MATERNAL ANXIETY DURING PREGNANCY: ITS RELATIONS TO BIRTH OUTCOMES AND TO OFFSPRING DEPRESSION DURING LATE CHILDHOOD AND ADOLESCENCE

by

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There has been renewed interest in recent years in the short- and long-term effects of prenatal maternal anxiety (PMA) on offspring. Although relations between PMA and adverse birth outcomes have been established previously, the nature of these relations is not well-characterized. Furthermore, it is unknown whether the effects of PMA last into late childhood and adolescence to increase the offspring's risk of depression. The goals of this dissertation were: 1) Characterize the relations between PMA and birth outcomes; 2) Determine the correlates of Major Depressive Disorder (MDD) among offspring; 3) Determine whether PMA predicts depressive symptoms in offspring at 10 to 16 years.

Women (n=829) of low socioeconomic status, recruited from a prenatal clinic, were assessed for trait anxiety (PMA) during their fourth and seventh gestational months, and at delivery, in a study of prenatal substance use. There were 763 live singleton births. At 10, 14, and 16 years post-partum, trait anxiety and depressive symptoms were measured in women and their offspring. Offspring were assessed at 16 years for MDD. Demographic, social, substance use, medical, psychological, and psychiatric status were controlled.

It was demonstrated in the first paper that PMA predicted lower birth weight, shorter birth length, and shorter gestational length, controlling for confounders. Women who reported chronic, severe trait anxiety were at the highest risk of having shorter gestations and delivering

smaller babies. The second paper established that female gender, a history of childhood

maltreatment, and a maternal history of MDD independently increased the odds of MDD in the

16-year-olds. Daughters of women with a history of MDD were particularly vulnerable. The

third paper found that PMA was related to level of depressive symptoms in late childhood and

adolescence. These effects were significant, controlling for current maternal depression. Female

gender and lower maternal education also predicted depressive symptoms in children ages 10-16

years. There was a significant interaction between gender and follow-up assessment.

These findings have public health implications: maternal psychological health during

pregnancy and throughout the child's development should be monitored in order to improve birth

outcomes and psychological health of children and adolescents.

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AKNOWLEDGEMENTS

Patience with small details makes perfect a large work.

~ Jalalludin Rumi

My use of this quote by the Persian poet is not meant to imply that my dissertation work is perfect by any means. However, I do mean to acknowledge those people who were the "small details" of this large work.

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1.0   INTRODUCTION/OVERVIEW

Little is known about the long-term effects on the psychological and psychiatric health of offspring exposed to prenatal maternal anxiety (PMA). It is conceivable that modifications of fetal brain development occur in the wombs of anxious women such that long-term effects are observed on the psychological and psychiatric profiles of the offspring.

Some of the existing human studies of PMA are limited in that key covariates have not been measured, follow-up times of the offspring tend to be short, and primarily behavioral and emotional symptoms (rather than either psychiatric diagnosis or symptoms of depression) in the offspring have been obtained. Thus, this proposal to study the effects of PMA is original in that I propose to explore longitudinal depressive symptoms and a specific psychiatric diagnosis, major depressive disorder (MDD), as outcomes in the offspring. The goal of this dissertation is to explore the hypothesis that, in our cohort of mothers and their children, prenatal maternal trait anxiety impacts fetal and child development, such that the adolescents are more prone to MDD, and they have more depressive symptoms in late childhood and adolescence. Thus, in achieving this goal, the specific aims of this research are to:

1. Identify covariates of prenatal maternal anxiety.

2. Determine adverse birth outcomes predicted by prenatal maternal anxiety.

3. Identify significant covariates of major depressive disorder in 16-year-old adolescents.

4. Determine the relation between prenatal maternal anxiety and major depressive disorder in the offspring.

5. Determine the correlations between maternal anxiety and depressive symptoms at prenatal, and 10, 14, and 16 year follow-up assessments.

6. Characterize the longitudinal course of the children's depressive symptoms.

7. Determine the relation between prenatal maternal anxiety and depressive symptoms in the offspring from ages 10 to 16 years.

The data are from the Maternal Health Practices and Child Development (MHPCD) project, a research program begun in 1982 that examines the long-term effects of prenatal substance use by women on their 763 singleton live-born offspring. The women were selected from a hospital-based prenatal clinic and were of lower socioeconomic status. In total, 1360 women were recruited during their fourth prenatal month. From these women, two cohorts were selected for studies of prenatal alcohol and marijuana use. The selection criteria for the alcohol cohort were as follows: women who drank alcohol at the rate of three or more drinks per week in the first trimester of pregnancy, and the next woman who drank less than that amount or who abstained. For the marijuana cohort, the criteria for selection were as follows: women who used marijuana as often as twice a month, and the next woman who used less or abstained were selected. Women may be in either or both cohorts. These two cohorts were combined for this dissertation project, yielding a total of 829 women at the first assessment (fourth gestational month). Subsequent assessments of the women were conducted at the 7th prenatal month, and with their child shortly after delivery, 8 and 18 months postpartum, 3, 6, 10, 14, and 16 years. At the 16-year follow-up, the retention rate was 77% of the birth cohort.

A discussion of anxiety follows, including its epidemiology, definition, co-occurrence with depression, its relation to stress, and its covariates. Following this will be a discussion of major depressive disorder in adolescents, its risk factors and important covariates. Finally, the effects of prenatal maternal anxiety on offspring and potential mechanisms mediating these effects will be addressed.

1.1 ANXIETY

1.1.1 Epidemiology of Anxiety Disorders

The National Comorbidity Survey Replication (NCS-R), which generates diagnoses according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; APA, 1994), reported lifetime generalized anxiety disorder (GAD) estimates ranging from 4.2% (12-month minimum duration requirement) to 12.7% (1-month minimum duration requirement) (Kessler, Brandenburk, Lane, Roy-Byrne, Stang, Stein, & Wittchen, 2005).

Much data on the distribution of anxiety disorders in the population is available from the Epidemiologic Catchment Area (ECA) study, one of the largest investigations of mental disorders in a community setting, and based on the older DSM-III (APA, 1980) criteria, which required a minimum duration of one month for GAD diagnosis (Kessler, McGonagle, & Zhao, 1994; Regier, Narrow, & Rae, 1990). Marital status is significantly associated with anxiety disorder, as shown by sharply higher rates of disorder among the separated or divorced groups. Married, single, or widowed adults have lower one-month prevalence rates in the 6-7% range, whereas the rate for those who are separated or divorced is 11% (Regier et al., 1990). There is

also a striking gradient by socioeconomic status. There is a significant step-like increase in the one-month prevalence of anxiety disorders from the highest SES group (rate, 4.6%) to the lowest SES group (rate, 10.5%). (Regier et al., 1990). Prevalence rates of anxiety disorders additionally vary by age group, and peak between the ages of 25 and 44 years (one-month prevalence of any anxiety disorder, 8.3%) (Regier et al., 1990). Although rates of anxiety disorders are lower in children than adults, these disorders nevertheless remain a significant problem. Costello et al. reported 2.4% as the 3-month prevalence rate of any anxiety disorder in children aged 9-16 years (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Anxiety disorders occur about twice as often in women (9.7%) as in men (4.7%) (one-month prevalence rates; Regier et al., 1990). Among all anxiety disorders, phobic disorders were found to be the most common sub-type in women (8.4% per month) (Regier et al., 1990).

1.1.2 Trait Anxiety

Clinical diagnosis of anxiety disorder differs from the measurement of anxiety symptoms. In the clinical setting, instruments based on the DSM-IV, are used to establish the presence of a *disorder*. To be diagnosed with an anxiety disorder, the patient must meet a minimal number of criteria. However, the State-Trait Anxiety Inventory (STAI) measures state and trait anxiety on a dimensional scale such that anxiety may be detected along a continuum (Spielberger, 1983). Thus, researchers are able to quantify anxiety symptoms in individuals with sub-clinical anxiety. In a geriatric sample, high scores on the state scale of the STAI have been shown to distinguish those with a psychiatric disorder (including generalized anxiety disorder, mixed anxiety-depression, depression, dysthymic disorder, and adjustment disorder) from those without a diagnosis (Kvaal, Ulstein, Nordhus, & Engedal, 2005).

Anxiety has been conceptualized in many ways in the literature as a trait, a state, a stimulus, a response, a drive, and a motive (Endler & Kocovski, 2001). In 1966, Spielberger distinguished state from trait anxiety by defining *trait* anxiety as the individual's predisposition to experience anxiety in a stressful situation, and *state* anxiety as a transient emotional response characterized by unpleasant feelings of tension and apprehensive thoughts (Spielberger, 1966). The STAI was developed to measure state and trait anxiety separately (Spielberger, 1983). Nevertheless, the two measures are highly correlated (Albrecht & Rankin, 1989). Trait anxiety tends to be stable over time and its test-retest reliability is high (range 0.73 to 0.86) (Spielberger, Gorsuch, & Lushene, 1970). The state-trait distinction continues to be used currently in psychometric assessments of anxiety.

1.1.3   Co-occurrence of Anxiety and Depression

There is controversy as to whether anxiety can be distinguished from depression, and vice versa. Regier and colleagues (1990) have found that 1.9% of the population has a clinical diagnosis of both an anxiety and depressive disorder during a six-month period.

Because of the higher relative rates of anxiety disorders, the co-morbid group represents 33% of those with affective disorders and 21% of those with anxiety disorders over a six-month period. Furthermore, Kaneda and Fujii (2000) found that state and trait anxiety and depressive symptoms are all positively correlated in both normal subjects as well as in patients with clinical anxiety disorders. They suggest that common mechanisms underlie the overlap in symptoms of anxiety and depression.

Alloy and colleagues (Alloy, Kelly, Mineka, & Clements, 1990) have argued that in clinical samples, anxiety is usually an inherent feature of depression. Others have argued that

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self-report measures of anxiety and depression indicate a common construct of negative

affectivity, neuroticism, or general psychological distress (Gotlib, 1984; Watson & Kendall,

1989). Others have argued that the constructs of anxiety and depression cannot be adequately

differentiated using self-report measures (Dobson, 1985; Feldman, 1993). Self-report measures

such as the Beck Depression Inventory and STAI are highly correlated, with correlation

coefficients ranging from 0.5-0.8 (Watson & Kendall, 1989). Endler, however, has insisted that

these findings are due to the limitations of the measures, rather than actual overlap of the two

constructs (Endler & Kocovski, 2001). Nevertheless, the fact remains that research on

depression and anxiety is limited by the inability to separate each of these constructs.

The strong association between anxiety and depressive symptoms extends to pregnant

women. In a sample of women, one group found that higher trait anxiety was correlated with

higher Beck Depression Index scores during pregnancy (Demyttenaere, Lenaerts, Nijs, & Van

Assche, 1995). More recently, it has been found that both, prenatally and postnatally self-

reported depressed women reported higher state and trait anxiety during pregnancy as compared

to women who did not report elevated depressive symptomatology (Da Costa, Larouche, Drista,

& Brender, 2000). Furthermore, there are implications of prenatal anxiety for the postpartum

period. Barnett and Parker found that primiparous mothers with high prenatal state anxiety, were

more depressed and more worried about themselves, their babies, and their marriage and had

more doubts about their mothering capacity in the postpartum period (Barnett & Parker, 1986).

1.1.4   Stress and Anxiety

There is no universal definition of stress; various definitions exist for various contexts.

Psychosocial stress is a complex construct, in that it is a "person-environment interaction" in

which there is a perceived discrepancy between environmental demands and the individual's

biological, psychological, or social resources (Lazarus & Folkman, 1986). This comprehensive

definition addresses the point of interaction between stimulus-focused and response-focused

definitions of stress. For example, stimulus-based stress research focuses on the stimulus by

measuring life events whereas response-based stress research focuses on the individual's

response by using instruments which measure anxiety (Lazarus & Folkman, 1984). Anxiety is a

construct of perceived stress, and is related to the relative change or adjustment associated with a

stimulus.

From a biological perspective, stress is any challenge, physical or psychological, that is

perceived to threaten homeostasis (i.e., the person's internal harmonious equilibrium) (Chrousos

& Gold, 1992). In response to stress, a person's neuroendocrine, immune, and vascular systems

are activated. Mild stress can be a positive stimulus to emotional and intellectual growth and

development. However, severe, protracted, or uncontrollable psychological distress can lead to a

breakdown of homeostasis, and thus to disease. For these reasons, stress is a widely studied

phenomenon.

There exist two related bodies of literature on stress/anxiety: studies in humans and

studies on animals. In fact, many of the human studies are justified by biological findings from

animal studies. Animal models often measure physiological responses to stressful stimuli such

as bright light or noise. Similarly, various stressors in humans are associated with activation of

primarily two physiologic systems: the hypothalamic-pituitary-adrenal (HPA)-axis and

sympathetic nervous system (catecholamine-autonomic) (Dimsdale & Moss, 1980; Tsigos &

Chrousos, 2002). Importantly, studies (e.g., Dimsdale & Moss, 1980) have found that self-

reports of increased anxiety correlate with exposure to the stressors. Such findings in which

stressors are associated with physiologic reactions in animals and humans, as well as anxiety in humans, implicitly justify generalizing from laboratory-based models of the effects of stressors to anxiety.

Although stress is often assessed on the basis of life event and anxiety questionnaires, some studies attempt to distinguish between stress, life events, and anxiety by using different measures for each. For example, one research group measured these variables in dental patients with periodontitis (Vettore, Leao, Monteiro da Silva, Quintanilha, & Lamarca, 2003). They used the Stress Symptoms Inventory (SSI) to detect whether patients present with a clinical stress syndrome, the Social Readjustment Rating Scale (SRRS) to measure a number of stressful life events and their impacts, and the Spielberger State-Trait Anxiety Inventory (STAI) to measure the two dimensions of self-reported anxiety. The authors found that it was not high scores on the stress measures, but rather high trait anxiety, which was significantly associated with periodontal disease. Indeed, separate measurements of anxiety, stressful life events/stressors, and stress symptoms are necessary because the response to stressors in humans varies greatly across individuals; the stressor interacts with an individual's trait anxiety, coping mechanisms, and social support (Lobel, 1994). Even twenty years ago, researchers recognized that more important than the presence of stressful agents is how a person handles or copes with them when the stressor is present (Lazarus & Folkman, 1984). Standardized measures of anxiety, such as the STAI, are a valuable means for studying stress response because of their high reliability and validity and because they offer norms against which to compare subjects' scores.

1.1.5   Prenatal Maternal Anxiety and its Covariates

Pregnancy stresses the adaptive capacities of the pregnant woman at the physiological, psychological, and social level (Carlson & LaBarba, 1979). Indeed, many investigators have documented increased anxiety during pregnancy (Beck et al., 1980; Davids, deVault, & Talmadge, 1961). Stressors implicated in maternal anxiety during pregnancy which were identified early on by researchers included the following: extensive contact with medical professionals (Mernissi, 1972), discontinuous contact with staff (Reid & Mellwaine, 1980), and repeated pelvic examinations (Fuller, Endress, & Johnson, 1979). In women who have a tendency towards anxiety, the stresses of pregnancy may exacerbate these tendencies. Furthermore, positive correlations in pregnant women have been found between trait anxiety and age, education level, number of years married, number of children, and occupation level (Albrecht & Rankin, 1989). The more highly anxious women in this study additionally reported decreased social support (associated with state anxiety) and fewer personal resources (associated with trait anxiety). Over the past couple of decades, additional correlates of maternal anxiety during pregnancy have been identified including: race, ethnicity, substance use, life events, social support, daily hassles, and adverse birth outcomes. Some of these correlates of anxiety during pregnancy may be confounders of the relation between prenatal maternal anxiety and outcomes in offspring. The proposed dissertation will investigate some of these correlates of prenatal maternal anxiety.

1.1.5.1 Race

Findings on the relation between race and prenatal anxiety are mixed. Differences in second and third trimester anxiety levels were found between Caucasian and Hispanic groups in a large

sample of 689 African American, Hispanic, and Caucasian women (Lederman, Harrison, & Worsham, 1994). Compared with the Caucasian group, Hispanic women reported significantly higher state and pregnancy-specific anxiety. Pregnancy-specific anxiety in this study related to the well-being of the woman's baby and herself in labor and delivery, and the role of motherhood. By contrast, another study did not show any significant differences in state anxiety levels (measured in mid- and late-pregnancy) among the African American, Hispanic, and Caucasian low-income pregnant women (Norbeck & Anderson, 1989).

1.1.5.2 Maternal Substance Use, Ethnic Group, and Life Events

Anxiety may influence the expectant mother's behaviors: tobacco, alcohol, cocaine, and caffeine intakes are higher and nutrition is poorer in more anxious people (Ratliff-Crain & Kane, 1995; Singer, Salvator, Arendt, Minnes, Farkas, & Kliegman, 2002; Steptoe, Wardle, Pollard, Canaan, & Davies, 1996). A strong correlation between lifetime anxiety disorders and substance use has been well-established in both the NCS and ECA studies (Kessler et al., 1996; Regier, Burke et al., 1990). According to the results from a large co-morbidity survey, in which anxiety disorders were classified as either substance-induced or non-substance-induced, about 15% of individuals with at least one 12-month non-substance-induced anxiety disorder had a substance use disorder as well (Grant et al., 2004). Thus, the direction of the relation between anxiety and substance use is not entirely clear.

Furthermore, substance use and ethnic group appear to be significant covariates of prenatal maternal anxiety. This relation is demonstrated from the results of a study of substance use in low-income pregnant women, in which Zambrana and Scrimshaw (1997) described intra- and inter-ethnic group differences in mean prenatal life events and trait anxiety score for each substance use pattern group. For Mexican American and Mexican immigrant groups, those

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women who smoked, used alcohol, or illicit drugs reported significantly more life events and anxiety than their counterparts who never used any substance. For African American respondents, mean number of life events was also significantly higher for women who reported use of any drugs than for those who reported no drug use. However, there was no within-group difference found for African American women on the mean anxiety score. The authors additionally noted intriguing results between ethnic groups. Among non-substance users, African American women reported more prenatal life events and more anxiety than the other two ethnic groups. However, paradoxically, Mexican American and Mexican immigrant women who smoked cigarettes or used illicit drugs reported more anxiety and life events during pregnancy than African American women in the equivalent drug using groups. Overall, the study showed a trend toward increased prenatal life events and associated anxiety for women who used substances during pregnancy, particularly illicit drugs or illicit drugs in combination with alcohol or tobacco.

There have been only a handful of studies that have not found an association between substance use and anxiety. For example, Albrecht and Rankin found that, in a sample of women from various socioeconomic, racial, and religious groups, there were no significant differences on the STAI between pregnant smokers and pregnant nonsmokers (Albrecht & Rankin, 1989). Despite this finding, the majority of the literature supports a correlation between substance use and anxiety disorders. The time-ordering of the relation between substance use and anxiety is not clear. Some evidence suggests that stressful, chronic life problems can contribute to substance use (Biener, 1987; Lillie-Blanton, Martinez, Taylor, & Robinson, 1993). Alternatively, it is possible that substance use during pregnancy leads to the women having more stressful life events and self-reported anxiety.

1.1.5.3 Social Support and Stress

One group conducted a study of psychosocial factors as predictors of well-being in 360 women during pregnancy (Paarlberg et al., 1996). They found that depressive symptoms and, to a lesser degree, anxiety during pregnancy, were associated with negative psychosocial factors, particularly a higher number of daily stressors and lower satisfaction with received social support. This study's findings confirmed those in a sample of pregnant women aged 20 to 40 years, in which Albrecht and Rankin found that increased state and trait anxiety were each significantly associated with decreased social support (Albrecht & Rankin, 1989). Furthermore, an intervention study found that assigning highly anxious primiparous mothers during the first postnatal year to social support intervention (professional support) significantly reduced state anxiety levels as compared with the control group (Parker & Barnett, 1987).

