weeks in math and language achievement tests in 3rd grade. However, sample sizes for this particular study were quite large (N=128,050), in order to be able to pick up on these differences. Birth-weight has been positively associated with infant cognitive outcomes in infants born at term (37-42 weeks gestation) and with normal birth-weight, more than 2500 grams (Shenkin et al., 2004). In Shenkin's 2004 systemic review of research that has tested the association of healthy birth-weights on achievement over time, he found there were significant positive links between higher birth-weights (4500 grams or higher) and higher infant verbal reasoning scores and mean IQs' verses healthy but lower birth-weight controls (2000-2500 grams). These studies' sample sizes (Corbett et al., 2004; Richards et al., 2002) were on average 25,000 infants or more, making it easier to pick up on subtle differences in effect sizes between birth-weight groups, sample sizes were potentially too small in the study to have measured a similar association.

Infant sex was also measured, however, infant sex was no significantly associated with maternal mental health or any of the covariates used in this study. Infant sex was considered in this study because of the important differences (verbal ability and behavior problems) that have been observed between boys, in particular, of mothers with mental health problems (Hay et al. 1995; Kurstjens, 2001). However, cognitive and behavioral differences that have emerged that are linked to gender, have been observed later in childhood. It is possible that sex may be associated with changes in memory or language later in life.

Prenatal mental health did not significantly moderate any association between either gestational age or birth-weight and changes in infant memory or language, and this was not

surprising given that prenatal maternal mental health problems were not in the range of extreme risk, as mentioned earlier. However, since there is no known research that has explored the association between prenatal maternal mental health in non-clinical samples and its association with birth-weight and gestational age, it was important to account for these birth outcomes in this study. In addition, since there was an interest in disentangling biological associations between prenatal maternal mental health and infant cognitive outcomes, it was important to measure how prenatal maternal mental health potentially moderated the association between birth outcomes and infant memory and language. Given that so few children exhibited health risks as a result of exclusion criteria and because of the relative resource and lack of risk associated with the demographic of mothers in this sample, it is perhaps not surprising though that birth outcomes were not directly associated with infant outcomes and that prenatal maternal mental health did not moderate any association between birth outcomes and either memory or language. Despite the restrictions embedded in this design it is promising that, in this specific sample, moderate levels of prenatal depression and anxiety were not associated with any significant changes in birth outcomes or infant memory and language outcomes in the first 2 years of life.

These results provide evidence that moderate levels of depression and anxiety during gestation may not be associated with 1) significant changes in infant memory or language from 9 to 21 months or 2) birth outcomes for children. Results did not provide evidence for the potential of prenatal programming, but did find some evidence for the importance of postnatal social factors.

There is significant research that has demonstrated the importance of the early environment, as it pertains to social resource, maternal sensitivity, and stimulation in the home, in predicting infant cognitive and behavioral outcomes (Murray et al., 1993; Murray et al.,

1996b.; Hay et al., 1995). Children of parents with less education, fewer resources, less social support, and greater stress are more likely to perform worse on early infant cognitive measures and long-term measures of achievement and I.Q. (Brooks-Gunn et al., 1994; Furstenberg et al., 1989; Murray et al., 1992).

Links between Prenatal Maternal Mental Health, the Home Environment, and Infant Cognition

Prenatal Maternal Mental Health and the HOME Environment

Parental mental health problems are associated with well-established risks in regard to parenting practice and infant cognitive outcomes (Murray, 1992; 1993; Field, 2010). Persistent maternal mental health difficulties during infancy can make it difficult for mothers to effectively care for and respond to the needs of their children (Bolby, 1952; Patel, 2007). These difficulties create developmental risks for children (Review by Field, 2010). When maternal depression persists after childbirth it has been associated with uncoordinated, unresponsive, and non-contingent maternal responses to infant cues which interfere with the “serve and return” interactions that are so critical to the infant’s development of early behavior, memory, and language production (Hay, Murray, & Cooper, 1997). Unfortunately, postnatal mental health scales were not administered, so analysis was done using prenatal maternal mental health measures. It was hypothesized that higher mental health problems in the prenatal period would be negatively associated with all aspects of parenting and the home environment. Results from preliminary correlation analysis demonstrated that heightened levels of prenatal anxiety and depression were negatively associated with the HOME parental warmth and the HOME parental learning and literacy subscales, but not with the HOME parental lack of hostility subscale.

Understanding these results in the context of the measures and the sample is important. The Infant-Toddler Home Observation of Parenting and the Environment was used to assess differences in parenting and the home environment (See Methods). The HOME measurements were designed to measure affordances in parenting and the home environment that are associated with benefits or risks to child development (Bradley, 2004). The HOME subscales used in this study are observational. Observational aspects of parenting and the home environment have been found to be more reliable than self-report, because they aren't informed by parental subjectivity (Leventhal et al., 2004). It is important to also acknowledge that the developers of the HOME subscales recognize that items are intended to identify children and adolescents who may be suffering from a serious lack of support for development (Bradley, 1993,1994; Bradley et al., 2000; Caldwell & Bradley, 1984) and therefore most reliable in capturing risks in relation to parenting and the home environment. However, the degree to which this is true varies between subscales. For example, despite literature suggesting that higher incidence of depression and anxiety is associated with harsher parenting style (Murray et. al., 1996); mental health symptoms were not associated with the HOME parental lack of hostility subscale. This is not surprising, as the lack of hostility measure is one of the HOME subscales that are more sensitive to detecting extreme risk (See Review by Bradley, 2004). Spanking is in many ways the most salient feature of this scale; it is, however, unlikely to be demonstrated in a home visit, unless parents are somewhat unrestrained in their expression of hostility toward their child (Bingenheimer et al., 2005). Spanking is also more frequent in African-American families, this sample is predominately European-American (Bradley, 2004; Mc Cloyd & Smith, 2002). Parental warmth and home stimulation measures demonstrate more reliability in assessing variation in parenting and the home environment in more advantaged homes (Bradley, 2004;1994). The parental

warmth subscale, however, can vary in its reliability across cultures (Bradely, 2004; Leventhal et al., 2004) because of how warmth and nurturance is distributed in more complex family structures (i.e. Latin American, in which multiple caregivers are typically more involved in raising the child). However, since this group was not culturally diverse and predominately European-American, assessment of the primary caregiver should have yielded more reliable results.

Despite this not being a highly at-risk maternal population, mental health was still negatively associated with the HOME parental warmth and the HOME parental learning and literacy subscale. The distribution of the scoring for the HOME parental warmth subscale ranged from 0-7, with 83% of families having scores of 6 or higher and the parental learning and literacy subscale scores ranged from 8-13, 80% receiving scores of 12 or higher demonstrating a somewhat truncated distribution. When comparing this distribution to other studies that have tested the association between the HOME subscales and infant outcomes (Bradley, 1989; 1999, 2001), the distribution here is more truncated. However, given that the families in aforementioned studies were much more socioeconomically at-risk it is not surprising they yielded a larger distribution of low scores on all measures. Despite this being a more advantaged sample, there was still a significant negative association between prenatal maternal mental health and the HOME parental warmth and the HOME parental learning and literacy subscales, albeit, the effect sizes were small (in the .1 to .3 range) and could have been potentially greater if the sample represented less of a truncated range for mental health and social risk.

The HOME Environment and Infant Cognition

Parenting was evaluated to determine if more of a social process explained the pathway between prenatal maternal mental health and child outcomes. If parenting had a unique

association with infant outcomes apart from prenatal maternal mental health, this would suggest that postnatal social factors are perhaps more critical in predicting changes in infant memory and language and also indicate that how parents interact with children is potentially more important than how they feel about themselves. If mental health moderated an association between HOME measures and infant outcomes, this would indicate mental health in this sample was important in differentiating parenting and aspects of the home that were critical to infant memory and language development. It was hypothesized that parenting and the home measures would be independently associated with both infant memory and language and that maternal mental health would moderate this association.