1.1.5.4 Birth Outcomes

Women who experience stress and anxiety during pregnancy have higher rates of adverse birth outcomes (Dole et al., 2003; Paarlberg, Vingerhoets, Passchier, Dekker, & Van Geijn, 1995; Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999). While Barnett and Parker (1986) found that highly anxious mothers had more delivery complications, the most consistent findings are for preterm births and low birth weight. One study showed that these two variables were significantly predicted by an indicator of stress (incorporating state anxiety, perceived chronic stress, and life event stress), after controlling for medical risk, parity, and maternal substance use (Lobel, Dunkel-Schetter, & Scrimshaw, 1992). Furthermore, in Hedegaard and colleagues' (Hedegaard, Henriksen, Sabroe, & Secher, 1993) cohort of several thousand women attending a prenatal clinic, psychosocial distress, as measured by the General Health Questionnaire

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(Goldberg, 1972), during late pregnancy (30th week), but not early pregnancy (16th week), predicted preterm delivery.

1.2   DEPRESSION

1.2.1   Major Depressive Disorder in Adolescents

Major depressive disorder (MDD) accounts for greater mortality, morbidity, and financial costs than any other psychiatric disorder (Murray & Lopez, 1996). Those who experience depression at an early age tend to struggle with the illness throughout their lives (Lewinsohn, Rohde, Klein, & Seeley, 1999). There are many parallels between MDD in adults, adolescents, and children (e.g., Ryan, Puig-Antich, Ambrosini, Rabinovich, Robinson, Nelson, et al., 1987), however there are some key differences. Symptoms of melancholia, psychosis, suicide attempts, lethality of suicide attempt, and impaired functioning are less common in younger patients. More common in earlier-onset depression are symptoms of separation anxiety, phobias, somatic complaints, and behavioral problems (Carlson, & Kashani, 1988; Kolvin, Barret, & Bhate, 1991; Mitchell, McCauley, Burke, Moss, 1988; Ryan et al., 1987). People who develop depression in childhood and adolescence have more relapses, more serious disorders, and higher rates of comorbid psychiatric disorders (Lewinshon, et al., 1999).

Adolescence is a time when many new cases of depression emerge. Unipolar depression is more common in adolescence (1-year prevalence estimates range between 0.4% and 8.3%) than in childhood (1-year prevalence estimates range between 0.4 and 2.5%) (Fleming & Offord, 1990; Birmaher, Ryan, Williamson, Brent, Kaufman, Dahl, et al., 1996; Lewinsohn, Clarke,

Seeley, & Rohde, 1994). Furthermore, adolescence is a particularly crucial time of development because, in addition to experiencing puberty, the children experience social stressors that they may not have experienced during childhood. Some adolescents may be better equipped to deal with the stressors than others, and the degree of their ability may contribute to their risk of developing depression. For these reasons, it is crucial that we gain a better understanding of the risk factors associated with MDD in adolescents.

1.2.2   Risk Factors for Depression

1.2.2.1 Parenting and Parental Psychopathology

In addition to the genetic contribution made by the parents, there is a strong environmental influence of the caregiver on child development and on development of psychopathology. Evidence suggests that responsive caregivers may help protect against depression and other forms of psychopathology (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Werner & Smith, 2001). Indeed, the quality of the caregiver-child interaction has been determined to be one of the most important factors that distinguishes abused children with normal developmental outcomes from those with abnormal outcomes (Kaufman & Henrich, 2000; Pynoos, Steinberg, & Wraith, 1995). One study reported an association between parental expressed emotion and serious child and adolescent affective disorders (Schwartz, Dorer, Beardslee, Lavori, & Keller, 1990). They found that a higher degree of maternal critical expressed emotion predicted a threefold increase in the risk (odds ratio) for children aged 6-19 years to have at least one of the following DSM-III diagnoses: depressive disorder (MDD or dysthymia), substance use disorder, or conduct disorder. More recently, Asarnow and colleagues (Asarnow, Tompson, Woo, & Cantwell, 2001) confirmed the findings of Schwartz et al. (1990) by demonstrating that maternal

emotion which is critical in nature (as measured by the Five Minute Speech Sample Expressed Emotion) shows some specificity as a risk factor for depression in youth (6-18 years of age)

Several reviews have established that parental depression is a very strong predictor of depression during childhood and adolescence (Beardslee, Versage, & Gladstone, 1998; Downey & Coyne, 1990; Gelfand & Teti, 1990). Consistent findings have come from longitudinal studies. For example, Weissman et al. investigated the effects of parental depression over the course of a 10-year period (years 1, 2, and 10) on children aged 6-23 years at the beginning of the study (Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997). At the 10-year follow-up point, they found significantly higher rates of major depression, phobias, panic disorder, and alcohol dependence in the offspring of affectively ill parents as compared with offspring in the non-ill group. However, even such well-designed longitudinal studies are potentially confounded by genetic risk of psychopathology.

1.2.2.2 Genetics

It is challenging to separate the specific effects of inheritance from those of the child's environment. Nevertheless, several authors have managed to find a role of genetics in depression. Eaves et al. (1997) reported a substantial genetic effect on Depressive Disorder (as measured by the Child and Adolescent Psychiatric Assessment) among a large population-based sample of twin pairs aged 8-16 years. In another study, prepubertal children with MDD had significantly higher familial rates of psychiatric disorders in first- and second-degree relatives than non-MDD controls (Puig-Antich, Goetz, Davies, & al., 1989). Furthermore, Weissman et al. were one of the first groups of researchers to notice the trend that relatives of probands whose depression had an age of onset before 20 years, had higher rates of depression than the relatives

of probands with later onset of disorder (Weissman et al., 1984). These early findings implied a genetic component to major depression that has an earlier onset.

More recently, the role of genetics in childhood-onset MDD gained further support from Neuman et al's findings, which used the Family History-Research Diagnostic Criteria (FH-RDC) assessment instrument to compare familial clustering of affective disorders among first-degree relatives of prepubertal versus adult probands with mood disorders (Neuman, Geller, Rice, & Todd, 1997). They found that the cumulative risk for lifetime major mood disorders in first-degree relatives of child probands was significantly higher than for relatives of adult probands. These findings indicate that there may be a larger genetic component in child-onset versus adult-onset affective disorders. Somewhat contradictory were the findings of Harrington et al. In a thorough longitudinal study which followed probands from childhood to adulthood, the group found that, compared with prepubertal cases of depressive disorder, postpubertal forms of the disorder had a more specific association with a family history of depression and more continuities to major depression in adulthood (Harrington et al., 1997). The prepubertal cases were instead more strongly associated with the environmental variable, family discord. While it is evident that genetics does play a role in MDD, the relative contribution of genetics to child- versus adolescent- versus adult-onset is not clearly established.

1.2.2.3 Demographics

In a large, longitudinal study of families followed from infancy to adolescence, Spence et al. found that poverty, distressed marital relationship, and marital break-up during the child's first five years produced small, but significant, increases in risk of high anxiety and depression symptoms in adolescence (Spence, Najman, Bor, O'Callaghan, & Williams, 2002).

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The association between low socio-economic status and mental disorders, including depression, is well established (Johnson, Cohn, & Dohrenwend, 1999). Furthermore, for depression, many study findings have supported a social causation, that is, adversity associated with low SES causes disorder (Dohrenwend, Levav, & Shrout, 1992; Johnson et al., 1999). The theory of social causation for depression is in contrast to the alternate theory of social selection, proposed to explain some psychiatric disorders, which states that constitutional and environmental factors contribute to the onset of psychiatric disorders, which in turn cause individuals to experience downward drift in SES (Wender, Rosenthal, Kety, Schulsinger, & Welner, 1973). Ritsher et al. were the first to control for parental depression in an inter-generational test of social causation (i.e., low SES causes depression) (Ritsher, Warner, Johnson, & Dohrenwend, 2001). They found that low SES (measured by parental education and occupation), after controlling for parental depression, was associated with increased risk of depression in the offspring.

Not all findings support the theory of social causation for depression. For example, an income intervention study by Costello et al. failed to support the theory (Costello, Compton, Keeler, & Angold, 2003). Over the course of eight years, 1420 rural children aged 9 to 13 years were given annual psychiatric assessments. Halfway through this study, a casino opened on an American Indian reservation, which allowed 14% of study families to rise above poverty level. After the casino opening, there were significant decreases in conduct and oppositional defiant disorders in the child sample. However, anxiety and depression symptoms were unaffected. These findings, which run counter to expectation, emphasize the importance of investigating the relation between poverty and specific psychiatric diagnoses and symptoms.

1.2.2.4 Gender & Age/Puberty

Prior to adolescence, there is no additional risk for depression associated with either gender. However, when puberty begins, there is a sharp divergence by gender, with the rate among girls becoming approximately twice that among males (Angold, Costello, & Worthman, 1998). Both biological and social factors have been implicated in the predominance of depression among adolescent girls. Hypotheses that have been proposed to explain the mechanism include: 1) Changing levels of various hormones, including testosterone and estrogen, may affect brain functioning; 2) Anatomic changes reflecting sexual maturity may influence social roles; 3) Other social changes may influence the number of depression-inducing life events; 4) Earlier pubertal timing of girls relative to male peers may cause social stress (Costello et al., 2002). There is some evidence that suggests exposure to increased levels of testosterone and estrogen at puberty, especially in the context of social stress, independently predicts the risk for depression in girls (Angold, Costello, & Worthman, 1999; Silberg et al., 1999).

1.2.2.5 Substance Use

As with anxiety disorders discussed earlier, national epidemiology surveys (Kessler et al., 1996) and clinical studies (Swendson & Merikangas, 2000) have established the strong lifetime association of mood disorders with substance use disorders. However, distinguishing between independent (i.e., non-substance-induced) and substance-induced mood disorders is challenging since diagnosis of current mood disorders among active substance users is complicated by the fact that many symptoms of intoxication and withdrawal from alcohol and other drugs resemble the symptoms of mood disorders. In light of this challenge, recent work by Hasin and Grant separated past from current major depression in a large study of previous alcohol abusers, and showed that intoxication and withdrawal symptoms did not entirely account for the association

between alcohol use and depression (Hasin & Grant, 2002). Even more recently, in the National Institute on Alcohol Abuse and Alcoholism's National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), the comorbidity of DSM-IV substance use disorders and nine independent mood and anxiety disorders was addressed (Grant, Moore, & Kaplan, 2003). Grant et al. found that all independent mood disorders significantly correlated to alcohol and drug use disorders (OR 1.3-12.5) (Grant et al., 2004). While these findings provide some insight into the prevalence and co-occurrence of mood disorders that are not substance-induced, questions regarding the mechanisms of comorbidity still remain. Some evidence suggests that depression tends to precede substance use. One recent prospective longitudinal study in a large sample of adults demonstrated that MDD significantly increased the risk for subsequent AUD (Gilman & Abraham, 2001).

Existing literature also supports a significant association between substance use and depression in adolescents. Consistent with the adult literature, Saluja et al. found through a school-based survey, that adolescents who use drugs have significantly higher levels of depressive symptoms (Saluja et al., 2004). Elevated depressive symptoms have been shown to be risk factors for poor prognoses (e.g., Angst & Merikangas, 1997; Fergusson, Horwood, Ridder, & Beautrais, 2005; Lewinsohn, Solomon, Seeley, & Zeiss, 2000). Saluja et al.'s study examined associations between depressive symptoms and specific types of drugs used by the adolescents in the 6th, 8th, and 10th grades. The relative risks for having concurrent depressive symptoms were significantly greater than 1.0 for users of all substances examined, including tobacco (female, 2.8; male, 2.3), alcohol (female, 3.0; male, 2.5), marijuana (female, 2.6; male, 2.2), cocaine (female, 2.5; male, 3.8), inhalants (female, 3.0, male, 4.0), and hallucinogens (female, 3.1; male, 3.0).

While the association between adolescent depression and substance use is well-established (Deykin, Levy, & Wells, 1987), the order of onset remains unclear. In the Great Smoky Mountain Study data, depressive symptoms initially appeared between ages 9 and 11 years, after the onset of alcohol use but before the onset of cigarette use (Costello, Erkanli, Federman, & Angold, 1999). However, in youth who developed a depressive disorder by age 16, alcohol use had begun even earlier than in those youth without disorder (more than two years earlier in girls and one year earlier in boys). Depressed boys were likely to begin to smoke cannabis one year after the onset of depressive symptoms and to develop cannabis abuse or dependence within another year, which was two years ahead of non-depressed boys. In contrast, the Dunedin longitudinal study found a sex-specific pathway from early female depression to substance use at age 15 (Henry et al., 1993). A prospective study by Williamson et al. which followed children through adolescence found that initially depressed children and children at high familial risk for depression had a nearly four-fold increase in risk for developing AUD by late adolescence compared with children at low familial risk for depression (Williamson et al., 2005). Furthermore, among children at high familial risk for depression, those who became depressed were five times more likely to develop AUD compared with those who did not develop depression. Some studies, such as the Oregon longitudinal study have been unable to find any temporal relation between depression and alcohol use or dependence (Rohde, Lewinsohn, & Seeley, 1996). Nevertheless, the literature has clearly established that substance use and depression in adolescents are highly correlated, and share common etiologies, including genetic and/or environmental factors (Burcusa, Iacono, & McGue, 2003; Prescott, Aggen, & Kendler, 2000).

1.2.2.6 Childhood Maltreatment, Violence Exposure, and Parental Substance Use

Maltreatment includes various forms of abuse and neglect. Childhood abuse and other stressful life events during childhood are associated with higher rates of MDD (Horesh, Sever, & Apter, 2003; Kendler, Thornton, & Gardner, 2000; Kessler & Magee, 1993). Population-based studies, including the large Adverse Childhood Experiences Study, document significant associations between depression (both, clinical depression and depressive symptoms) and abuse, neglect, and related forms of environmental adversity (Edwards, Holden, Felitti, & Anda, 2003; Famularo, Kinscherff, & Fenton, 1992; Kaufman, 1992). A recent study discovered that effects of exposure to multiple forms of abuse (including verbal, emotional, sexual, and/or physical abuse) on depression in young adults were more than additive (Teicher, Samson, Polcari, & McGreenery, 2006).

The study by Teicher et al. (2006) also found strong effects on depression of witnessing domestic violence. Another couple of related studies found that exposure to violence (including that in the home and community) predicts a diagnosis of a major depressive episode (MDE) in adolescents (Hanson, Self-Brown, Fricker-Elhai, Kilpatrick, Saunders, & Resnick, 2006; Self-Brown, LeBlanc, Kelley, Hanson, Laslie, & Wingate, 2006). Parental substance use (especially alcohol), a correlate of both child abuse and domestic violence, predicted MDE (Hanson et al., 2006). Furthermore, parental substance use moderated the relation between abuse and depression in the adolescents.

1.3   MATERNAL AND OFFSPRING PSYCHOPATHOLOGY

1.3.1   Effects of Prenatal Maternal Anxiety on Offspring

Animal studies have demonstrated that prenatal stress can have direct long-term effects on the offspring's ability to cope in stressful situations; prenatally stressed animals have prolonged elevation of plasma glucocorticoids in response to stressful and novel situations, thus indicating a dysregulated HPA axis (Henry et al., 1994; Weinstock, 1997; Schneider & Moore, 2000). In humans, dysregulation of the HPA axis is thought to play a role in the etiology of MDD, however its role specifically in early-onset MDD is unclear (Arborelius et al., 1999; Holsboer, 2000).

Most of the extant studies on prenatal maternal anxiety and stress have focused on short-term outcomes, such as preterm birth and low birth weight (e.g., Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993). There have been several studies additionally addressing the association between maternal anxiety and infant temperament. For example, Van den Bergh (1990) assessed anxiety during each trimester of pregnancy in 30 women, and their infant's temperament at 10 and 28 weeks of age. She found that state anxiety during each trimester predicted infant temperament ratings. Maternal anxiety primarily related to infant negative emotionality. A few additional studies have followed the offspring of prenatally anxious mothers into early-middle childhood, but have measured only behavioral and emotional problems in these young children (Martin, Noyes, Wisenbaker, & Huttunen, 1997; O'Connor, Heron, Golding, & Glover, 2003). Martin and colleagues (1997) in the Helsinki Longitudinal Temperament Project, a prospective study of 6,401 children, found a significant relation between prenatal maternal emotional distress (a latent variable including anxiety, depression, and mood

lability) and negative emotionality assessed in the offspring at age 5 years. The major methodological limitation of this study, however, was that the measurement of preschool temperament was based on maternal report: mothers in the study with a depressed or anxious predisposition may have experienced more distress during pregnancy, and viewed their children as exhibiting more negative emotionality.

Recently, O'Connor and colleagues (2003) have shown through the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective community study, that prenatal maternal stress has a significant effect on the fetus that lasts at least into middle childhood, as evidenced by increased behavioral and emotional problems in 6 ½ year-old offspring of prenatally-anxious women. Once again, this study is limited by use of maternal report of children's behavioral/emotional problems. Nevertheless, these significant findings in humans are consistent with the vast body of animal literature, which has found prenatal maternal stress effects on long-term behavior in the offspring.

Another study (Van den Bergh & Marcoen, 2004) showed that, after controlling for key covariates, maternal state anxiety during pregnancy significantly predicted attention deficit hyperactivity disorder (ADHD) symptoms, externalizing problems, and self-report anxiety in 8- and 9- year olds. Their outcome measures of symptoms were based on clinical questionnaires and standardized observation scales completed by mother, teacher, observer, and child. Many additional studies of behavioral and emotional outcomes in prenatal anxiety/stress-exposed children have been comprehensively reviewed (Van den Bergh, Mulder, Mennes, & Glover, 2005).

A study by Allen and colleagues (Allen, Lewinsohn, & Seeley, 1998) examined prenatal and perinatal risk factors of psychopathology in adolescence. The authors found that the two

perinatal variables that most strongly predicted MDD in the adolescents were maternal emotional health (anxiety and depressive symptoms) and not having breast fed the infant. Prenatal maternal emotional health was no longer a significant predictor after adjusting for the mediating variable, maternal depression throughout the child's lifetime. This could suggest three possibilities. The risk for adolescent depression is conferred by the effects of maternal depressive behavior throughout the child's lifetime, a possibility supported by the literature (Downey & Coyne, 1990). Alternatively, the association between maternal and child depression is due to a common environmental or genetic factor that influences both individuals. A final and likely possibility is that, due to the retrospective design of the study, the women's report of their emotional health during pregnancy (14 to 18 years prior) is biased by their current psychological state. Because our data were gathered prospectively, we are able to overcome this limitation. Furthermore, we have separate measures of the pregnant women's psychological health: trait anxiety, trait anger, and depressive symptoms.