The HOME parental learning and literacy subscale was associated with infant memory and language outcomes, and the HOME parental warmth subscale was associated with infant language outcomes. Tests were conducted to determine if prenatal maternal mental health moderated any of the above association between HOME subscales and infant memory and language. Levels of prenatal maternal mental health did not significantly moderate any of the association between HOME subscales and memory or language. These results held when controlling for prenatal social risks.

There are many ways to interpret these results. These findings are optimistic and indicate that how parents interact with young children may be more critical than their psychological state or mood in predicting early infant cognition. These results support what other research has demonstrated that stimulating, engaged parenting has benefits for infant memory and language, even for children born to mothers with some prenatal mental health problems and social risk, and they also provide support for prior research that has demonstrated how critical parental interactions and stimulation are to cognitive development in early infancy (Belsky et al., 2011;

McLoyd et al., 1991; Tamis-LeMonda, 2013; 2014). Even in the context of extreme poverty (Tamis-LeMonda, 2014) and other social risks (Belsky et al., 1984) parenting often intervenes on child developmental outcomes. It is possible that with adequate measures of postpartum mental health problems maternal mental health would have moderated the association between the HOME measures and infant outcomes. Prenatal mental health problems are, however, commonly one of the greater risk factors in predicting postnatal mental health problems (O'Hara et al., 1996; Heron et al, 2004), so it is possible that results would have been the same.

It was hypothesized that the HOME parental warmth and the HOME parental learning and literacy subscales would be positively associated with infant memory and language. While the HOME parental learning and literacy subscale was associated with both infant memory and language, the HOME parental warmth subscale was only associated with infant language. The hypothesized association between parental warmth and memory was derived from research that has identified a link between parental warmth and hippocampal development in animals (Champagne et al., Meany et al. 2001, Oberlander et al., 2008) and humans (Luby, Barch, Belden, Gaffrey, Tillman, Babb, Nishino, Suzuki & Botteron, 2012; Rao, Betancourt, Giannetta, Brodsky, Korczykowski, Avants, & Farah, 2010). Since the association between parenting and hippocampal variation that is linked to memory may not be established until later in childhood or adolescence (Farah et al., 2008), it is possible that an association between parental warmth and memory could emerge later in development. Therefore the null association between parental warmth and memory of course doesn't confirm the possibility that memory development doesn't have its foundations in early childhood and that, nurturing interactions in early infancy don't influence memory development, differences may just emerge later in development. This would coincide with prior research that has demonstrated an association between early parental warmth

and the emergence of later critical cognitive and behavioral skills like working memory and self-regulation (Reese, Brooks-Gunn, Klebanov, & Noble, In Review). Additionally, since items in the HOME parental warmth subscale are solely observational (Fuligni et al., 2013), which is largely an asset because of bias attributed to self-report measures, it is possible that other attributes of parental warmth, i.e. sustained attachment, that are unobservable in a home visit and potentially more related to memory development were not captured (Page, Combs-Orme, & Cain, 2007).

The HOME parental warmth subscale was more strongly associated with infant language than the HOME parental learning and literacy subscale, which is not what was anticipated. However, greater parental warmth is associated with increased verbal interactions between parents and children (Pungello et al., 2009). Also, better infant language may engender higher quality parenting (Song, Spier, & Tamis-LeMonda, 2013). Verbally engaged, responsive parenting is particularly critical to language development during infancy, making children of parents with postnatal mental health issues, for example, more vulnerable to language delays (ibid, 2009). Language development in early infancy is also highly susceptible to the onset and frequency of language exposure (Mayberry et. al., 2007), and children from more resourced more well-educated families are introduced to a more complex and higher frequency of vocabulary from birth, leading to significant gains in language earlier in infancy and increasing disparities over time (Hart & Risley, 1995). It is possible in part that because, on average, because this was a well-educated sample of parents (with the lowest educated group having between 11 and 14 years of education) it was easier to pick up on language differences that were more related to nurturing, close interactions with the primary caregiver, verses aspects of the external environment. Also, while the HOME learning and language subscale measures aspects

of the home environment that may support language development (Bradley, 1994) (i.e. the number of reading materials in the room; verbal praise by parent for developmental accomplishments) it is not a standardized measure of parents' verbal ability or use of language in the home. The HOME parental learning and literacy subscale is more accurately a measure of the level of parental engagement and the degree to which the home environment is stimulating and enriching to the child (ibid). For this reason, it is not surprising that there was a main association of the HOME parental learning and literacy subscale on infant memory as well, as there is animal and human research that demonstrates a positive association of stimulating, enriched environments on infant memory development (Farah et al., 2008; Yang et al., 2007) as well.

Given that the HOME measurement of parenting and the learning environment tends to be more strongly correlated with infant cognitive outcomes later in infancy, we may have suspected to see an age by HOME parental warmth and HOME learning and literacy interaction on infant cognitive outcomes. Infant cognitive outcomes in this study were measured in early infancy (from 9 to 21 months). There is research that has shown that correlations between the Infant and Toddler HOME measures with infant outcomes (mainly measured through Bayley's MDI) rarely exceed .40 during the first year of life (See Review by Bradley et al., 1994) and the strength of the relation tends to increase in the second year of life ranging from .25 to .50, it is possible we would have found stronger correlations post 2 years of age, if we had this data. However, as reported, there was no significant interaction by age for any of the parenting variables that was associated with memory or language outcomes. Prior results that demonstrate stronger associations with infant outcomes later in infancy could be an artifact of the infant tests typically used, like the MDI, which tend to be more language heavy by age 2. Belsky and

colleagues (1984) found that early cognitive competencies such as executive function exhibited during play activities to be highly correlated with infant outcomes earlier in infancy. It is possible that similar to prior research that has used more ecologically valid measures of early infant cognition (Belsky's 1984; Murray et. al, 1996; Hay et al., 1995), this study was able to more reliably capture early infant cognitive outcomes because VPC and DI as well PLS were as ecologically valid instruments that measured infant cognitive outcomes in the context of play and stimulus interactions that were developmentally appropriate. Although it is impossible to determine if differences at any or each of the time points captured in this study will be indicative of language or memory or language problems that will emerge later on, and despite choosing statistical methods that were appropriate for managing missing data at each time point, it is also possible with more representative samples at each time point, a difference by age could have been detected.

Although there were no epigenetic or biological measurements in this study, the analysis demonstrated the extent to which prenatal maternal mental health in a nonclinical sample could be associated with changes in infant memory and language from 9 to 21 months. Levels of depression and anxiety in this sample were not associated with significant changes in birth outcomes or language and memory. Mental health problems in this sample although correlated with parenting did not significantly moderate any changes infant memory or language from 9 to 21 months. A stimulating home environment and parental warmth, even for mothers with some mental health problems and some social risk, may be more a relevant link to early infant cognition than moderate levels of psychosocial risk during gestation.

Limitations

It is important to contextualize these findings and explore how the study's design and the sample inform the results. This study has numerous strengths, including a partial longitudinal design with extremely high retention rates, and the ability to directly measure the association between prenatal maternal mental health and child outcomes across two different neurocognitive systems, while including multiple measures of prenatal social risk and measurable postnatal confounds related to mental health risk. There are however, some limitations to the design. It is possible that effects sizes would have been bigger if sample sizes were larger at each time point. Future research that includes biological and epigenetic measures during the prenatal and infancy period as well as multiple measures of depression and anxiety will help to explain if any change in infant memory or language is attributed to biological processes during gestation.

Prenatal maternal mental health did not significantly moderate any of the postnatal health or social predictors' associated with infant memory or language. Measures of mental health during infancy would be necessary to better understand how postnatal mental health problems interact with birth outcomes and parenting in their association with infant memory and language outcomes. It is possible that including a measure of mental health problems in the post-partum period would have yielded significant changes in infant memory and language because of the combined biological and social risks associated with prenatal mental health problems that continue into the postnatal period (Field, 2010; Robertson et al., 2004). Postpartum depression and anxiety, as reported earlier, are negatively associated with parental warmth and sensitivity (Brooks-Gunn et al., 2005), particularly in families living in poverty. It is also possible that parenting measured at baseline (9 months) would have been much more susceptible to the confounding influences of parental environment, like postpartum mental health problems which are highly correlated with infant outcomes (Field et al., 2010; McLeod, 199; Murray et al., 1993).