1.3.2 Potential Biologic Mechanisms of Prenatal Maternal Stress /Anxiety

As previously mentioned, the stress response ("fight or flight") is mediated by several neurological and endocrine messages along both, the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS). Dysregulation of each of these systems has been implicated in depression (Arborelius et al., 1999; Holsboer, 2000; Ressler & Nemeroff, 2000). In the HPA-axis, stress perceived by the brain stimulates release of corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamus, which in turn cause the release of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH then stimulates the release of cortisol, the major glucocorticoid in humans, from the adrenal glands. Cortisol

enhances catabolic processes while suppressing anabolic pathways, to insure mobilization of energy stores. The other major physiologic system activated in response to stress is the SNS. A series of sympathetic nerves originate in the spinal cord and extend to the effector organs (e. g., heart, blood vessels, skeletal muscles, adrenal medulla). At most sites in the body, the chemical transmitter is norepinephrine (noradrenaline). The adrenal medulla responds to sympathetic nervous impulses by secreting the catecholamine hormones (epinephrine and norepinephrine). The SNS activation results in increased pupil size, mobilization of fat and glycogen, heart rate, blood pressure, cardiac output, and a diversion of blood flow from the skin and splanchnic vessels (including those of the uterus), to supply the vessels in skeletal muscle.

While short-term activation of the stress-response HPA-axis and sympathetic nervous systems are appropriate in times when a "fight or flight" response is required, prolonged activation may lead to several unhealthy consequences in the chronically stressed person, including suppression of anabolic processes, depletion of energy stores, and suppression of the immune system (Jacobson & Sapolsky, 1991; McEwen, 1995; Sapolsky, 1992). With such negative consequences of elevated stress in the stressed person, himself/herself, one may speculate as to the effect of elevated stress in pregnant women on the developing fetus.

Stressed pregnant rodents have offspring with altered HPA-axis response, altered levels and distribution of neurotransmitters, including norepinephrine, dopamine, serotonin, acetylcholine, and modified limbic structures in the brain (see reviews by Kofman, 2002; Wadhwa, 1998; Weinstock, 2001). Offspring of prenatally-stressed non-human primates have altered endocrine, immune, and neurobehavioral systems (Coe & Lubach, 2000; Schneider, Moore, Roberts, & Dejesus, 2001; Wadhwa, 2005). Such physiologic changes decrease learning,

increase anxiety, and change social behavior (as evidenced by increased withdrawal) (Kofman, 2002).

Fetal programming results when an insult that occurs to the fetus during a critical period produces long-lasting or life-long effects on the organism (Lucas, 1994). The maternal-placental-fetal neuroendocrine system, the HPA-axis, is thought to be the primary mediator of the effects of maternal stress on the fetus (Wahdwa, 2005). In the fetus, glucocorticoids have dose-dependent effects on morphologic development (Lederman, 1996). The HPA axis is particularly susceptible to fetal programming by glucocorticoids (e. g., Barker, 1998). Formation of the hypothalamus, pituitary, and adrenal glands occurs throughout gestation, with fetal HPA activity beginning at midgestation (Gitau, Fisk, Teixeira, Cameron, & Glover, 2001). Elevated prenatal maternal cortisol levels may directly or indirectly impact HPA-axis development in the susceptible fetus. The permanent modification of the HPA-axis *in utero* may lead to HPA-axis dysregulation throughout postnatal and childhood development, such that, when exposed to the stressors of adolescence, he/she is more susceptible to developing depression.

Some elevation of plasma cortisol in pregnant women is normal. There is a physiologic increase in maternal CRH levels from mid-second trimester of pregnancy, followed by a sharp rise in the last few weeks of pregnancy. Additionally, the placenta secretes large amounts of CRH into maternal and fetal plasma during pregnancy, which regulates pituitary-adrenal function (Goland, Conwell, Warren, & Wardlaw, 1992). In order to protect the developing fetus, the placenta contains the enzyme 11β-hydroxysteroid dehydrogenase Type 2 (11β-HSD2), which rapidly inactivates maternal cortisol before it enters fetal circulation (Lindsay, Linday, Edwards, & Seckl, 1996). Thus, a direct action of maternal cortisol on the fetus is unlikely during the normal physiologic conditions of pregnancy. The enzyme's function under high levels of stress

and anxiety is unknown. Thus, it is possible that elevated prenatal maternal cortisol beyond normal pregnancy levels overwhelms the placental enzyme's ability to inactivate the cortisol, such that the hormone reaches the fetus and directly modifies HPA-axis development. An alternate mechanism is one involving action of fetal cortisol. Levels of prenatal maternal cortisol positively correlate with fetal cortisol (Gitau, Cameron, & Fisk, 1998). Cortisol has differential feedback effects, depending on the site considered. In the hypothalamus, cortisol suppresses the release of CRH, whereas in the placenta, cortisol stimulates the expression of CRH (Laatikainen, 1991). This suggests a positive feedback mechanism between placental CRH and fetal cortisol and a mechanism that supports a maternal/fetal stress response (Lederman, 1996).

Additionally, indirect mechanisms of maternal stress/anxiety have been suggested. Maternal anxiety during pregnancy is associated with decreased uterine blood flow (Teixeira, Fisk, & Glover, 1999). Myers' study of primates outlined a mechanism that explains this association: maternal exposure to stressors causes sympathetic activation and release of catecholamines into the blood stream, which reduce uterine blood flow, resulting in fetal hypoxia (Myers, 1977; Teixeira, Fisk, & Glover, 1999). Other mediators may play a role in the hypothesized relationship between prenatal maternal anxiety and depression in the offspring. For example, prenatally stressed and anxious women have more birth complications (specifically, prematurity and low birthweight; Bhagwanani, Seagraves, Dierker, & Lax, 1997; Lou et al., 1994). Indeed, it has been shown that premature delivery is a risk factor for developmental disorders (Den Ouden & Blanco, 2000). It has not been shown that birth outcomes are mediators of a potential relation between prenatal maternal anxiety and psychopathology in the offspring.

1.4   SUMMARY OF PROPOSAL

To my knowledge, there have been no previous prospective longitudinal studies investigating the role of prenatal maternal anxiety in predicting either depressive symptoms in late childhood and adolescence or lifetime diagnosis of major depressive disorder in adolescent offspring. It is my aim to determine whether prenatal maternal trait anxiety, which does not necessarily constitute an anxiety disorder, can contribute to development of depressive symptoms in the offspring significant enough to constitute psychiatric disorder in adolescence. Thus, I hypothesize, in our cohort of women and their children from the MHPCD project, self-reported prenatal maternal trait anxiety will significantly and positively predict diagnosis of MDD in the 16-year-old offspring, after controlling for current depressive symptoms in the mothers. If, however, prenatal maternal anxiety does not significantly predict a lifetime diagnosis of major depressive disorder in the adolescents, I will modify my outcome to explore depressive symptoms at ages 10, 14, and 16 years.

1.5   MANUSCRIPTS

Three peer-reviewed manuscripts have resulted from the work presented in this dissertation. They are as follows:

1. **Hosseini, S. M.**, Wroble Biglan, M., Larkby, C., Brooks, M. M., Gorin, M. B., & Day, N. L. "Trait anxiety in pregnant women predicts offspring birth outcomes." Chapter 2 is based on the work presented in this manuscript, which has been submitted to Paediatric and Perinatal Epidemiology.

2. **Hosseini, S. M.**, Day, N. L., Brooks, M. M., Wroble Biglan, M., Gorin, M. B., & Larkby, C. "Covariates of major depressive disorder in mid-adolescence." Chapter 3 is based on the work presented in this manuscript, which will be submitted to the Journal of the American Academy of Child and Adolescent Psychiatry.

3. **Hosseini, S. M.**, Larkby, C., Brooks, M. M., Wroble Biglan, & Day, N. L. "Maternal anxiety symptoms during pregnancy predict depressive symptoms in children from ages 10 to 16 years." Chapter 4 is based on work presented in this manuscript, which will be submitted to the Journal of Child Psychology and Psychiatry.

1.6 HYPOTHESES FOR MANUSCRIPTS

Manuscript 1. "Trait anxiety in pregnant women predicts offspring birth outcomes"

I. The following variables will be significantly associated with higher PMA:

    a. **Demographics**

        H1: Less educated

        H2: Lower income

        H3: African American

        H4: Unemployed

        H5: Single

    b. **Social/Other**

H1: Less perceived social support

H2: More life events during pregnancy

H3: Any negative or neutral feelings about their pregnancy

H4: No church attendance

c. **Substance use** (measured at each trimester)

H1: More marijuana

H2: More tobacco

H3: More alcohol

H4: Any illicit drugs (not including cocaine)

H5: Any cocaine

d. **Medical**

H1: More medical problems

H2: Lower gravida status

H3: More previous miscarriages

H4: Any hospitalizations during pregnancy

H5: Any illnesses during pregnancy

e. **Psychological**

H1: Depressive symptoms

H2: Trait anger

f. **Adverse birth outcomes**

H1: Lower birthweight

H2: Shorter birth length

H3: Smaller head circumference

H4: Shorter gestational age

H5: More pregnancy complications

H6: More labor and delivery complications

H7: Small for gestational age (SGA)

H8: Lower than maximum Apgar score

II. PMA measured at each assessment will predict adverse birth outcomes, after controlling for confounders in the other domains.

III. PMA which is severe and chronic will have the greatest impact on birth outcome.

Manuscript 2. "Covariates of major depressive disorder in mid-adolescence"

I. The following adolescent variables will bivariately be associated with MDD at age 16 years:

    a. **Demographics**

        H1: Female gender

    b. **Social support**

        H1: Fewer close friends

        H2: Lower frequency of outings

    c. **Current substance use**

        H1: Any alcohol

        H2: Any tobacco

        H3: Any marijuana

    d. **More severe childhood maltreatment** (reported at age 16)

    e. **More delinquent behavior**

f. **Pubertal status**

      H1: More advanced pubertal status at age 14

      H2: Developed earlier than peers

g. **More anxiety**

h. **Lower grade point average**

i. **Poorer general health**

II. The following maternal variables will bivariately be associated with MDD at age 16 years:

a. **Demographics**

      H1: Lower income

      H2: Lower education

      H3: Unemployment

      H4: Single

      H5: No male in household

b. **Psychological**

      H1: Higher trait anxiety

      H2: More depressive symptoms

      H3: Higher trait anger

c. **Psychiatric**

      H1: Major Depressive Disorder (MDD)

H2: MDD only

H3: Comorbid MDD

H4: Any DSM-IV disorder other than MDD

H5: Generalized anxiety disorder (GAD)

H6: Any alcohol disorder

H7: Any marijuana disorder

H8: Any cocaine disorder

III. A multivariate model of MDD will include both offspring and maternal variables.

Manuscript 3. "Maternal anxiety symptoms during pregnancy predict depressive symptoms in children from ages 10 to 16 years"

I. PMA is associated with depressive symptoms in the offspring.

II. After controlling for confounders, PMA will remain a significant predictor of longitudinal depressive symptoms in the offspring.

III. Potential mediators of the PMA/offspring depressive symptoms relation include:

    a. Adverse birth outcomes:

        i. Lower birthweight (or low birth weight)

        ii. Shorter birth length

        iii. Shortened gestational age (or preterm birth)

        iv. Small size for gestational age

2.0 MANUSCRIPT 1: TRAIT ANXIETY IN PREGNANT WOMEN PREDICTS OFFSPRING BIRTH OUTCOMES

2.1 SUMMARY

The goal of our study was to characterize the relations between trait anxiety symptoms of women during their pregnancies and birth outcomes of offspring using a longitudinal cohort from the Maternal Health Practices and Child Development Project. We used the State-Trait Personality Index (STPI) anxiety measure, based on Spielberger's State-Trait Anxiety Inventory (STAI) to measure self-reported trait anxiety at two gestational assessments (fourth and seventh months) and at a third assessment shortly after delivery. Demographic, social, psychological, substance use, and medical factors were assessed prenatally, and outcomes of the 763 live, singleton births were determined at delivery. In regression models, trait anxiety at the second and third assessments predicted lower birthweight and shorter birth length, controlling for confounds. Anxiety reported at the third assessment predicted shortened gestational age, controlling for confounds. At the first and second assessments, the relation of birthweight and birth length to maternal trait anxiety was only significant for severe anxiety. Women whose anxiety reached severe levels for at least two assessments were significantly more likely to deliver offspring of lower birthweight and shorter birth length than those women who reported severe anxiety at none or one of the assessments. Additionally, offspring of women who experienced severe anxiety

during three trimesters had shorter mean gestational age compared to offspring of women who did not report severe anxiety at any assessment. Women who report chronic, severe trait anxiety are at the highest risk of having shorter gestations and delivering smaller babies.

2.2   INTRODUCTION

Women who experience stress and anxiety during pregnancy are reported to have higher rates of adverse birth outcomes (Dole et al., 2003; Paarlberg, Vingerhoets, Passchier, Dekker, & Van-Geijn, 1995; Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999), including lower 5-minute Apgar scores and more obstetric complications (Crandon, 1979a; 1979b). However, these studies and others focused on the effects of anxiety during pregnancy controlled only for some of the potential confounds of the relations between anxiety and birth outcomes (McDonald, Gynther, & Christakos, 1963; Ottinger & Simmons, 1964).

More recent studies of birth outcomes have focused on determining the role of prenatal stress rather than that of anxiety. Several of these have shown that prenatal stress predicted preterm births and low birthweight, outcomes that may have long-term implications for health (Bhagwanani, Seagraves, Dierker, & Lax, 1997; Lou et al., 1994) .Preterm delivery is a risk factor for developmental disorders (Den-Ouden & Blanco, 2000) and low birthweight has been shown to predict hypertension, insulin resistance, glucose tolerance, and cardiovascular disease (Barker, 1998a; 1998b).Lobel and colleagues found that prenatal stress (a combination of state anxiety aggregated over the course of pregnancy, perceived chronic stress, and life event stress) predicted preterm births and low birthweight, after controlling for medical risk, parity, and substance use (Lobel, Dunkel-Schetter, & Scrimsaw, 1992). Prenatal stress as defined in these

studies was composed of several variables, and only sometimes included trait anxiety. Therefore, it is unclear from these studies whether trait anxiety during pregnancy would predict shorter gestational age and smaller birth size of the offspring after potential confounds such as demographic factors, social support, substance use, medical problems, depression, and trait anger have been considered.

Several mechanisms have been proposed to explain the link between stress and anxiety during pregnancy and birth outcomes. First, anxiety may influence the expectant mother's behaviors: tobacco, alcohol, cocaine, and caffeine intakes are higher and nutrition is poorer in more anxious people (Ratliff-Crain & Kane, 1995; Singer et al., 2002; Steptoe, Wardle, Pollard, Canaan, & Davies, 1996).Each of these behaviors is associated with adverse birth outcomes, including preterm delivery and lower birthweight (Singer et al., 2002; Bloomfield et al., 2003; Bracken, Triche, Belanger, Hellenbrand, & Leaderer, 2003; Day et al., 1989; Windham, Hopkins, Fenster, & Swan, 2000). Second, maternal anxiety during pregnancy may increase fetal exposure to maternal glucocorticoids and lead to lower birthweight and higher glucocorticoid levels in offspring (Reynolds et al., 2001; Yehuda et al., 2005).Additionally, increased uterine artery resistance in anxious, pregnant women may lead to restriction of fetal nutrient supply and limit fetal growth (Lou et al., 1994; Teixeira, Fisk, & Glover, 1999).Further, compromised uteroplacental blood flow in anxious women activates the fetal hypothalamic-pituitary-adrenal (HPA) axis (Challis et al., 2001), which in turn, may prematurely activate the myometrium, resulting in delivery.

We considered the relation of women's anxiety at each trimester of pregnancy to birth outcome. First, we explored whether anxiety was bivariately correlated with the following birth outcomes: pregnancy, labor and delivery complications; birthweight, length, head

circumference, and gestational age; small-for-gestational-age (SGA); and the 5-minute Apgar score. Bivariate associations of depression and trait anger, two variables that are highly correlated with anxiety, were also tested with respect to birth outcomes. For each trimester, we determined whether trait anxiety predicted birth outcomes, after controlling for confounds in the following domains: demographic, social, substance use, medical, and psychological. Among those birth outcomes predicted by anxiety in the multivariable models, we evaluated effects of both severity of anxiety and duration of severe anxiety.

2.3   METHODS

2.3.1   Study Design

Data were obtained from the Maternal Health Practices and Child Development (MHPCD) Project, a longitudinal study begun in 1982 to examine the long-term effects of prenatal substance use on the physical and mental health of offspring. Data used in our present analysis were collected from 1983 to 1985. The women were selected from a hospital-based prenatal clinic and were of low socioeconomic status. In total, 1360 women were recruited during their fourth prenatal month. From these women, two cohorts were selected for studies of the effects of prenatal alcohol and marijuana use. The selection criteria were as follows: 1) women who drank alcohol at the rate of three or more drinks per week in the first trimester of pregnancy, and those who drank less than that amount or who abstained; 2) women who used marijuana as often as twice a month, and those who used less or abstained. Women could be in either or both cohorts. The present analysis combined these two cohorts, accounting for a total of 829 women at the first

assessment (fourth gestational month). Subsequent assessments were obtained at the seventh prenatal month and at delivery. Birth outcomes were obtained for 763 live-born singleton babies. The retention rate was 92%. The Institutional Review Board of the University of Pittsburgh approved the study and all women gave informed consent.

2.3.2   Measurements

Demographic factors, substance use, social, medical, and psychological status were measured at each of the three assessments. Outcomes were measured at delivery.

2.3.2.1 Demographics

Racial status and age were self-designated by the participants at the first assessment. Marital status, monthly income, employment status, and education were ascertained from the women at each time point.   The following variables were dichotomized: race (African American/Caucasian), marital status (married/unmarried), and employment status (employed or in school/unemployed and not in school). Age, monthly income, and education were treated as continuous variables for all analyses.

2.3.2.2 Social & Other

The perceived social support variable used in our analyses was a composite of the following questions asked of each woman at the fourth month assessment: 1) how frequently she talks to friends, 2) how frequently she talks to relatives, 3) if she has someone to turn to in times of need, and 4) how satisfied she is with the help from friends and relatives. The women were also asked whether and how often they attended church. Stressful life events were assessed at delivery by

asking the women to report events that occurred at anytime during pregnancy. Participants were asked to describe how they felt about their pregnancy; their responses to this question were then dichotomized into positive and negative/neutral groups.

2.3.2.3 Substance Use

At each assessment, women were asked to report their use during the past trimester of alcohol, cigarettes, marijuana, cocaine, and other illicit drugs. The women were asked about the quantity and frequency of the usual, maximum, and minimum use of alcohol and marijuana. Alcohol and marijuana use variables for all trimesters were log transformed in order to reduce skewness of the distributions. Women were also asked about the quantity and frequency of tobacco, cocaine, and other illicit drug use. The average daily number of alcoholic drinks, marijuana joints, and cigarettes used were calculated for each trimester and treated as continuous variables. Because cocaine and other illicit drug use were low, these variables were dichotomized (any/none).

2.3.2.4 Medical

Maternal height, pre-pregnancy weight, and total number of physical health problems were obtained from the women's medical charts and treated as continuous variables. The women's gravidity was obtained, as was number of previous miscarriages. In order to reduce skewness of the distribution, the maximum category for number of miscarriages represented 4 or more. Both, gravidity and number of miscarriages were treated as categorical variables. Women were designated as having any illness or hospitalization during pregnancy at the time of delivery and this was treated as a dichotomized variable.

2.3.2.5 Psychological Measures

Trait anxiety is defined as the individual's predisposition to experience anxiety in a stressful situation, and *state* anxiety as a transient emotional response characterized by unpleasant feelings of tension and apprehensive thoughts (Spielberger, 1966). The two measures are highly correlated (Albrecht & Rankin, 1989). In this study, trait anxiety (score range: 10-40) and trait anger (score range: 10-40) were assessed at each study time point using the State-Trait Personality Inventory (STPI; Spielberger, 1979). The items of the STPI are a subset of the parent scales, the State-Trait Anger Scale (STAS) (Spielberger, Jacobs, Russell, & Crane, 1983) and the State-Trait Anxiety Inventory (STAI) (Spielberger, 1983), both of which are used extensively. Ten anxiety items and 10 anger items make up two subscales of the STPI. The selection of items was based on the following criteria: high corrected item-total correlations, relatively low item-scale correlations with the other subscale (anger vs. anxiety), and high factor loadings. The trait anxiety and trait anger questions on the STPI assessed how MPHCD participants generally felt since the previous assessment, and in the case of the fourth prenatal month assessment, how they had felt since becoming pregnant.

Depressive symptoms were assessed at each time point using the Center for Epidemiologic Studies-Depression Scale (CES-D; range: 0-60) (Radloff, 1977), a 20-item questionnaire that was developed to measure symptoms in both general and psychiatric populations. As for the STPI, for the administration of the CES-D, the instructions were modified such that the women were asked to report how they had generally felt about each of the items since the previous assessment.

Higher scores on each of the scales indicate more anxiety, anger, and depressive symptoms. The sample mean of a particular question was used to replace missing data if, at

most, 10% of the responses to questions were missing (i.e., a maximum of 1 item for each of the anxiety and anger scales and a maximum of 2 items for the depression scale). Thus, for the first, second, and third trimester scores, 1 missing trait anxiety item was filled in for 20, 25, and 21 women, respectively; 1 missing trait anger item was filled in for 6, 15, and 11 women, respectively; 1 missing depression item was filled in for 18, 25, and 26 women, respectively; and 2 missing depression items were filled in for 5, 2, and 10 women, respectively.

2.3.2.6 Birth Outcomes

Pregnancy, labor, and delivery complications (Hobel, Hyvarinen, Okada, & Oh, 1973; Littman & Parmelee, 1978; Zax, Sameroff, & Babigian, 1977) were abstracted from the medical charts by trained nurse clinicians after delivery. Examples of pregnancy complications include: anemia, infections, hypertension, and abnormal bleeding. Examples of labor complications include: precipitous labor, induction, pitocin augmentation, and preterm delivery. Examples of delivery complications include: anesthesia, meconium stained fluid, nuchal cord, cesarian section, and forceps delivery. The number of pregnancy complications was categorized as 0, 1, 2+. Labor and delivery complications were combined and categorized as 0, 1, 2, 3, 4, 5+ complications. Infant birthweight (grams), birth length (centimeters), head circumference (centimeters), and gestational age (determined using the Dubowitz scale) were measured by study personnel who were trained to a standardized assessment and were monitored for reliability. Small-for-gestational-age (SGA) was defined as having a birthweight below the tenth percentile for gestational age. The 5-minute Apgar score was taken from the medical record and dichotomized as follows: maximum score (9) and below maximum score (1-8).

2.3.3 Statistical Analyses

2.3.3.1 Bivariate Analyses

Confounds in the relations between anxiety and each of the birth outcomes were identified using bivariate analyses. We report the association of each covariate with third trimester anxiety unless otherwise noted: This best reflects the final live-birth sample. As a conservative approach, significant ($p<0.05$) as well as marginally significant ($p<0.10$) covariates of anxiety were tested for associations with the birth outcomes in order to increase the number of variables considered as potential confounds. Further, because there was such a high correlation between anxiety, depression, and trait anger, we examined the bivariate associations between the birth outcomes and each of these psychological variables.

2.3.3.2 Multivariate Regressions for Birth Outcomes

Multivariate analyses were performed to provide quantitative results for all outcomes that were significantly associated with anxiety on a bivariate level during at least one trimester. The analyses were done using a blocked entry stepwise multiple regressions. All significant ($p<0.05$) confounds from the demographic, social, substance use, and medical domains were allowed to enter stepwise in the first block of the regression model. The psychological variables (trait anxiety, depression, and trait anger) were then allowed to enter stepwise in the second block. Forward logistic regression was used for categorical outcomes that were bivariately associated with anxiety during at least one trimester in the bivariate analyses. Parallel to the approach taken for the continuous outcomes, a two-block approach was used for these categorical outcomes. Separate regressions were run for each trimester to determine the effects of timing of anxiety.

Influential points were identified by residual analyses. The final models contain all data points because the removal of influential points did not significantly affect the models.

2.3.3.3 Severity of Anxiety

Quartiles of anxiety were defined across pregnancy to provide descriptive analyses of the data. Mean values of birthweight, length, and gestational age were compared across these quartiles of anxiety using one-way ANOVAs with Tukey's *post hoc* analyses. Severe anxiety was defined as anxiety in the fourth quartile.

2.3.3.4 Duration of Severe Anxiety

To determine whether birth outcomes varied with the duration of severe anxiety throughout pregnancy, categories were defined as follows: 0) below the fourth (highest) quartile of anxiety for all three assessments; 1) in the fourth quartile for one assessment; 2) in the fourth quartile for two assessments; 3) in the fourth quartile for all three assessments. Means of birthweight, length, and gestational age were compared across categories using one-way ANOVA with Tukey's *post hoc* analyses.

2.4   RESULTS

2.4.1   Sample Description

At delivery, the mean age of the women was 23 years (SD 4.0 years). Sixty-seven percent of the women were single, 73% were unemployed, 51% were African-American, and 49% were

Caucasian. Their mean education was 12 years (SD 1.4 years) and the median family income was $300-$399/month. During the third trimester, the average daily volume of alcohol consumed by the women was 0.16 drinks (range 0-25). On average, they smoked 9.2 (range 0-70) cigarettes per day and 0.15 (range 0-9) marijuana joints per day during the third trimester. Other illicit drug use was rare: approximately 1% in the third trimester. Table 2-1.

Table 2-1 Sample characteristics and bivariate associations with trait anxiety during pregnancy

Variable	Mean (SD or range) or Percentage	Association of variable with anxiety [a,b]
Demographic:		
Age, years	23 years (4)	-0.07, ns
Proportion African American	51	$t(758)=2.3^*$
Median family income, $/month	300-399	-0.10^{**}
Proportion unemployed	73	$t(755)=3.0^{**}$
Proportion single	64	$t(757)=1.0$, ns
Education, years	12 (1.4)	$\rho =-0.08^*$
Social/Other:		
Perceived social support, # of people	3.3 (0.6)	-0.26^{**}
Number of life events during pregnancy	1.7 (1.8)	0.08^*
Percentage with negative or neutral feelings about pregnancy	17	$t(758)=-6.2^{**}$
Percentage attending church	37	$F(760)=2.0$, ns
Substance Use for 1st trimester:		
Marijuana joints/day	0.39 (range, 0-9)	$\rho =0.03$, ns
Cigarettes/day	8.3 (range, 0-50)	$\rho =0.10^{**}$
Alcoholic drinks/day	0.62 (range, 0-20)	$\rho =0.11^{**}$
Percentage illicit drugs users	11	$t(759)=-1.5$, ns
Percentage cocaine users	4	$t(759)=0.4$, ns

Table 2-1 (continued)

Variable	Mean (SD or range) or Percentage	Association of variable with anxiety [a,b]
Substance Use for 2nd trimester:		
Marijuana joints/day	0.14 (range, 0-6)	ρ =0.11*
Cigarettes/day	8.5 (range, 0-70)	ρ =0.12**
Alcoholic drinks/day	0.14 (range, 0-12)	ρ =0.06, ns
Percentage illicit drugs users	3	$t(689)$=-2.3*
Percentage cocaine users	2	$t(689)$=-1.9, ns
Substance Use for 3rd trimester:		
Marijuana joints/day	0.15 (range, 0-9)	ρ =0.07, ns
Cigarettes/day	9.2 (range, 0-70)	ρ =0.08*
Alcoholic drinks/day	0.16 (range, 0-25)	ρ =0.03, ns
Percentage illicit drugs users	1	$t(758)$=-1.3, ns
Percentage cocaine users	1	$t(758)$=0.2, ns
Medical:		
Maternal height, inches	64 (2.8)	-0.14**
Maternal pre-pregnancy weight, lbs	136 (33.7)	-0.01, ns
Medical problems	0.62 (0.9)	0.08*
Gravida status	1.4 (1.5)	$F(760)$=1.1, ns
Previous miscarriages	3.1 (3.4)	$F(759)$=1.9, ns
Percentage hospitalized during pregnancy	8	$t(66)$=-1.9, $p<0.1$
Percentage ill during pregnancy	40	$t(758)$=-0.6, ns

Table 2-1 (continued)

Variable	Mean (SD or range) or Percentage	Association of variable with anxiety [a,b]
Psychological Scores for 1st trimester:		
CES-D Depression	20.8 (8.7)	0.71**
STPI Trait Anger	18.7 (5.7)	0.56**
Psychological Scores for 2nd trimester:		
CES-D Depression	21.4 (8.1)	0.73**
STPI Trait Anger	18.2 (5.3)	0.58**
Psychological Scores for 3rd trimester:		
CES-D Depression	40.5 (8.5)	0.71**
STPI Trait Anger	17.8 (5.3)	0.60**
Birth Outcomes:		
Birthweight, kg	3.20 (5.64)	See Table 2a
Birth length, cm	49.3 (2.5)	
Head Circumference, cm	341 (15)	See Table 2a
Gestational Age, weeks	39.7 (2.2)	
Pregnancy Complications	1.0 (1.0)	
Labor and Delivery Complications	2.4 (1.6)	See Table 2a
Small-for-gestational-age, % of babies	10	
5 minute Apgar, % below maximum score	13	

* $p<0.05$ ** $p<0.01$

[a] Reported associations are with 3rd trimester anxiety, unless otherwise indicated.

[b] Pearson correlation coefficients reported, unless otherwise noted.

2.4.2 Bivariate Analyses

At the bivariate level, trait anxiety assessed at the third time point was associated ($p<0.05$) with the following demographic variables: African-American race, lower family income, higher rate of maternal unemployment, and less education (Table 2-1). Social variables associated with the third assessment of trait anxiety included less perceived social support and more life events during pregnancy. In addition, women who were more anxious reported more negative/neutral feelings toward their pregnancy. Anxiety in the first assessment was correlated with tobacco and alcohol use. In the second trimester, anxiety was associated with tobacco, marijuana, and other illicit drug use. During the third trimester, only tobacco use was correlated with anxiety. Medical variables associated with anxiety at the third assessment were shorter maternal height and a greater number of medical problems. Higher levels of depression and trait anger correlated significantly with trait anxiety at all trimesters.

There were significant correlations between trait anxiety during at least one trimester and birthweight, length, and head circumference; shorter gestational age; more pregnancy complications, and a higher rate of SGA (Table 2-2). The correlations between birth outcome in offspring and depressive symptoms in women were generally less strong than those for anxiety symptoms, with the exception of pregnancy complications being more strongly associated with depressive symptoms (Table 2-3). Trait anger symptoms were less strongly correlated with the birth outcomes than either anxiety or depressive symptoms (Table 2-4).

Table 2-2 Bivariate associations of anxiety at each trimester with birth outcomes

Birth Outcome	1st Trimester	2nd Trimester	3rd Trimester
Birthweight	-0.12**	-0.13**	-0.13**
Birth length	-0.09*	-0.13**	-0.13*
Head Circumference	-0.06, ns	-0.09*	-0.08*
Gestational Age	-0.06, ns	-0.07, ns	-0.10**
Pregnancy Complications	$\chi^2(1)=4.9$*	$\chi^2(1)=5.1$*	$\chi^2(1)=4.8$*
Labor and Delivery Complications	0.03, ns	0.04, ns	0.01, ns
Small-for-gestational-age	$t(759)=-2.5$**	$t(689)=-1.9$, ns	$t(758)=-1.5$, ns
5 minute Apgar	$t(756)=-0.18$, ns	$t(688)=-0.28$, ns	$t(755)=-0.32$, ns

Pearson correlation coefficients reported, unless otherwise noted.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

Table 2-3 Bivariate associations of depression at each trimester with birth outcomes

Birth Outcome	1st Trimester	2nd Trimester	3rd Trimester
Birthweight	-0.11**	-0.10**	-0.08*
Birth length	-0.07, ns	-0.10*	-0.08*
Head Circumference	-0.08*	-0.07, ns	-.06, ns
Gestational Age	-.06, ns	-.06, ns	-0.08*
Pregnancy Complications	$\chi^2(1)=9.9$**	$\chi^2(1)=5.9$*	$\chi^2(1)=2.4$, ns
Labor and Delivery Complications	0.07, ns	0.05, ns	0.06, ns
Small-for-gestational-age	$t(755)=-1.6$, ns	$t(686)=-0.13$, ns	$t(748)=0.25$, ns
5 minute Apgar	$t(752)=1.6$, ns	$t(685)=0.87$, ns	$t(745)=0.52$, ns

Pearson correlation coefficients reported, unless otherwise noted.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

Table 2-4 Bivariate associations of trait anger at each trimester with birth outcomes

Birth Outcome	1st Trimester	2nd Trimester	3rd Trimester
Birthweight	-0.06, ns	-0.002, ns	-0.08*
Birth length	-0.08*	-0.02, ns	-0.08*
Head Circumference	-0.04, ns	-0.001, ns	-0.05, ns
Gestational Age	-0.03, ns	-0.01, ns	-0.08*
Pregnancy Complications	$\chi^2(1)=2.1$, ns	$\chi^2(1)=0.13$, ns	$\chi^2(1)=0.11$, ns
Labor and Delivery Complications	0.05, ns	0.03, ns	0.05, ns
Small-for-gestational-age	$t(759)=-1.2$, ns	$t(689)=0.33$, ns	$t(759)=-0.55$, ns
5 minute Apgar	$t(756)=-0.65$, ns	$t(688)=0.23$, ns	$t(756)=0.29$, ns

Pearson correlation coefficients reported, unless otherwise noted.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

2.4.3   Multivariate Regression Analyses

All of the potential confounds were allowed to enter stepwise into the regression model. In a second step, anxiety, depression, and trait anger scores were allowed to enter the model. Anxiety in the first trimester did not predict birthweight, length or gestational age after confounds were considered. However, both second (Table 2-5) and third trimester anxiety (Table 2-6) significantly predicted lower birthweight and shorter birth length, even after controlling for confounding variables. Third trimester anxiety score predicted shorter gestational age (Table 2-6). For all three birth outcomes, neither depression nor trait anger was a significant predictor.

Other significant predictors of birthweight included African American race and heavier cigarette use. These same two variables, in addition to lower education and more life events,

also predicted shortened birth length. There were no other significant predictors of shortened gestational age.

The data in Tables 2-5 and 2-6 are reported as unstandardized Betas so effect sizes can be calculated. For every five-point increase in the second trimester anxiety score, birthweight was decreased by 55 grams. A five point increase in the third trimester anxiety score predicted a 66-gram decrease in birthweight. For every five-point increase in the anxiety scores in the second or third assessments, birth length was decreased by 0.2 cm. Gestational age was shorter by approximately 1.6 days for each five-point change in the third trimester anxiety score.

Table 2-5 Effect of second trimester anxiety on birth outcomes, after adjusting for confounds

Outcome	R-square change due to anxiety	Unstandardized Beta (Δ outcome measurement for 5 point Δ anxiety score)
Birthweight [a]	0.009***	-55.04 g
Birth length [b]	0.006*	-0.19 cm
Gestational age [c]	ns	n/a

Table 2-6 Effect of third trimester anxiety on birth outcomes, after adjusting for confounds

Outcome	R-square change due to anxiety	Unstandardized Beta (Δ outcome measurement for 5 point Δ anxiety score)
Birthweight [a]	0.008***	-65.50 g
Birth length [b]	0.008*	-0.22 cm
Gestational age [c]	0.009**	-0.23 wks

[a] Other significant predictors of lower birthweight included: African American race*** and heavier cigarette use***. Depression, trait anger, education, work status, and alcohol use did not enter the model.
[b] Other significant predictors of shorter birth length included: African American race***, heavier cigarette use***, lower education**, and more life events*. Depression, trait anger, social support and alcohol did not enter the model.
[c] There were no other significant predictors of gestational age besides anxiety. Depression and trait anger did not enter the model.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$

2.4.4 Severity of Anxiety

In these analyses, the anxiety scores were divided into quartiles for each assessment. At assessments 1 and 2, mean birthweight did not differ significantly across the lower three quartiles of anxiety. However, the children of mothers in the top quartile of anxiety during the first assessment were lower birthweight (mean 3,066 g) compared to those of women in the first (3,269 g) and third (3,222 g) quartiles of anxiety ($F(3) = 3.77$, $p<0.01$; Figure 2-1). Furthermore, mothers in the top quartile of anxiety during the second assessment delivered lower birthweight children (3,079 g) compared to women in the first three quartiles of anxiety (3,294 g, 3,250 g, and 3,283g, respectively; $F(3) = 5.10$, $p<0.01$). We had similar findings for birth length at the first ($F(3) = 2.70$, $p<0.05$) and second ($F(3) = 6.48$, $p<0.001$) assessments (Figure 2-2). By contrast, at the third assessment, with each quartile of anxiety, offspring birthweight (3,277; 3,193; 3,133; 3,104 g; Figure 2-1) and birth length (49.5, 49.4, 49.0, 48.8 cm; Figure 2-2) appeared to decrease linearly. None of the observed differences in gestational age between quartile groups were significant, although the data follow the same trend at each assessment as for birthweight and length, including a linear trend for the third assessment (40.0, 39.8, 39.6, 39.4 weeks; Figure 2-3).
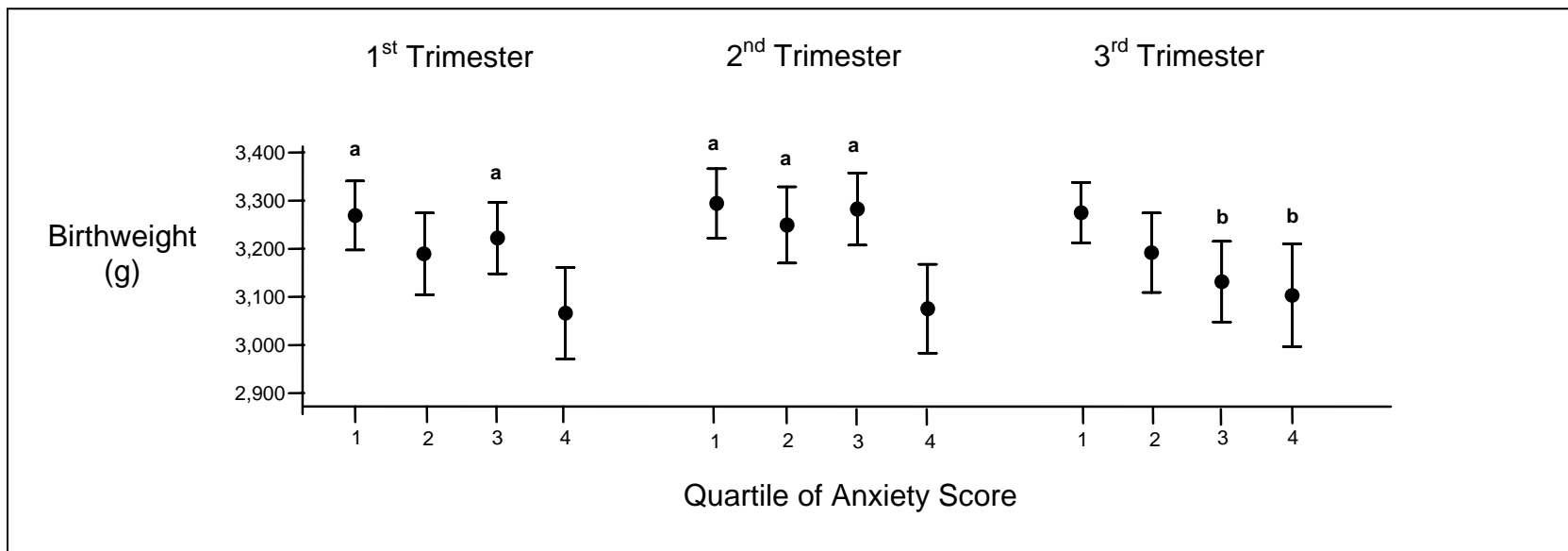
Figure 2-1 Effect of level of maternal anxiety on birthweight of offspring