Measures of anxiety and depression at multiple time points would have also allowed for an understanding of whether chronicity of anxiety and depression symptoms was associated with changes in infant memory or language. While findings that demonstrate specific associations between timing of mental health symptoms on infant outcomes is mixed (Davis et al., 2010; Roesch et al., 2004); measurements of maternal mental health at multiple time points would have further validated these particular findings to demonstrate that is was not only moderate levels of symptoms but also chronicity and timing of symptomology that was relevant to null findings. Prenatal maternal mental health problems are one of the most common links to postnatal mental health problems, so it is likely that prenatal maternal mental health symptomology was a reliable predictor of postnatal mental health problems (Sandman et al., 2012). However, not having those measures is a significant limitation and weakness of the study, in regards to isolating the association between the prenatal and postnatal environment on infant outcomes.

There was a significant main association of two of the infant and toddler HOME subscales on memory and language outcomes. Since these measurements were taken only at 15 months, there is an assumption and limitation built into the study that parenting was constant from 9 to 21 months, across all child cognitive outcomes. It would have obviously been favorable to have all measurements of parenting and the home environment conducted prior to the child outcomes to reliably demonstrate a main association of the HOME parental warmth and the HOME learning and literacy subscale on infant outcomes at each time point. There is competing research on when parental interactions are most critical to cognitive development. There is some research that suggests that parental interactions between 6 to 9 months are some of the most critical to memory and language development (Barr et al., 1996; Barr et al., 2002; Bauer, 2009), and during this period mothers may also be more likely to be experience greater

mental health symptoms (Robertson et al., 2004; Whiffen et al., 1993) as they go through hormonal recovery postpartum. It is possible if there were parenting measures before 9 months; early parenting may have been more sensitive to mental health and would have potentially demonstrated some significant link to infant outcomes.

A more representative sample that included mothers and families from culturally diverse backgrounds and from the highest and the lowest socioeconomic groups would have helped to determine more inclusively how mental health and social risk intervene with parenting in their association with infant memory and language. Fewer material resources can influence child development via parenting style and access to quality education (Chase-Lansdale, 1997; Kiernan, 2011; McLoyd, 1991; Smith, 1997), and simultaneously challenge the coping mechanisms and biological stress response of parents and their children, further influencing developmental outcomes (Boyd et al. 2009; Bredy et al., 2003; Lupien et al., 2009). Parenting practice is highly correlated with socioeconomic factors like maternal education and income (Paige et al, 2007; Fuligini et al., 2011) and particular HOME subscales intervene in culturally specific ways in their association with child outcomes (Ipsa, Brooks-Gunn & al., 2004). Culturally diversity was very limited in this sample. The majority of children were Caucasian ($N = 168$), with an additional 7 children of mixed race, 2 Hispanic, and 2 American Indian/Alaskan Native. While there was variation in terms of socioeconomic diversity, only 4% of the present sample was living below the poverty line and the majority of mothers in the sample had some post-secondary education. Without a more representative sample, it is difficult to generalize how parenting and aspects of the home may be associated with infant outcomes for non-white families that don't fall into the highest and lowest gradients of SES. Since socioeconomic status is highly predictive of mental health problems (WHO, 2012), controlling for social risk in this particular sample

yields a relative finding. One can't determine if prenatal maternal mental health would have had a significantly moderated an association between parenting and infant outcomes if this group was more at-risk.

Thus, the combination of the lack of socioeconomic and cultural diversity, timing of the parenting measures and absence of postnatal mental health measures within this particular sample make it difficult to generalize these findings to all groups and to reliably determine if mental health intervened in the association between HOME subscales and infant outcomes. Despite these limitations, these results inform the literature. They provide evidence that some depression and anxiety may not significantly be associated with birth outcomes and infant cognitive outcomes in the first two years of life. Additionally, these findings suggest that in a non-high risk sample, parenting is more important than moderate mental health issues in predicting infant memory and language.

Summary

While causal links between parenting and infant cognitive outcomes cannot be established from these findings, there is evidence that parenting and the home environment, even in the presence of social risk and mental health problems, are associated with infant memory and language in early infancy. In this sample of somewhat advantaged mothers mental health problems were not severe; however, the results are important, given that pregnancy is a time when all women are at greater risk of depression and anxiety (Sandman et al., 2012). It is, therefore, promising that moderate mental health risks were not associated with changes in birth outcomes or infant memory or language in the first two years of life. It is also important that, even when experiencing some anxiety and depression, parenting was a significant predictor infant cognitive outcomes.

Implications for Future Research and Interventions

These results emphasize the importance of early parental engagement and the home environment in the development of early memory and language skills for young children, and they provide support for research and intervention approaches that target parenting practices. The early disparities in cognitive development associated with parenting have implications for long-term problems with achievement and further development (Brooks-Gunn et al., 1994; Chase-Lansdale, Gordon, Brooks-Gunn, & Klebanov, 1997; Gutteling et al., 2006; Mennes, Stiers, Lagae, & Van den Bergh, 2006; Noble, Houston, et al., 2012). Prior research that has demonstrated that even in the face of severe mental health problems and social adversity (Fulginiti et al., 2011; Pungello et al., 2009); parenting intervenes in predicting child outcomes. Maternal depression and anxiety symptoms alone may not have measurable links with children's development (Cooper et al., 2003; Forman et al., 2007; Murray et al., 2003); and interventions that focus on both mothers and young children can be more effective in improving child outcomes (Cicchetti, Rogosch, & Toth, 2000).

Including parents as part of the equation in early childhood programming is important, particularly in light of research that has demonstrated programs like Early Head Start alone have improvements that fade by the end of third grade (Puma et al. 2010). Parenting interventions have demonstrated success in reorganizing impaired attachment between mother and child and redefining parents' perceptions of themselves and their institutionalized acuity for parenting in general (Page et al., 2007; Belsky et al., 1984), all of which have been linked positively to early developmental outcomes. A meta-analysis of early parenting intervention programs by Bakermans-Kranenburg and colleagues (2003) found that even simple, cost-effective parenting programs can have a big impact on improving parental interactions with young children,

particularly programs that are behaviorally focused on sensitivity improvements and attachment. Kaminski and colleagues conducted a similar review (2007) looking more broadly at range of early parenting programs and found that those that were focused on increasing consistent parental engagement patterns between mother and child had the greatest effect size in terms of influencing child behavior, however, smaller effect sizes were consistently found in programs that were geared exclusively at enhancing cognitive outcomes for children. More inclusive and costly programs that combine early health and parenting supports, like Nurse Family Partnership Programs have been successful in improving parenting practice and have been linked to long-term benefits for mothers and children's health and positive child behavioral outcomes that endure through adolescence (Olds, 2006).

In sum, research suggests that programs that go beyond supports for just children and extend to supporting the proximal environment of the child are quite powerful (Feldman et. al, 2000). Numerous studies show that the quality of a child's early environment is highly predictive of later development; and interventions that seek to enhance the quality of the home environment early in life are linked to more sustainable academic achievement, healthy neurodevelopment, reductions in psychopathology, and the development of critical behaviors like self-control (Cicchetti et al.,2002; Masten & Gerwitz, 2006; Shonkoff, 2000). Current Head Start interventions being piloted (Noble, Duch & colleagues, 2012), that integrate parental education as a critical part of school readiness provide a promising approach for scaffolding older, preschool children's enrichment. Additionally, future intervention studies that take a two generational approach (See Review by Brooks Gunn & Chase-Landsdale, 2014) and focus on parenting investments that are linked to improving early interactions between parents and children that are linked to specific neurodevelopmental outcomes in early infancy may provide

the most thorough next step to providing long term positive changes in parenting and early child outcomes. A more specified approach to early parenting interventions that includes modeling of specific behaviors, while simultaneously providing mothers with strategies and materials to interact in more stimulating, reliable ways with their children are important next steps in ensuring optimal development of critical cognitive skills early in development for all children before disparities are established.