[a] Significantly different ($p<0.05$) from 4th quartile within the trimester
[b] Significantly different ($p<0.05$) from 1st quartile within the trimester
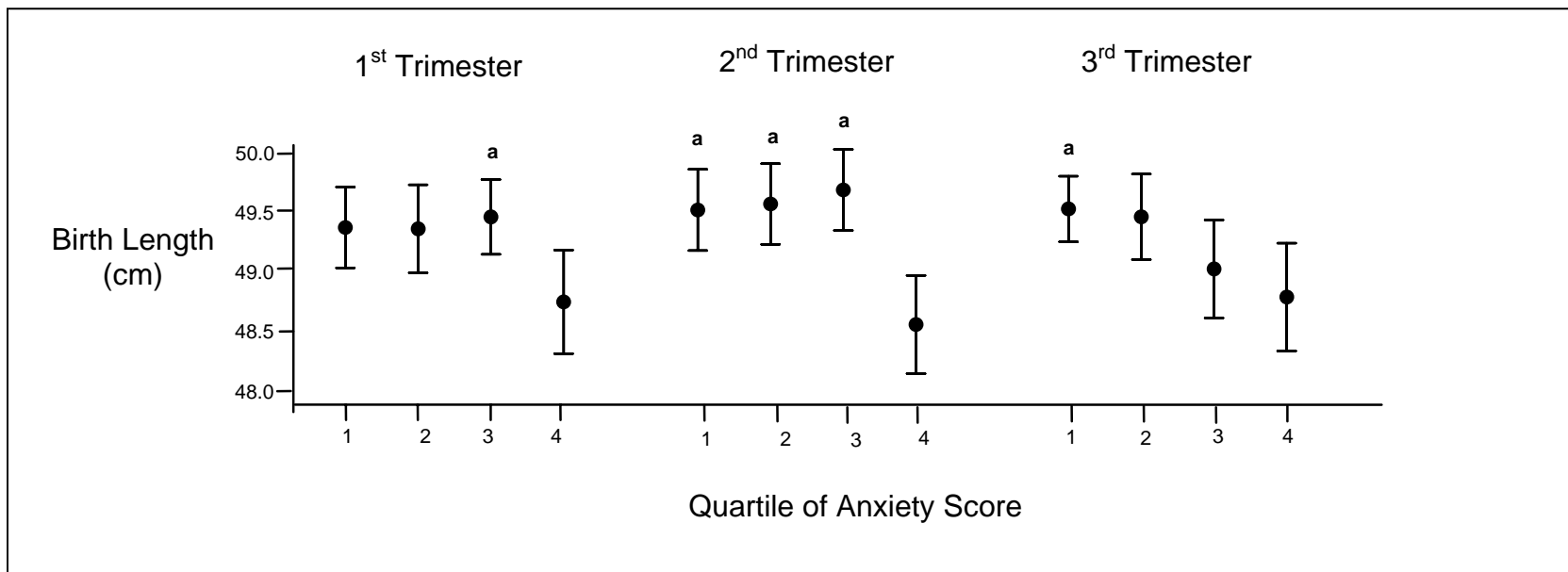
Figure 2-2 Effect of level of maternal anxiety on birth length of offspring

[a] Significantly different ($p<0.05$) from 4th quartile within the trimester
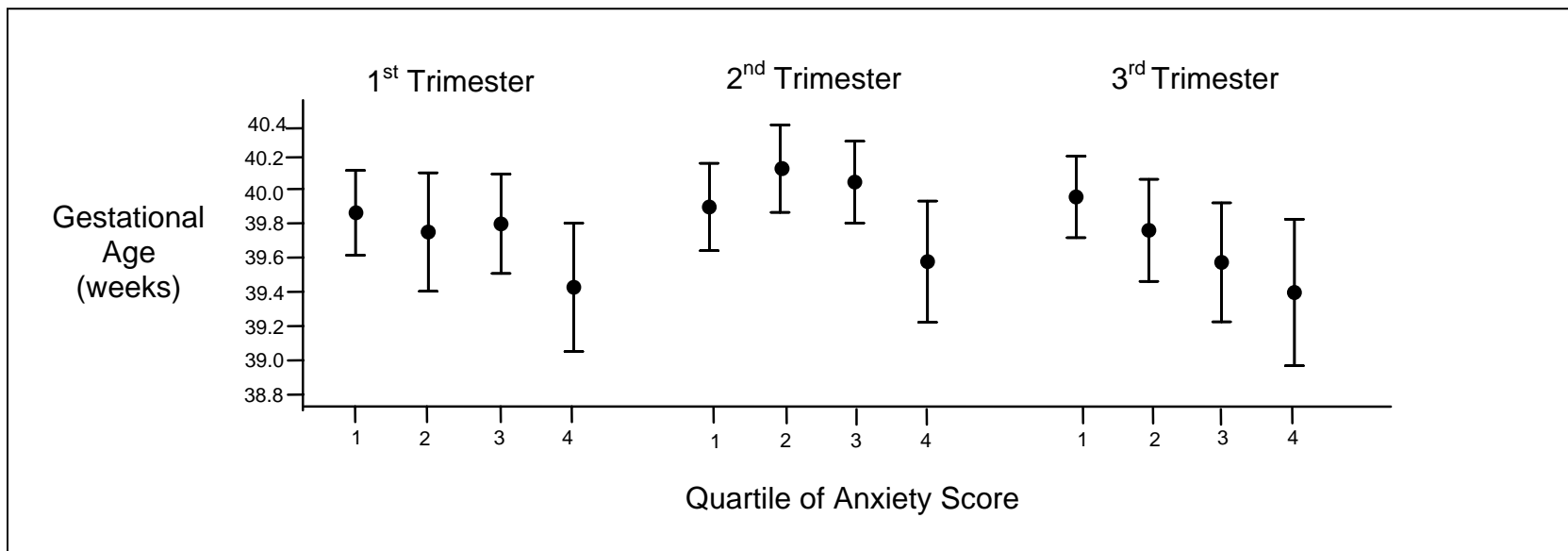
Figure 2-3 Effect of level of maternal anxiety on gestational age of offspring

2.4.5 Duration of Severe Anxiety

The effects of duration of severe anxiety on the birth outcomes are shown in Figures 2-4, 2-5, and 2-6. Severely anxious women were categorized by the number of assessments, 0 through 3, at which they reported severe anxiety (anxiety score in the fourth quartile). Offspring of women who experienced severe anxiety during three trimesters had lower mean birthweight (3,021 g, $F(3) = 5.67$, $p<0.001$; Figure 2-4) and shorter mean birth length (48.3 cm, $F(3) = 6.16$, $p<0.001$; Figure 2-5) compared to offspring of women who did not report severe anxiety at any trimester (3,278 g and 49.6 cm, respectively) and compared to women who reported severe anxiety during only one trimester (3,276 g and 49.6 cm, respectively). There was a marginally significant ($p=0.053$) difference between offspring of those women with no severe anxiety and those who reported anxiety at two assessments (3,081 g and 48.7 cm). Gestational age followed the same pattern as birthweight and length. There were no significant group differences for either first or second trimester anxiety. However, gestational age was significantly shorter for offspring of mothers who experienced severe anxiety during all trimesters, as compared with those who did not report severe anxiety at any of the assessments (39.4 vs. 40.0 weeks, $F(3)=2.80$, $p<0.05$; Figure 2-6).
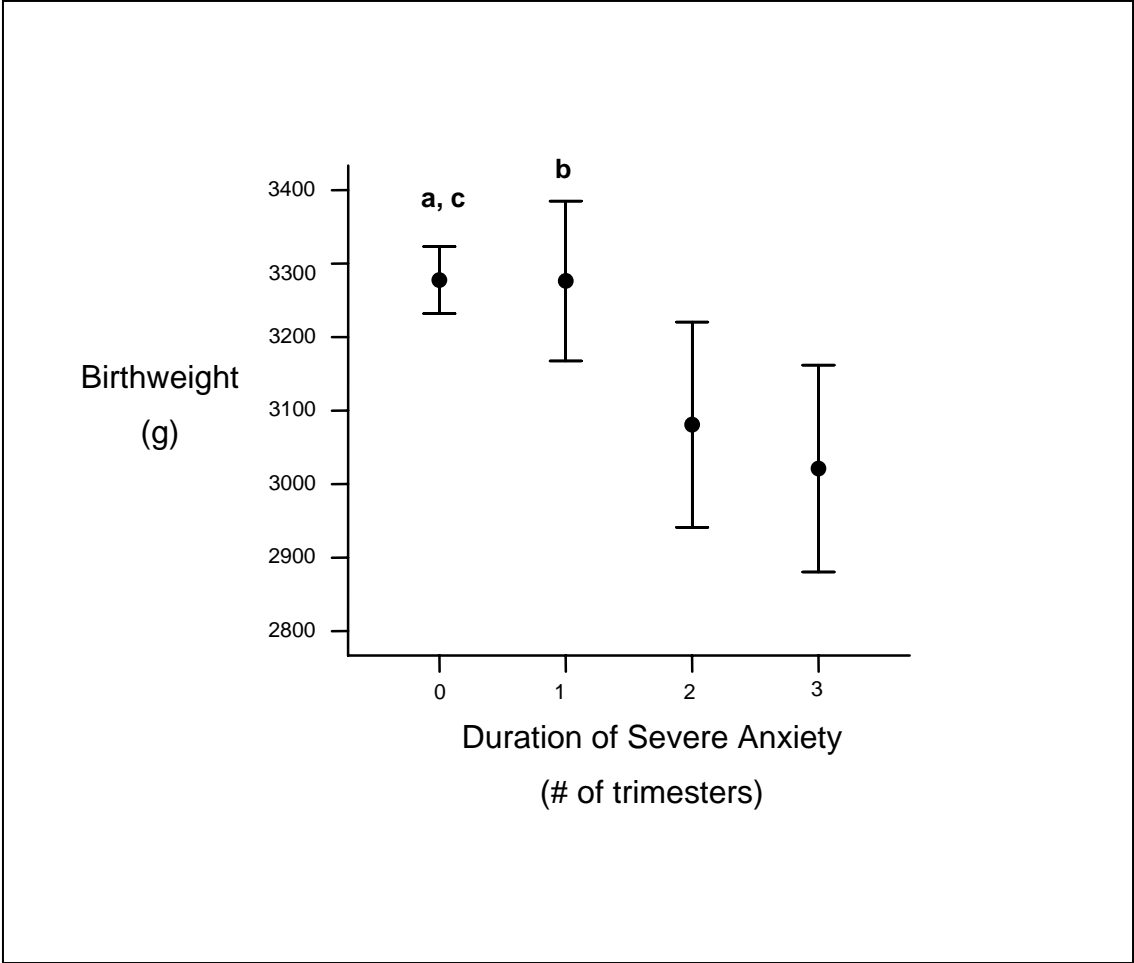
Figure 2-4 Effect of severe anxiety duration on offspring birthweight

[a] Significantly different ($p<0.01$) from "3 trimesters" group
[b] Significantly different ($p<0.05$) from "3 trimesters" group
[c] Marginally significant difference ($p=0.052$) from "2 trimesters" group
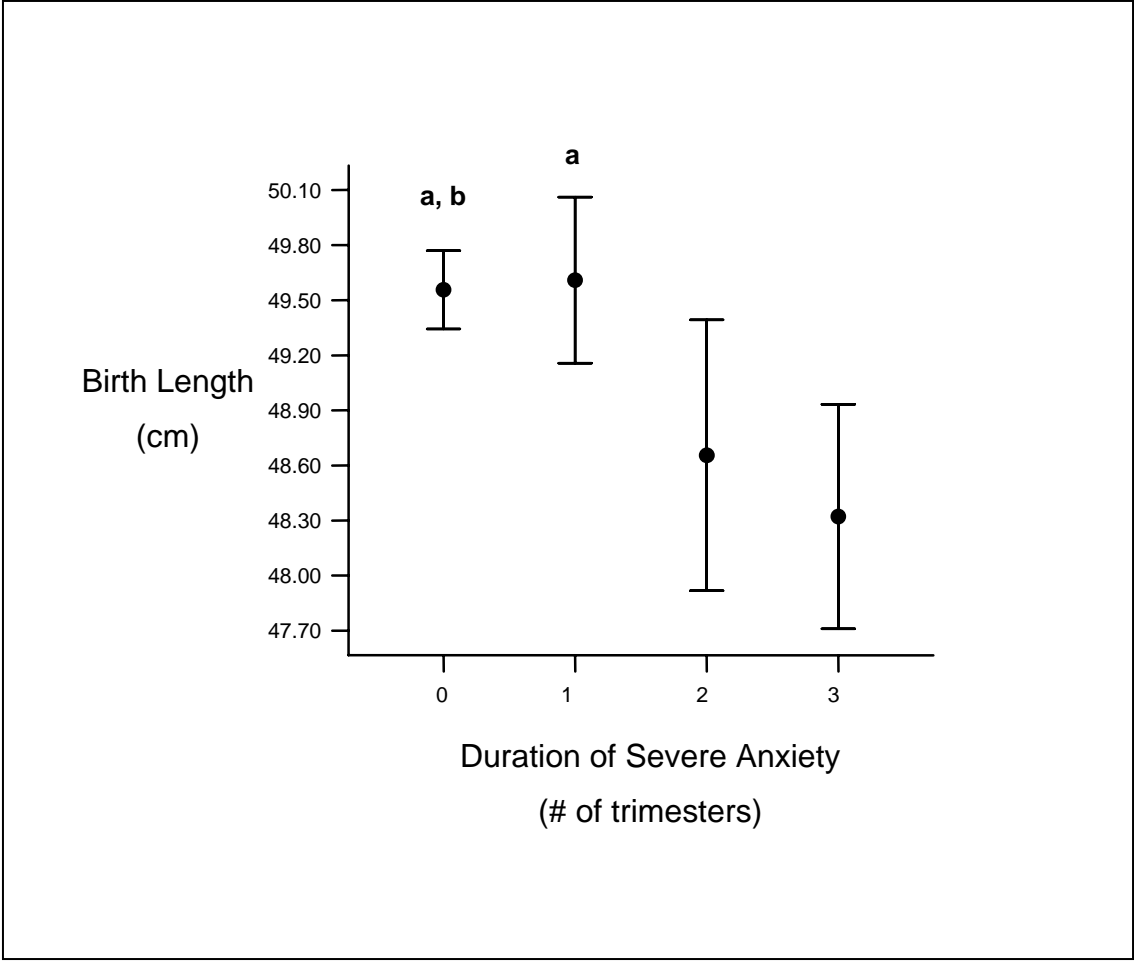
Figure 2-5 Effect of severe anxiety duration on offspring birth length

[a] Significantly different ($p<0.01$) from "3 trimesters" group
[b] Marginally significant difference ($p=0.053$) from "2 trimesters" group
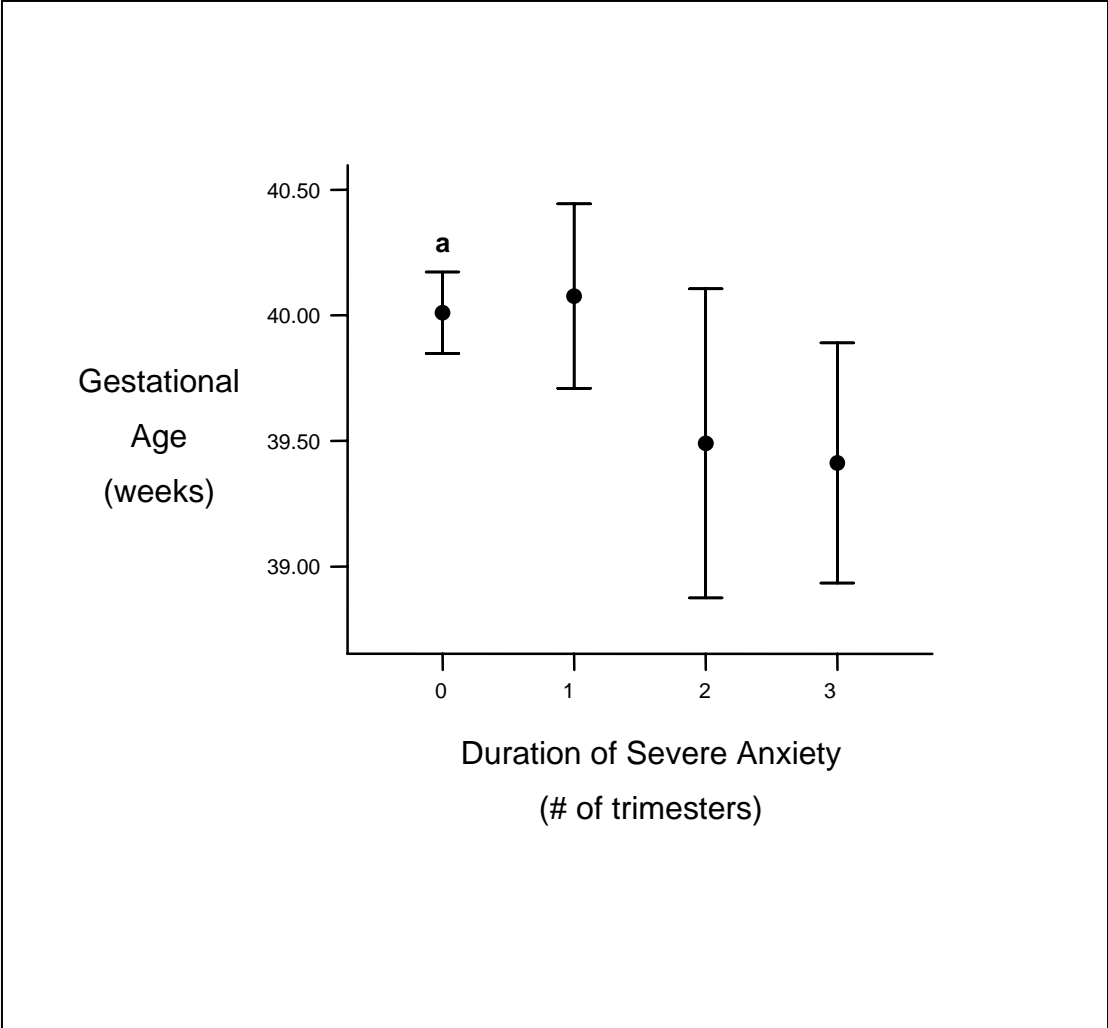
Figure 2-6 Effect of severe anxiety duration on offspring gestational age

[a] Significantly different ($p<0.05$) from "3 trimesters" group

2.5   DISCUSSION

Trait anxiety measured in pregnant women at the second and third assessments predicted reduced birthweight and length after controlling for confounds. Additionally, after controlling for confounds, anxiety during the third trimester predicted shorter gestational age. Descriptive analyses demonstrated that in the first and second trimesters, the effects of anxiety were significant only among those women who had severe anxiety. The association between level of third trimester anxiety and the severity of birth outcomes, however, appeared linear. Our analyses of duration of anxiety indicate that women who experienced severe, chronic anxiety (i.e., in the top quartile of anxiety during at least 2 assessments) delivered significantly smaller babies, indicating that these women are of the greatest concern.

African American race and heavier cigarette use also predicted lower birthweight and shortened birth length, which is consistent with prior literature that African American women (Collins & Hammond, 1996) and cigarette users (Windham et al., 2000) deliver smaller babies. Additional significant predictors of birth length included lower education and more stressful life events.

Our finding that trait anxiety during pregnancy predicts smaller babies is consistent with reports that elevations in stress-related hormones suppress production or release of growth hormone in the fetus (Clapp, 1992). Furthermore, similar to our findings for shortened gestation length, Wadhwa and colleagues reported a relationship between stress and preterm birth, adjusting for confounding variables (Wadhwa, et al., 2001). Another group found that a decrease

in perceived stress among pregnant women during the second trimester was associated with increased gestation age (Ruiz, Fullerton, Brown, & Schoolfield, 2001).

We found that anxiety during the third trimester predicted shorter gestational age. The consistency of our findings with those of other studies supports the validity of the effects of third trimester anxiety. In Hedegaard and colleagues' cohort of several thousand women attending a prenatal clinic, psychosocial distress (anxiety and depression), during late pregnancy (30th week), but not early pregnancy (16th week), predicted preterm delivery (Hedegaard, Henriksen, Sabroe, & Secher, 1993). Both gestational age and baby size were predicted by anxiety reported at the third assessment in our study, which suggests that reduction in birth size associated with anxiety is better explained by a reduction in gestation length than by intrauterine growth retardation. Several studies have suggested that corticotrophin releasing hormone (CRH) controls the timing of labor and delivery (McLean et al., 1995; Sandman, Wadhwa, Chicz-DeMet, Dunkel-Schetter, & Porto, 1997). A marked increase in maternal plasma levels of ACTH and cortisol in the third trimester may trigger early labor and delivery (Ruiz, et al., 2001; Wadhwa, Porto, Chicz-De-Met, & Sandman, 1998).

Our study was limited by the fact that measures of third trimester trait anxiety were ascertained from the mother within the first two days after delivery; thus her report of trait anxiety so close to delivery may reflect state anxiety related to the stress of delivery and to concern over a preterm delivery and/or smaller baby. Despite this limitation in the timing of the third assessment, a major strength of our study was our choice of the independent variable: trait anxiety. We analyzed trait anxiety separately from depression, trait anger, social support, and stressful life events, in contrast to Rini and colleagues (Rini, et al., 1999), who combined measures of state and pregnancy-specific anxiety into a measure of prenatal psychosocial stress.

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Our approach allowed us to try to assess the independent contribution of trait anxiety to birth outcome while controlling for other psychological stressors. Nevertheless, while trait anxiety was a stronger predictor of birthweight, length, and gestational age than either trait anger or depression, we must keep in mind that these measures are highly correlated.

The effects on birth outcomes among offspring of severely anxious and chronically severely anxious women in our cohort are not clinically significant. Even the most severely affected women in our cohort (i.e., those in the highest severity and longest duration anxiety groups) delivered offspring whose average birthweight was approximately 3.0 kg, which is well above the cut-point for low birthweight (2.5 kg). Likewise, the average gestation for offspring of severely anxious and chronically severely anxious women is approximately 39.4 weeks, which is clearly above the 37-week cut-off for preterm delivery. These means are significant, however, when viewed from a population basis, where changes in outcome shift the entire mean of the cohort downward. Furthermore, though small, these decreases in birth size and gestational age may affect the mental well-being of the child later in life (Record, McKeown, & Edwards, 1969; Matte, Bresnahan, Begg, & Susser, 2001; Richards, Hardy, Kuh, & Wadsworth, 2001).

Low to moderate levels of anxiety in women during either the first or second trimester did not significantly affect the birth outcomes, but women who are severely anxious during much of their pregnancy should be considered for anxiety-reducing interventions. Our finding that anxiety affected birth outcome points to the need of assessing whether prenatal care that addresses the psychological well-being of pregnant women would result in improved birth outcomes. Anxious women should be identified early in or even prior to pregnancy and targeted for anxiety reduction.

3.0   MANUSCRIPT 2: COVARIATES OF MAJOR DEPRESSIVE DISORDER IN

MID-ADOLESCENCE

3.1   SUMMARY

The objective of this paper was to determine the covariates of Major Depressive Disorder (MDD) among low socioeconomic adolescents. Data come from the Maternal Health Practices and Child Development (MHPCD) Project, a longitudinal study of mothers and their offspring. Domains of data include demographic, social, substance use, biological, psychological, and psychiatric measures. Offspring and mothers were assessed for a lifetime diagnosis of MDD using the Diagnostic Interview Schedule-IV (DIS-IV) and DSM-IV criteria. Significant adolescent and maternal covariates of adolescent MDD were determined using logistic regression.

The prevalence of MDD among the 16-year-old adolescents was 13 %. Female gender (adjusted OR 3.77, 95% CI 2.00-7.12), history of severe childhood maltreatment (third tertile of Child Trauma Questionnaire score, adjusted OR: 3.88, 95% CI 1.82-8.26), and maternal diagnosis of MDD (adjusted OR 1.80, 95% CI 1.02-3.18) were significant covariates. There was a significant interaction between offspring gender and maternal MDD (OR 4.58, $p<0.05$). Female gender, a history of childhood maltreatment, and maternal history of MDD increased the odds of MDD in adolescents. Daughters of women with a history of MDD are particularly

vulnerable. These risk factors should prompt early screening and intervention for these adolescents.

3.2   INTRODUCTION

Major depressive disorder (MDD) accounts for greater mortality, morbidity, and financial costs than any other psychiatric disorder (Murray & Lopez, 1996). Those who experience depression at an early age struggle with the illness throughout their lives (Lewinsohn, Rohde, Klein, & Seeley, 1999). Many new cases of depression emerge in adolescence. The one-year prevalence of unipolar depression among adolescents is between 4% and 7%, whereas in children it is about 2% (Costello, Erkanli, Federman, & Angold, 2002). People who develop depression in childhood and adolescence have more recurrences of depression, and higher rates of comorbid psychiatric disorders as young adults (Lewinsohn et al., 1999). Thus, understanding the risk factors associated with MDD in adolescents is critical.

Correlates of adult MDD have been identified. Many, such as substance use (Kessler, Nelson, McGonagle, Edlund, Frank, & Leaf, 1996; Swendson & Merikangas, 2000) and family history of depression (Kendler, Neale, Kessler, Heath, & Eaves, 1997) are well-established. Childhood abuse, neglect, and stressful life events are also associated with higher rates of MDD in adulthood (Horesh, Sever, & Apter, 2003; Kendler, Thornton, & Gardner, 2000; Kessler & Magee, 1993).

Fewer studies have identified the covariates of MDD during adolescence. Demographic characteristics associated with adolescent MDD include female gender (Costello et al., 2002; Kessler & Magee, 1993; Burke, Burke, Regier, & Rae, 1990) and poverty. One study found that

those with juvenile-onset depression were more likely than those with adult-onset depression to have a history of perinatal insults, caregiver instability, criminality, and a family history of psychopathology (Jaffee, Moffitt, Caspi, Fombonne, Poulton, & Martin, 2002). Parental depression (Beardslee, Versage, & Gladstone, 1998; Downey & Coyne, 1990; Gefland & Teti, 1990) and parental marital problems, especially in the first three years of the child's life (Spence & Najman, 2002) are significant predictors of MDD. This increased family risk is due to a combination of genetic and environmental influences (Eaves, Silberg, Meyer, Maes, Simonoff, Pickles, et al., 1997).

This paper identifies the significant correlates of MDD in a racially-balanced, low socioeconomic status cohort of adolescents. We hypothesized that adolescent variables in the domains of demographics, social support, substance use, childhood maltreatment, delinquent behavior, puberty, anxiety, academic performance, and general health, in addition to maternal, psychological, and psychiatric status would be associated with adolescent MDD.

3.3   METHOD

3.3.1   Study Design

The MHPCD Project is a longitudinal study begun in 1982 to examine the long-term effects of prenatal substance exposure on the offspring. The women were selected from a prenatal clinic and were of lower socioeconomic status. In total, 1360 women were recruited during their fourth prenatal month. From these women, two cohorts were selected for studies of prenatal alcohol and marijuana use. The selection criteria for the alcohol cohort were: women who drank

alcohol at the rate of three or more drinks per week in the first trimester, and the next woman who drank less than that amount or who abstained. For the marijuana cohort, women who used marijuana as often as twice a month, and the next woman who used less or abstained were selected. Women could be in either or both cohorts. This analysis combined the two cohorts, for a total of 829 women at the fourth gestational month. Subsequent assessments were at seven months and delivery. At delivery, 763 women and their babies were evaluated. Later assessments of the mothers and children were at 8 and 18 months, 3, 6, 10, 14, and 16 years. The Institutional Review Boards of Magee-Womens Hospital and University of Pittsburgh approved the study. All women gave signed, informed consent for themselves and their children.

3.3.2 Sample

At 16 years, 592 caregivers and their children were interviewed. The retention rate was 78% of the birth cohort; 52 mothers refused assessment, 69 were lost, 35 had moved out of the area, 5 children were in foster care, 1 child was institutionalized, 3 children were adopted, and 6 children died. There were no differences on maternal age, income, or education among those who were assessed at the 16-year phase compared to those who were not assessed. The group that was not assessed had significantly more Caucasians (60%) than those who were assessed (45%).

This analysis was limited to caregivers who were biological mothers (n=509). Among these, a structured diagnostic interview was available for 499 child/mother dyads.

3.3.3　Measurements

Adolescent social support, substance use, history of maltreatment, delinquent behavior, pubertal status, anxiety, grade point average, and general health were measured at the 16-year phase, as were maternal demographic, psychological, and psychiatric characteristics.

3.3.3.1 Adolescent Variables:

Major Depressive Disorder

Lifetime diagnosis of MDD was assessed with the Diagnostic Interview Schedule, version IV (DIS-IV; Robins, Cottler, Bucholz, & Compton, 1995; Robins, Cottler, Bucholz, Compton, North, & Rourke, 2000). A diagnosis was given if the adolescent had at least one occurrence of MDD prior to or concurrent with assessment.

Demographics

Adolescent age, race (African American/Caucasian) and gender were collected.

Current Social Support

Adolescents were asked how many close friends they had (none, 1, 2, 3 or more). They were also asked how often they went out with their friends (none, 1, 2 or more times per week).

Current Substance Use

Adolescents reported their use of alcohol, cigarettes, marijuana, and other illicit drugs during the past month. The distribution of substance use was positively skewed and non-use rates were high (43% reported no alcohol use, 58% reported no marijuana use, 59% reported no cigarette use), so use of each substance was analyzed as a dichotomous variable (none versus any use).

Childhood Maltreatment

The Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1993) assessed childhood abuse and neglect. The CTQ, a 25-item self-report inventory, screens for a childhood history of emotional, physical, and sexual abuse, emotional and physical neglect. Item scores range from "never true" to "very often true" on a 5-point scale. The score is summed across items and ranged from 25 to 125. The lowest score represented no history and the highest scores indicated severe childhood maltreatment.

Additionally, the CTQ has a three-question "denial scale" that detects respondents who give exaggerated or desirable responses. These items were not included in the total score. Ninety who reported greater than one of these as being "very often true," were removed from the analyses. Those removed were comparable in age and gender to those kept in the analyses except that significantly more African Americans (65%) were in the removed group, compared to the remaining group (65% vs. 53%, respectively).

Delinquent Behavior

The Self-Report Delinquency Scale (SRD; Elliot, Huizinga, & Ageton, 1985) measured delinquent behavior in each of five categories: status offenses, theft, property damage, drug selling, and violence. The subscales were summed to obtain a total score.

Puberty

At age 14, adolescents reported their pubertal status on the Pubertal Development Scale (Petersen, Crockett, Richards, & Boxer, 1988). Scores range from 1 (pre-puberty) to 5 (post-puberty). A score of 3 separated those who were pre-pubescent and in early puberty from those who were in advanced puberty and post-pubertal. Because so many of the girls at age 14 were above this cut-point, we used an additional measure of earlier maturation. At age 16, the

adolescents rated their development relative to others their age from "much earlier," to "much later." This variable was categorized as "developed earlier" and "developed same or later".

Psychological & Physical Health

Current anxiety in the adolescents was measured by the Revised Children's Manifest Anxiety Scale (RCMAS; Reynolds & Richmond, 1978), a 28-item self-report inventory. Scores ranged from 0 to 28. Grade point average (GPA) was used as an indicator of academic performance. Finally, adolescents were asked to rate their general health from poor to excellent. Few teenagers reported poor or fair health, and these two groups were combined, making four categories.

3.3.3.2 Maternal Variables:

Demographics

Education was summarized as three groups: <12, 12, and >12 years. Marital status (married/unmarried), employment status (employed/unemployed), and adult male in the household (yes/no) were considered. Missing data were rare and were replaced with sample means for family income (n=2) and maternal education (n=1).

Psychological

Trait anger and trait anxiety symptoms were assessed at each phase using the State-Trait Personality Inventory (STPI; Spielberger, 1979). The items of the STPI are a subset of the STAS (State-Trait Anger Scale; Spielberger, Jacobs, Russell, & Crane, 1983) and the STAI (State-Trait Anxiety Inventory; Spielberger, 1983), The STPI trait anxiety and trait anger scores each ranged

from 10 to 40. The sample mean was used to replace a single missing item on the trait anxiety (n=10) and trait anger scales (n=9).

Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression Scale (CES-D; Radloff, 1977), a 20-item questionnaire. Scores range from 0 to 60. Sample means were substituted for individual answers for 19 women who each had 1 missing item and for 4 women who had 2 missing items on this scale.

Psychiatric Diagnosis

We used the DIS-IV (Robins et al., 1995; Robins et al., 2000) to assess lifetime history of DSM-IV disorders. For the analyses, MDD diagnoses were used in total (MDD only plus comorbid MDD) and separated into two mutually exclusive groups (MDD only, and MDD comorbid with other psychopathology). Other diagnoses were grouped as follows: 1) generalized anxiety disorder (GAD), 2) any alcohol, marijuana, or cocaine disorder and, 3) any psychiatric disorder other than MDD. The categories of substance use disorders (SUDs: abuse, dependence, and withdrawal) were combined for each substance.

3.3.4   Data Analyses

Continuous data were categorized by tertiles or quartiles. For each variable, the bivariate odds of adolescent MDD were calculated for the discrete categories using the lowest risk group as the reference group. Variables associated ($p<0.10$) with adolescent MDD in the bivariate analyses were candidates for the multivariate model. Stepwise logistic regression was used with an entry p-value of 0.05. Child anxiety score was not included because it was highly correlated with the MDD diagnosis. Goodness of fit was evaluated using the Hosmer-Lemeshow test.

After the main effects model was constructed, interaction effects between each pair of covariates were tested. An interaction term was included in the logistic regression model only if it was statistically significant ($p<0.05$). The potential mediation of the relation between childhood maltreatment and adolescent MDD by adolescent substance use was first examined using Baron and Kenny's Causal Step test (Baron & Kenny, 1986; Judd & Kenny, 1981).

3.4   RESULTS

3.4.1   Bivariate Analyses

Among the 499 adolescents in this study, 65 (13.0%) had a lifetime diagnosis of MDD, including 7% of the boys and 18.7% of the girls. The majority of cases had an onset of MDD at 11 years or later (mean=13.8 years, SD=2.5, range: 1 to 17 years old). The odds of MDD were significantly higher in females (OR 3.04, 95% CI 1.70-5.45) and adolescents who had at most one close friend (2.17, 1.05-4.50) (Table 3-1). Adolescents who were alcohol (1.87, 1.07-3.27) or tobacco users (1.77, 1.05-2.99), had a history of severe maltreatment (3.23, 1.55-6.73), moderate (3.62, 1.28-10.29) or severe (11.55, 4.36-30.60) anxiety symptoms, and poor or fair general health (3.95, 1.78-8.77) were significantly more likely to have MDD. Age, race, frequency of social outings, marijuana use, delinquent behavior, pubertal status, self-perception of pubertal timing, and GPA were not significant.

Table 3-1 Adolescent characteristics: Unadjusted odds ratios for adolescent MDD

	N	Non-MDD (%)	MDD (%)	Odds Ratio (OR)	95% CI for OR
Total Cohort	499	434 (87.0)	65 (13.0)		
Demographic Factors					
Age quartiles at assessment					
1st ≤16.3	125	113 (90.4)	12 (9.6)	1.00	
2nd 16.3-16.8	127	111 (87.4)	16 (12.6)	1.36	0.61-3.00
3rd 16.8-17.2	124	106 (85.5)	18 (14.5)	1.60	0.74-3.48
4th ≥17.2	123	104 (84.6)	19 (15.4)	1.72	0.80-3.72
Race					
Caucasian	229	198 (86.5)	31 (13.5)	1.00	
African American	270	236 (87.4)	34 (12.6)	1.09	0.65-1.83
Gender					
Male	242	225 (93.0)	17 (7.0)	1.00	
Female	257	209 (81.3)	48 (18.7)	3.04***	1.70-5.45
Social Support					
Number of close friends					
≥ 3	252	223 (88.5)	29 (11.5)	1.0	
2	188	165 (87.8)	23 (12.2)	1.07	0.60-1.92
1 or 0	59	46 (78.0)	13 (22.0)	2.17*	1.05-4.50

Table 3-1 (continued)

Frequency of outings					
≥ 2	306	272 (89.2)	33 (10.8)	1.0	
1	134	112 (83.6)	22 (16.4)	1.63	0.91-2.91
none	59	49 (83.1)	10 (16.9)	1.69	0.78-3.65
Current Substance Use					
Alcohol use (drinks/day)					
None	217	197 (90.8)	20 (9.2)	1.00	
Any	282	237 (88.4)	45 (11.6)	1.87*	1.07-3.27
Cigarette use (number/day)					
None	297	266 (89.6)	31 (10.4)	1.00	
Any	199	165 (82.9)	34 (17.1)	1.77*	1.05-2.99
Marijuana use (joints/day)					
None	292	258 (88.4)	34 (11.6)	1.00	
Any	205	174 (84.9)	31 (15.1)	1.35	0.80-2.28
Child Maltreatment a (CTQ) Tertiles					
1st ≤29	131	120 (91.6)	11 (8.4)	1.00	
2nd 30-36	131	112 (85.5)	19 (14.5)	1.85	0.84-4.06
3rd ≥37	140	108 (77.1)	32 (22.9)	3.23**	1.55-6.73
Delinquent Behavior Quartiles					
1st ≤1	162	147 (90.7)	15 (9.3)	1.0	
2nd 2 or 3	125	107 (85.6)	18 (14.4)	1.65	0.80-3.42
3rd 4-6	98	83 (84.7)	15 (15.3)	1.77	0.82-3.81
4th ≥6	108	91 (84.3)	17 (15.7)	1.83	0.87-3.84

Table 3-1 (continued)

Frequency of outings

≥ 2	306	272 (89.2)	33 (10.8)	1.0	
1	134	112 (83.6)	22 (16.4)	1.63	0.91-2.91
none	59	49 (83.1)	10 (16.9)	1.69	0.78-3.65

Current Substance Use

Alcohol use (drinks/day)