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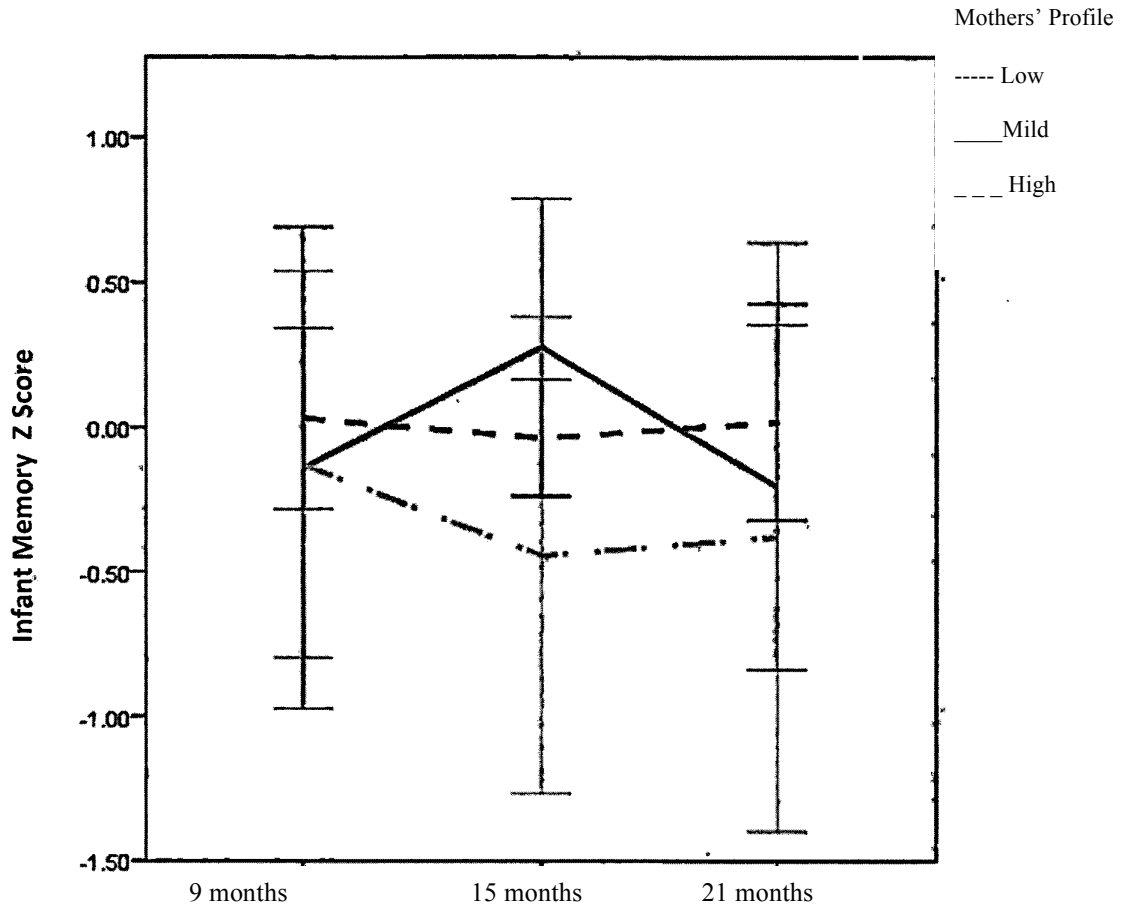
Appendix A1

LMM: Continuous Variable Robustness Check: Depression & Anxiety on Infant Cognitive Outcomes