None	217	197 (90.8)	20 (9.2)	1.00	
Any	282	237 (88.4)	45 (11.6)	1.87*	1.07-3.27

Cigarette use (number/day)

None	297	266 (89.6)	31 (10.4)	1.00	
Any	199	165 (82.9)	34 (17.1)	1.77*	1.05-2.99

Marijuana use (joints/day)

None	292	258 (88.4)	34 (11.6)	1.00	
Any	205	174 (84.9)	31 (15.1)	1.35	0.80-2.28

Child Maltreatment a (CTQ) Tertiles

1st ≤29	131	120 (91.6)	11 (8.4)	1.00	
2nd 30-36	131	112 (85.5)	19 (14.5)	1.85	0.84-4.06
3rd ≥37	140	108 (77.1)	32 (22.9)	3.23**	1.55-6.73

Delinquent Behavior Quartiles

1st ≤1	162	147 (90.7)	15 (9.3)	1.0	
2nd 2 or 3	125	107 (85.6)	18 (14.4)	1.65	0.80-3.42
3rd 4-6	98	83 (84.7)	15 (15.3)	1.77	0.82-3.81
4th ≥6	108	91 (84.3)	17 (15.7)	1.83	0.87-3.84

Table 3-1 (continued)

Pubertal Status					
Petersen scale, females, age 14					
≤3	7	5 (71.4)	2 (28.6)	1.00	
≥4	215	179 (83.3)	36 (16.7)	0.50	0.94-2.69
Petersen scale, males, age 14					
≤3	116	109 (94.0)	7 (6.0)	1.00	
≥4	85	77 (90.6)	8 (9.4)	1.62	0.56-4.65
Perceived they developed earlier than peers (%)					
No	385	337 (87.5)	48 (12.5)	1.00	
Yes	113	96 (85.0)	17 (15.0)	1.24	0.68-2.26
Anxiety Quartiles					
1st ≤2	133	128 (96.2)	5 (3.8)	1.0	
2nd 3-5	124	116 (93.5)	8 (6.5)	1.77	0.56-5.55
3rd 6-8	121	106 (87.6)	15 (12.4)	3.62*	1.28-10.29
4th ≥9	119	82 (68.9)	37 (31.1)	11.55***	4.36-30.60
Grade Point Average Quartiles					
1st ≥3.21	104	92 (88.5)	12 (11.5	1.0	
2nd 2.51-3.20	113	103 (91.2)	10 (8.8)	0.74	0.31-1.80
3rd 1.91-2.50	140	121 (86.4)	19 (13.6)	1.20	0.56-2.61
4th ≤1.90	119	99 (83.2)	20 (16.8)	1.55	0.72-3.35
General health self-rating					
Excellent	149	136 (91.3)	13 (8.7)	1.00	
Very good	110	101 (91.8)	9 (8.2)	0.93	0.38-2.27
Good	178	152 (85.4)	26 (14.6)	1.79	0.88-3.62
Fair/poor	62	45 (72.6)	17 (27.4)	3.95***	1.78-8.77

[a] Those children with 'denial' subscale scores of >1 were removed from the CTQ analysis so there were only 402 subjects. * $p<0.05$, ** $p<0.01$, ***$p<0.001$

The rate of MDD was significantly higher among adolescents whose mothers had a lifetime history of MDD (including MDD only and comorbid MDD) (OR 1.95, 95% CI 1.15-3.29) or specifically comorbid MDD (1.78, 1.02-3.11; Table 3-2).

MDD was not higher among offspring whose mothers had a diagnosis of MDD only, GAD, or SUD. Family income, education, employment status, marital status, presence of an adult male in the household, or trait anger also did not differentiate between adolescents with and without MDD.

Table 3-2 Maternal characteristics: Unadjusted odds ratios for adolescent MDD

	N	Non-MDD (%)	MDD (%)	Odds Ratio (OR)	95% CI for OR
Total Cohort	499	434 (87.0)	65 (13.0)		
Demographic Factors					
Income quartiles ($/month)					
4th ≥2800	117	103 (88.0)	14 (12.0)	1.0	
3rd 1700-2800	124	105 (84.7)	19 (15.3)	1.33	0.63-2.80
2nd 1100-1700	128	115 (89.8)	13 (10.2)	0.83	0.37-1.85
1st ≤1100	130	111 (85.4)	19 (14.6)	1.26	0.60-2.64
Education (years)					
> 12	208	186 (89.4)	22 (10.6)	1.00	
12	243	209 (86.0)	34 (14.0)	1.38	0.78-2.44
< 12	48	39 (81.3)	9 (18.8)	1.95	0.84-4.56
Employment Status					
Yes	372	325 (87.4)	47 (12.6)	1.00	
No	127	109 (85.8)	18 (14.2)	1.14	0.64-2.05
Marital Status					
Yes	201	179 (89.1)	22 (10.9)	1.00	
No	296	253 (85.5)	43 (14.5)	1.38	0.80-2.39
Male in household					
Yes	254	223 (87.8)	31 (12.2)	1.00	
No	245	211 (86.1)	34 (13.9)	1.16	0.59-1.95

Table 3-2 (continued)

Psychological

    Trait Anxiety Quartiles

1st ≤13	145	126 (86.9)	19 (13.1)	1.00	
2nd 13.1-16	123	116 (94.3)	7 (5.7)	0.40*	0.16-0.99
3rd 16.1-20.9	105	90 (85.7)	15 (14.3)	1.11	0.53-2.29
4th >20.9	123	100 (81.3)	23 (18.7)	1.53	0.79-2.96

    Depression Quartiles

1st ≤33	136	123 (90.4)	13 (9.6)	1.00	
2nd 33.1-39	116	106 (91.4)	10 (8.6)	0.89	0.38-2.12
3rd 39.1-48	134	111 (82.8)	23 (17.2)	1.96 $p<0.1$	0.95-4.06
4th >48	112	93 (83.0)	19 (17.0)	1.93 $p<0.1$	0.91-4.11

    Trait Anger Quartiles

1st ≤13	154	133 (86.4)	21 (13.6)	1.00	
2nd 13.1-15	96	85 (88.5)	11 (11.5)	0.82	0.38-1.79
3rd 15.1-19	155	136 (87.7)	19 (12.3)	0.89	0.46-1.72
4th >19	91	78 (85.7)	13 (14.3)	1.06	0.50-2.23

Psychiatric

    Major Depressive Disorder

    (MDD)

No	320	287 (89.7)	33 (10.3)	1.00	
Yes	175	143 (81.7)	32 (18.3)	1.95*	1.15-3.29

    MDD Only

No	444	388 (87.4)	56 (12.6)	1.00	
Yes	51	42 (82.4)	9 (17.6)	1.49	0.69-3.22

Table 3-2 (continued)

MDD Comorbid					
No	371	329 (88.7)	42 (11.3)	1.00	
Yes	124	101 (81.5)	23 (18.5)	1.78*	1.02-3.11
Any DSM-IV disorder other than MDD					
No	390	338 (86.7)	52 (13.3)	1.00	
Yes	105	92 (87.6)	13 (12.4)	0.92	0.48-1.76
Generalized Anxiety Disorder (GAD)					
No	446	388 (87.0)	58 (13.0)	1.00	
Yes	51	44 (86.3)	7 (13.7)	1.06	0.46-2.48
Any alcohol disorder					
No	397	349 (87.9)	48 (12.1)	1.00	
Yes	96	79 (82.3)	17 (17.7)	1.57	0.86-2.86
Any marijuana disorder					
No	453	392 (86.5)	61 (13.5)	1.00	
Yes	41	37 (90.2)	4 (9.8)	0.68	0.24-2.02
Any cocaine disorder					
No	448	388 (86.6)	60 (13.4)	1.00	
Yes	47	42 (89.4)	5 (10.6)	0.77	0.29-2.02

*$p<0.05$, ** $p<0.01$, ***$p<0.001$

3.4.2 Multivariate Analyses

Variables that were bivariately associated with MDD were entered stepwise into a multivariate regression model. Mother's MDD diagnosis was the only significant predictor among the maternal characteristics (adjusted OR=1.80, 1.02-3.18) (Table 3-3). Adolescent female gender (adjusted OR 3.75, 95% CI 1.99-7.08) remained significant. The odds ratio for the highest CTQ tertile was significant (3.88, 1.82-8.26) and marginally significant for the second tertile (2.22, 0.99-4.97, p=0.053). This model had acceptable goodness of fit (Hosmer-Lemeshow χ^2=4.31, p=0.83). The significant relation between CTQ and MDD was not mediated by current adolescent substance use.

Table 3-3 Multivariate model 1: Significant covariates of MDD in adolescents

Variables Entered	Adjusted Odds Ratio	95% C.I. for Odds Ratio	p-value
Female Gender	3.77	2.00-7.12	0.001
CTQ Score of Adolescents			0.002
2nd tertile	2.22	0.99-4.97	0.053
3rd tertile	3.88	1.82-8.26	<0.001
Maternal MDD	1.80	1.02-3.18	0.044

Number of close friends, alcohol use, cigarette use, and general health of the adolescents were not significant. Maternal trait anxiety symptoms, depressive symptoms, and comorbid MDD were not significant.

The interaction between offspring gender and maternal MDD diagnosis was significant (p=0.03, Table 3-4 and Figure 3-1). This interaction was not explained by differences in social support, childhood maltreatment, or current substance use.

Table 3-4 Multivariate model 2: Significant interaction between gender and maternal MDD

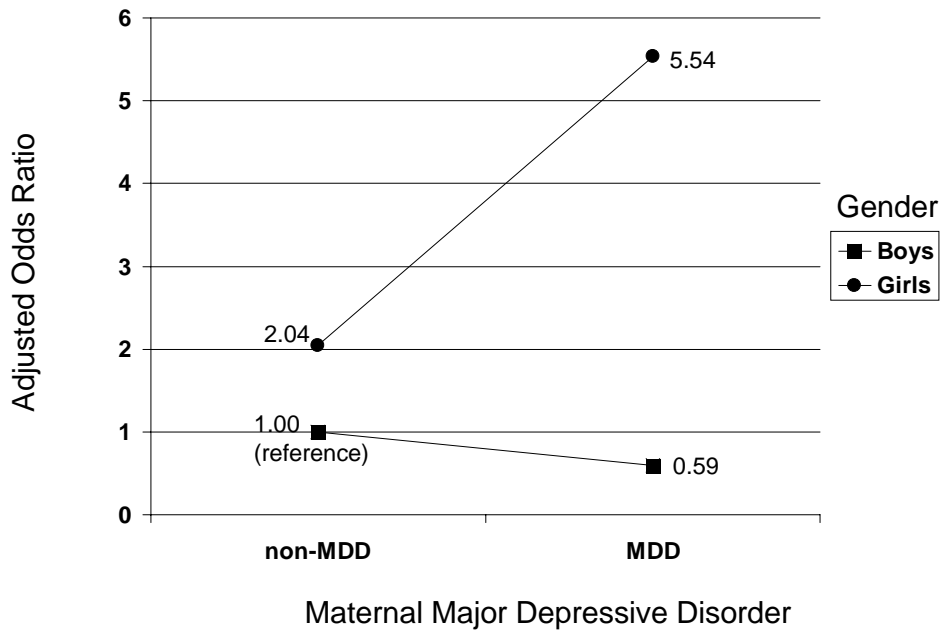| Variables Entered	Adjusted Odds Ratio	95% C.I. for Odds Ratio	p-value
Female Gender	2.04	0.92-4.52	0.080
CTQ Score of Adolescents			0.002
2nd tertile	2.19	0.97-4.94	0.059
3rd tertile	3.99	1.86-8.58	<0.001
Maternal MDD	0.59	0.18-1.96	0.393
Maternal MDD x Gender	4.58	1.15-18.13	0.030

Figure 3-1 Adjusted odds of adolescent MDD: Interaction between gender and maternal MDD

3.5   DISCUSSION

The lifetime prevalence of adolescent MDD was 13%, which parallels the high prevalence of maternal MDD (35%) in this cohort. Although the prevalence of MDD in boys (7.0%) matched the rate reported elsewhere (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003), the rate of MDD in girls (18.7%) was much higher (11.7%). Other estimates of lifetime prevalence of adolescent MDD are somewhat higher than what we found (15-20%; Birmaher, Ryan, Williamson, Brent, Kaufman, Dahl et al., 1996; Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman et al., 1994; Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993).

The adjusted odds ratio of MDD among the girls was almost four times that of the boys, consistent with findings by Angold and colleagues (1998). Proposed mechanisms for this gender difference include 1) Exposure to increased levels of testosterone and estrogen at puberty, especially in the context of social stress, (Angold et al., 1999), 2) Anatomic changes in girls reflecting their sexual maturity may be experienced negatively (Stattin & Magnusson, 1990), and 3) Social changes in school, or in relationships with parents, peers, and romantic/sexual partners may increase the number of depression-inducing life events among girls (Cyranowski, Frank, Young, & Shear, 2000).

In the multivariate model, the odds of MDD in the adolescents were almost twice as high in offspring of mothers with MDD as in the offspring of women without MDD. The majority of maternal cases of MDD were comorbid with at least one other psychiatric diagnosis, likely indicating more severe disease than those women with only a psychiatric diagnosis of MDD. Parental psychopathology is one of the strongest factors for depression in offspring (Beardslee et al., 1998; Downey & Coyne, 1990; Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997).   However, current maternal depressive symptoms and history of other psychiatric

disorders were not associated with adolescent MDD. The association between maternal and adolescent MDD may reflect the disorder's genetic component, environmental effects, or both.

The interaction of offspring gender and maternal MDD were consistent with other results (Fergusson, Horwood, & Lynskey, 1995). The lack of association between pubertal status and depression could have resulted from the narrow range in pubertal status at age 14.

A history of severe childhood maltreatment increased the adjusted odds of MDD in adolescents by almost four times. Young and colleagues (1997) reported that 35% of adult outpatients treated for major depression and anxiety had a history of childhood emotional, physical, or sexual abuse. Chapman et al. (2004) found a dose-response relation between adverse childhood events and lifetime depression in adults. Evidence suggests that childhood maltreatment is associated with dysregulation of the HPA axis, which may increase the risk of MDD (DeBellis, Chrousos, Dorn, Burke, Helmers, Kling, et al., 1994; Kaufman, Birmaher, Perel, Dahl, Moreci, Nelson, et al., 1997).

Although current adolescent substance use and maternal demographics have been associated with adolescent MDD and depressive symptoms (e.g., Costello, Erkanli, Federman, & Angold, 1999), we did not find this association. Unlike other studies, however, we included a history of childhood maltreatment and maternal MDD as covariates of adolescent MDD. Monthly income, education, and employment status were also not significantly associated with adolescent MDD. The likely reason for this is that there was a narrow SES range in this cohort.

3.5.1 Limitations

The mothers in our study were selected on the basis of their prenatal substance use, although their use was, in general light to moderate and the sample included women who abstained from

use throughout pregnancy. In addition, this is a low SES cohort. Thus, they are not representative of women in the general population.

Others have shown that paternal psychiatric diagnoses increase risk of MDD in offspring (Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005). A limitation of our study is a lack of data on the fathers.

The high correlation between self-reported anxiety and MDD obviated the use of both in the regression model. However, although anxiety and depressive disorders share symptoms, a diagnosis of MDD is distinguished from GAD by whether the patient has primarily a depressed or anxious mood. Thus, we are confident that we have established significant predictors and covariates of major depressive disorder in adolescents.

The diagnostic data used here are lifetime diagnoses. Our present study did not focus on whether the mother's first MDD episode preceded the child's. This limits our ability to make statements about causality.

3.5.2 Clinical Implications

Female gender, a history of childhood maltreatment, and a maternal history of MDD each increased the odds of adolescent MDD. The likelihood of having an MDD diagnosis is further increased among female adolescents whose mothers have a history of MDD. Our findings suggest that routine psychiatric assessment of maltreated children and daughters of women with MDD would improve the early identification and treatment of adolescent depression.

4.0   MANUSCRIPT 3: THE RELATION BETWEEN MATERNAL ANXIETY DURING PREGNANCY AND LEVEL OF DEPRESSIVE SYMPTOMS IN LATE CHILDHOOD AND ADOLESCENCE OF OFFSPRING

4.1   SUMMARY

For this study, we hypothesized that after controlling for confounding variables, prenatal maternal anxiety will predict depressive symptom level in children from ages 10 to 16 years. Women (n=829) of low socioeconomic status, recruited from a hospital-based prenatal clinic to study prenatal alcohol and marijuana use, were assessed for trait anxiety using the State Trait Personality Inventory (STPI; Spielberger, 1979) during their fourth gestational month. At the 10, 14, and 16-year follow-ups, trait anxiety (STPI) and depressive symptoms were measured in women (Center for Epidemiologic Studies-Depression Scale; CES-D; Radloff, 1977) and their offspring (Children's Depression Inventory; CDI; Kovacs, 1981, 1992). Repeated measures mixed linear models were used to test the hypothesis. Covariates included prenatal and current demographic, social, and maternal substance use, child gender, and follow-up year.

Results were as follows: 1) Maternal anxiety and depressive symptoms were highly correlated across the follow-up assessments. 2) Boys' levels of self-reported depressive symptoms were highest at 10 years and decreased significantly at the 14 and 16-year assessments; girls' level of symptoms did not change over time. 3) Prenatal maternal anxiety

significantly predicted depressive symptoms in offspring from age 10 to 16 years. 4) Prenatal maternal anxiety remained a significant predictor of depressive symptoms in offspring, controlling for current maternal depressive symptoms. 5) The relation between prenatal maternal anxiety and child depressive symptoms was marginally significant (p=0.09) after adding child gender and prenatal maternal educational status. 6) There was a significant interaction between gender and follow-up year in predicting depressive symptom level in offspring from age 10 to 16 years.

Maternal anxiety during pregnancy has long term effects on the level of depressive symptoms in offspring during late childhood and adolescence. To reduce the risk of children developing depressive symptoms, healthcare providers should aim prevention efforts at improving psychological health and reducing anxiety during or prior to pregnancy.

4.2   INTRODUCTION

There has been renewed interest in recent years in the effects of gestational stress and anxiety on the offspring (Van den Bergh, Mulder, Mennes, & Glover, 2005). Maternal anxiety during pregnancy predicts negative emotionality in infants at 10 and 28 weeks of age (Van den Bergh, 1990). Another study showed that prenatal maternal stress has a significant effect on the fetus in middle childhood, evidenced by increased behavioral and emotional problems in 6 ½ year-old offspring (O'Connor, Heron, Golding, & Glover, 2003).

Fetal programming results when an insult to the fetus produces long-lasting or life-long effects. Two areas of the developing brain are likely affected by prenatal exposure to anxiety: The prefrontal cortex, which is responsible for organizing and integrating brain signals involved

in behavioral/emotional regulation in children and adults (Grossman, Chruchill, McKinney, Kodish, Otte, & Greenough, 2003; Ladd, Huot, Thrivikraman, Nemeroff, Meaney, & Plotsky, 2000), and the hypothalamic-pituitary-adrenal (HPA) axis, which has a role in the etiology of major depressive disorder (MDD; Arborelius, Owens, Plotsky, & Nemeroff, 1999; Holsboer, 2000).

Elevated anxiety levels in pregnant women result in elevated glucocorticoids (specifically cortisol in humans) that could affect the developing fetal HPA-axis. Glucocorticoids are central to the physiological response to stress in mammals, including humans. The HPA-axis is particularly susceptible to perinatal programming by glucocorticoids, at least in animal models (Barker, 1998; Schneider & Moore, 2000; Welberg, Seckl, & Holmes, 2001) and dysregulation of the HPA-axis prenatally could lead to the development of depression or depressive symptoms. There is recent evidence in humans indicating that prenatal anxiety predicts HPA-axis dysregulation in childhood, as measured by higher salivary cortisol levels in 10-year-old children (O'Connor, Ben-Shlomo, Heron, Golding, Adams, & Glover, 2005).