	N	df	F	p
Memory	179			
Depression		1	.065	.800
Anxiety		1	.856	.378
R*				
Soc_Risk		1	.330	.567
Age		2	.392	.677
Depression * Age		2	.378	.686
Anxiety * Age		2	.771	.796
Intercept		1	.567	.453
Language	179			
Depression		1	.849	.358
Anxiety		1	.549	.456
R**				
Soc_Risk		1	1.9	.161
Age		2	.090	.914
Depression*Age		2	.251	.779
Anxiety*Age		2	1.2	.300
Intercept		1	.163	.687

Note: Depression and Anxiety were measured independently and simultaneously as a block on memory and language, there was no significant difference in variance explained for by anxiety, depression or anxiety and depression combined on memory (R=.001; R=.001;R=.000) or language (R=.000;.001;.000).

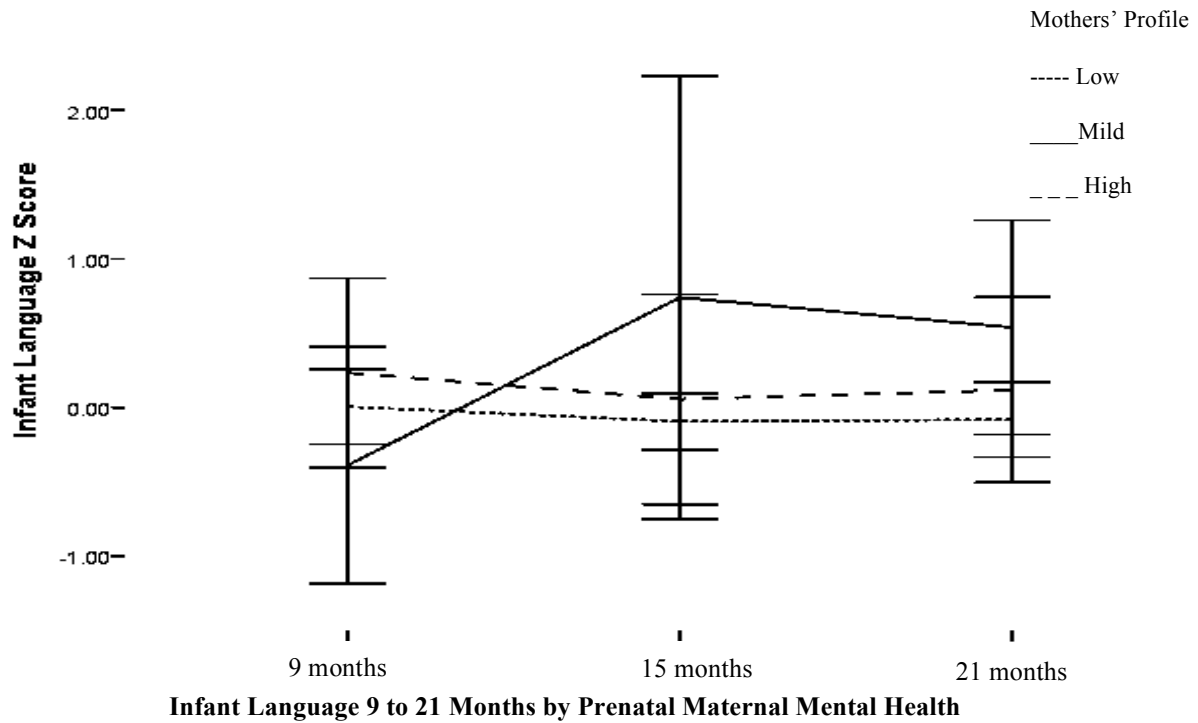
Appendix A2



Infant Memory 9 to 21 Months by Prenatal Maternal Mental Health

Note: Low group= mothers with lowest levels of depression and anxiety (N=133); Mild Group=mothers with moderate levels of depression and anxiety (N=24); High=mothers with the highest levels of depression and anxiety (N=16). Memory Scores are Z Transformed.

Appendix A3



Note: Low group= mothers with lowest levels of depression and anxiety (N=133); Mild Group=mothers with moderate levels of depression and anxiety (N=24); High=mothers with the highest levels of depression and anxiety (N=16). Language scores are Z transformed.