Direct effects of maternal cortisol are unlikely during the normal physiologic conditions of pregnancy, as the placenta contains the enzyme 11β-hydroxysteroid dehydrogenase Type 2 (11β-HSD2), which rapidly inactivates maternal cortisol before it enters fetal circulation (Lindsay, Linday, Edwards, & Seckl, 1996). However, the effects of maternal stress and anxiety on the functioning of this enzyme are unknown. It is possible that maternal cortisol that is elevated beyond normal pregnancy levels, could overwhelm the placental enzyme's ability to inactivate the cortisol, allowing the hormone to reach the fetus and modify HPA-axis development. An alternate mechanism involves fetal cortisol. Maternal cortisol positively correlates with fetal cortisol (Gitau, Cameron, & Fisk, 1998), and there is positive feedback

between fetal cortisol and placental Corticotropin Releasing Hormone (CRH), which supports the maternal stress response (Laatikainen, 1991; Lederman, 1996). Maternal stress/anxiety may also affect the fetal brain through decreased uterine blood flow (Teixeira, Fisk, & Glover, 1999) and fetal hypoxemia (Myers, 1977).

It is our aim to determine whether prenatal maternal anxiety contributes to level of depressive symptoms in the offspring during late childhood and adolescence. We will examine depressive symptoms beginning at 10 years, a time when depressive symptoms are likely to first appear (Birmaher, Ryan, Williamson, Brent, Kaufman, Dahl et al., 1996). To evaluate these effects through adolescence, we will follow the children's depressive symptoms to age 16 years. We hypothesize that prenatal maternal anxiety will predict depressive symptoms in the offspring, after controlling for current maternal depressive symptoms, and other confounding variables.

4.3   METHODS

4.3.1   Study Design

The Maternal Health Practices and Child Development (MHPCD) Project is a longitudinal study, begun in 1982, that examines the long-term effects of prenatal substance use on the physical and mental health of offspring. The women were selected from a hospital-based prenatal clinic and were of lower socioeconomic status. In total, 1360 women were recruited during their fourth prenatal month. From these women, two cohorts were selected for studies of prenatal alcohol and marijuana use. The selection criteria for the alcohol cohort were: women who drank alcohol at the rate of three or more drinks per week in the first trimester of pregnancy, and the next

woman who drank less than that amount or who abstained. For the marijuana cohort the criteria were: women who used marijuana as often as twice a month, and the next woman who used less or abstained. Women could be in either or both cohorts. The present analysis combined these two cohorts, for a total of 829 women at the first assessment (fourth gestational month). This study uses data from the fourth prenatal month and the 10, 14, and 16-year follow-up assessments. Analyses included children and their biological mothers who had at least one follow-up assessment at 10 (n=588), 14 (n=527), or 16 years (n=509). Other caregiver/child dyads were excluded from the analyses so that we could control for the association between prenatal anxiety and current maternal depressive symptoms. The Institutional Review Boards of Magee-Womens Hospital and of the University of Pittsburgh approved the study and all women gave signed, informed consent for themselves and on behalf of their children.

4.3.2 Measurements

4.3.2.1 Demographic Status

Race and age were self-designated by the women at the first assessment. Marital status, monthly family income, employment status, and education were ascertained at all time points. Whether or not the women lived with a male in the household was assessed at all follow-up time points. The following variables were dichotomized: race (African American/Caucasian), marital status (married/unmarried), and employment status (employed or in school/ unemployed and not in school). Age, monthly income, and educational level at the prenatal assessment were categorized to reduce skewness. Using quintiles, we created five approximately equal groups for maternal age and monthly income variables. The number of years of maternal schooling at the prenatal assessment (<12 years, 12 years, or >12 years) was used as the measure of education.

4.3.2.2 Maternal Social Support and Life Events

Social support was a composite of questions from the first assessment: 1) how frequently she talks to friends, 2) how frequently she talks to relatives, 3) if she has someone to turn to in times of need, and 4) how satisfied she is with the help from friends and relatives. Stressful life events were assessed at delivery by asking the women to report events that occurred during pregnancy.

4.3.2.3 Prenatal Substance Use

At each prenatal assessment, women reported their use during the previous trimester of alcohol, cigarettes, marijuana, cocaine, and other illicit drugs. The women were asked about the quantity and frequency of the usual, maximum, and minimum use of alcohol and marijuana. Women were also asked about the quantity and frequency of tobacco, cocaine, and other illicit drugs. The average daily number of alcoholic drinks, marijuana joints, and cigarettes used were calculated and treated as continuous variables. Alcohol and marijuana use variables for all time points were log-transformed to reduce skewness of the distributions. Because the use of cocaine and other illicit drugs was low, illicit drug use was dichotomized (any/none).

4.3.2.4 Maternal and Child Psychological Measures

Maternal

Trait anxiety is a predisposition to experience anxiety in a stressful situation. State anxiety is a transient emotional response characterized by unpleasant feelings of tension and apprehensive thoughts (Spielberger, 1966). The two measures are highly correlated (Albrecht & Rankin, 1989). In this study, trait anxiety (score range: 10-40) was assessed in women using the State-Trait Personality Inventory (STPI; Spielberger, 1979). Ten items from the State-Trait Anxiety

Inventory (STAI; Spielberger, 1983) were selected for this measure based on the following criteria: high corrected item-total correlations, relatively low item-scale correlations with the trait anger subscale of the STPI, and high factor loadings. This instrument was used because it was shorter. The time frame of the STPI was modified for our study, and women reported on how they had felt over the last trimester. The trait anxiety measure at the fourth prenatal month was selected as the measure for these analyses for the following reasons: 1) the correlation was very high between the assessments of the first, second, and third trimester ($r=0.65$ to 0.75); 2) there were more missing subjects at the seventh gestational month assessment (n=69); 3) as we were interested in anxiety reports during pregnancy, it was inappropriate to use the assessment of anxiety soon after delivery.

Depressive symptoms in women were assessed during pregnancy and at follow-up time points using the Center for Epidemiologic Studies-Depression Scale (CES-D; range: 0-60; Radloff, 1977), a 20-item questionnaire developed to measure symptoms in general and psychiatric populations. The women reported how they felt about each of the items over the previous trimester. Subsequent assessments asked the women to report on how they felt during the past two weeks.

The STPI and the CES-D were administered to the women at each phase. Our analyses use the trait anxiety assessment at the fourth prenatal month and the CES-D assessments from the 10, 14, and 16-year follow-ups. Current depressive symptoms in the women refer to those measured at the same assessment as their children's depressive symptoms.

Higher scores on both of the scales indicate more symptoms. The sample mean of a particular question was used to replace missing data if no more than 10% of the responses to questions were missing (i.e., a maximum of 1 item for the anxiety scale and a maximum of 2

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items for the depression scale). Thus, for the prenatal assessment, 1 missing trait anxiety item was imputed for 20 women. For the 10, 14, and 16-year follow ups, 1 missing CES-D item was imputed for 12, 7, and 18 women, respectively; 2 missing CES-D items were imputed for 0, 3, and 4 women, respectively.

Child

The Children's Depression Inventory (CDI; Kovacs, 1981, 1992) was used to assess self-reported depressive symptoms in the offspring at ages 10, 14, and 16 years. The CDI consists of 27 items which assess negative mood, anhedonia, ineffectiveness, negative self-esteem, and interpersonal problems in the past 2 weeks. Each item is assessed with statements corresponding to a score ranging from 0 to 2, with 0 = absence of symptom, 1 = mild symptom, and 2 = definite symptom. These scores correspond to the child's selection of the statement that best describes himself/herself: I am sad once in a while (0); I am sad much of the time (1); I am sad all the time (2). The total raw score means are reported in these analyses (range: 0-44). In order to reduce the missing data, up to 4 items on the CDI were filled in using regression imputation. Thus, 1 item was imputed at the 10, 14, and 16-year assessments for 30, 16, and 8 subjects, respectively. Two items were imputed for 5, 5, and 3 subjects, respectively. Three items were imputed for 1, 1, and 13 subjects, respectively. At the 16-year assessment, 4 items were imputed for one subject only.

4.3.3   Data Analysis

The CDI score was log-transformed to reduce positive skewness and all estimates reported are for the transformed outcome. Data were included in the analyses for all follow-up points at

which the child and biological mother were assessed. Potentially confounding variables were identified using bivariate analyses (Pearson correlations, t-tests, and Analysis of Variance) of prenatal maternal demographic, social, and substance use variables with prenatal maternal anxiety and CDI scores at 10, 14, and 16. To test group differences of CDI scores by gender and follow-up year, t-tests and Analysis of Variance (ANOVA) were used, respectively.

Repeated measures mixed linear models were used to determine whether prenatal maternal anxiety symptoms predicted depressive symptoms in offspring across ages 10, 14, and 16 years. This approach allowed us to include the CDI data from all subjects assessed at each time point. The covariates were added to the models based on the following: 1) well-established literature on their correlation with child depression level; and/or 2) from bivariate analyses at each follow-up. Models were created by adding one fixed effect variable at a time. Prenatal maternal anxiety (the main predictor of interest) and year of follow-up (10, 14, 16) were tested first. Next, current maternal depressive symptoms were considered. The following confounding variables were finally tested stepwise: child gender, race, first trimester maternal cigarette use, and maternal education level at the first assessment. First trimester substance use was chosen *a priori* for entry into the model because it was measured at the same time as prenatal anxiety. After the significant main effects were identified, all possible statistical interactions between variables were tested. Participant-specific intercepts were modeled as random effects.

4.4 RESULTS

4.4.1 Sample Description

Table 4-1 summarizes the demographic and substance use characteristics of women at the fourth gestational month, and at the 16-year follow-up. The sample is racially balanced between Caucasians and African Americans. The sample is of low socioeconomic status and the majority of the women at both the prenatal and the 16-year phases were single and high-school educated. At the prenatal assessment, the majority of the women was unemployed and not in school, whereas 16 years later, the majority was employed or in school. Substance use by the women at the first trimester was as follows: 0.39 marijuana joints/day; 8.3 cigarettes/day; 0.62 alcoholic drinks/day. (Table 4-1) Mean use of all substances was lower at later trimesters, with the exception of cigarettes.

Table 4-1 Demographic characteristics at prenatal and 16-year phases

Maternal Variable	Prenatal (n=763) [a]	16-year Follow-up (n=509)
Demographics:		
Age (years)	23 (4)	40 (4)
African American (%)	51	54
Median family income (monthly)	300-399	1700
Employed (%)	27	74
Single (%)	64	60
Education (years completed)	12 (1.4)	12 (2.0)
Male in household(%)	(not available)	50
Substance Use	**First Trimester**	
Marijuana joints/day	0.39 (range, 0-9)	0.09 (range, 0-6)
Abstainers (%)	60.3	
Cigarettes/day	8.3 (range, 0-50)	8.1 (range, 0-60)
Abstainers (%)	49.1	
Alcoholic drinks/day	0.62 (range, 0-20)	0.86 (range, 0-26)
Abstainers (%)	36.9	
Illicit drugs (%)	11	5
Cocaine (%)	4	3

[a] Means with standard deviations in parentheses are presented, unless otherwise noted.

The birth cohort was generally healthy with means: birth weight, 3.20 kg; birth length, 49.3 cm; head circumference, 34.1 cm; and gestational age, 39.7 weeks. Eleven percent of the offspring were low birth weight (<2500 g); 9% were preterm (<37 weeks gestation); and 10% were small for gestational age. The cohort of children at the three follow-up assessments was balanced with respect to gender (49-50% male) and race (46-47% Caucasian).

4.4.2 Maternal and Child Psychological Variables

The women in our study took neither antidepressants nor anxiolytics during pregnancy. The mean anxiety scores for the women at the prenatal phase and at 10, 14, and 16 years were 17.8,

16.7, 16.6, and 17.1, respectively; mean depression scores were 20.8, 18.2, 18.6, and 20.3, respectively (Table 4-2).

Mean CDI scores for offspring over the three follow-up assessments were 7.4, 7.0, and 6.3, for 10, 14, and 16 years, respectively (Table 4-2). These scores differed over time ($F(1603,2)=2.47$, $p=0.085$). Table 4-2 provides the correlations between psychological variables for mothers and their children. Prenatal maternal anxiety symptoms were significantly correlated ($p<0.01$) with maternal anxiety and depressive symptom measures at each of the three follow-up points ($r=0.37$, for anxiety, at all points; $r=0.34$, 0.31, and 0.28, for depression, at 10, 14, and 16 years, respectively. Prenatal maternal anxiety symptoms were significantly associated with child depressive symptoms at ages 10 and 16 years ($r=0.12$, $p<0.01$ and $r=0.11$, $p<0.05$, respectively), whereas prenatal maternal depressive symptoms were significantly correlated with child depressive symptoms at only age 16 ($r=0.14$, $p<0.01$; Table 4-2).

Table 4-2 Psychological descriptive statistics and correlations for mothers and their children

Follow-up Period	Maternal Anxiety Symptoms (STPI)				Maternal Depressive Symptoms (CES-D)				Child Depressive Symptoms (CDI)		
	Prenatal	10-yr	14-yr	16-yr	Prenatal	10-yr	14-yr	16-yr	10-yr	14-yr	16-yr
Descriptive Statistics											
n	761	588	527	505	757	587	526	507	580	523	503
Mean Score	17.8	16.7	16.6	17.1	20.8	18.2	18.6	20.3	7.4	7.0	6.3
Standard Deviation	4.7	4.7	9.9	5.3	8.7	9.5	9.9	10.7	6.6	6.4	5.8
Pearson Correlations											
Maternal Anxiety Symptoms											
Prenatal	-	0.37**	0.37**	0.37**	0.71**	0.34**	0.31**	0.28**	0.12**	0.08	0.11*
10-yr		-	0.53**	0.55**	0.31**	0.77**	0.46**	0.47**	0.11**	0.04	0.11*
14-yr			-	0.64**	0.32**	0.45**	0.74**	0.55**	0.06	0.07	0.16**
16-yr				-	0.34**	0.52**	0.55**	0.78**	0.09	0.07	0.21**
Maternal Depressive Symptoms											
Prenatal					-	0.36**	0.38**	0.39**	0.07	0.06	0.14**
10-yr						-	0.55**	0.57**	0.13**	0.07	0.09*
14-yr							-	0.64**	0.09*	0.11*	0.18**
16-yr								-	0.09*	0.09*	0.20**
Child Depressive Symptoms											
10-yr									-	0.30**	0.31**
14-yr										-	0.61**
16-yr											-

Note: Only biological mothers were included in the analyses.

* $p < 0.05$ ** $p < 0.01$

4.4.3 Bivariate Analyses of Prenatal Covariates

Significant covariates of prenatal anxiety included: African American race, lower family income, lower education, less social support, more cigarette and alcohol use during the first and second trimesters, and more cigarette use during the third trimester. Marijuana, cocaine and other illicit drug use were not associated with prenatal anxiety. Of these significant correlates of prenatal anxiety, the confounding variables (i.e., those significantly associated with both prenatal anxiety and CDI score at least at one follow-up assessment) included: race, education level, and cigarette use at all trimesters (Table 4-3). Female gender was associated with higher CDI score at the 14 and 16-year follow-up assessments ($t(484)=3.78$, $p<0.001$, and $t(501)=2.53$, $p=0.012$). Unexpectedly, female gender was associated with higher PMA ($t(588)=2.4$, $p=0.015$). Thus, not only was gender a covariate of child depressive symptoms, but it was also a confounding variable in the relation between PMA and child depressive symptoms.

Table 4-3 Associations of maternal variables during pregnancy with prenatal maternal anxiety and Children's Depression Inventory scores at follow-up phases

Maternal Variable	Associations Between Maternal Characteristics and Offspring Psychological Scores			
	Prenatal Anxiety (n=763)	Age 10 CDI (n=588)	Age 14 CDI (n=527)	Age 16 CDI (n=509)
Demographic/social variables during pregnancy:				
Age [a]	0.93	2.10	0.77	1.07
African American [b]	2.4*	2.59**	- 2.19*	-1.33
Lower family income [a]	2.93*	1.70	0.17	0.78
Unemployed [b]	0.88	1.49	1.44	1.05
Single [b]	1.92[m]	1.14	-1.54	-0.70
Lower Education [a]	3.43*	2.72 [m]	4.44*	3.34*
Life events [a]	2.03	0.80	0.19	0.77
Social support [a]	13.9**	0.97	0.63	0.52
Substance Use for 1st trimester:				
Marijuana joints/day [c]	0.037	0.138**	-0.006	0.026
Cigarettes/day [c]	0.089*	0.048	0.121**	0.066
Alcoholic drinks/day [c]	0.105**	0.031	0.067	0.042
Illicit drug use [b]	-1.46	-0.36	-0.24	0.30
Cocaine use [b]	0.37	-0.22	0.34	0.18

[a] F statistic reported. [b] t-statistic reported. [c] Pearson correlation coefficient reported.

* $p<0.05$ ** $p<0.01$ [m] Marginally significant ($p<0.1$)

4.4.4 Mixed Linear Models

4.4.4.1 Main Effects

PMA measured at the fourth prenatal month significantly predicted (p=0.002) depressive symptoms in offspring from 10 to 16 years, adjusting only for the follow-up year (Table 4-4). After adjusting for follow-up year and current maternal depressive symptoms, prenatal maternal anxiety symptoms remained a significant predictor (p=0.033) of depressive symptoms in offspring. After adding gender and maternal education to the model, PMA was marginally significant (p=0.09). Table 4-4

Table 4-4 Prenatal maternal anxiety predicts depressive symptoms in children: Adjusted main effects models

Step 1	β	p-value	95% CI of Estimate
Prenatal maternal anxiety	0.0085	0.002	0.0032, 0.0137
Follow-up year	-0.0089	0.005	-0.0151, -0.0028
Step 2	**β**	**p-value**	**95% CI of Estimate**
Prenatal maternal anxiety	0.0059	0.033	0.0004, 0.0112
Follow-up year	-0.0102	0.001	-0.0164, -0.0040
Current maternal depressive symptoms	0.0043	<0.001	0.0022, 0.0063
Step 3	**β**	**p-value**	**95% CI of Estimate**
Prenatal maternal anxiety	0.0048	0.093	-0.0008, 0.0105
Follow-up year	-0.0106	0.001	-0.0171, -0.0042
Current maternal depressive symptoms	0.0043	<0.001	0.0022, 0.0064
Maternal education	-0.054	0.013	-0.0959, -0.011
Offspring gender (male)	-0.0521	0.050	-0.1041, -0.0001

4.4.4.2 Statistical Interactions

We tested all combinations of the variables that had significant main effects for statistical interactions. There was a significant interaction between follow-up age and gender (p<0.001;

Table 4-5; Figure 4-1), and a marginally significant interaction between gender and maternal depressive symptoms ($p=0.055$).

At the 10-year follow-up, the girls' mean CDI was not significantly different from that of the boys. However, at the 14 and 16-year follow-ups, girls reported significantly higher levels of depressive symptoms than boys ($t(484)=3.78$ and $t(501)=2.53$, respectively). (Figure 4-1) The boys' mean CDI score decreased over time (7.8, 5.8, 5.4, $F(728, 2)=8.75$, $p<0.001$, for 10, 14, and 16 years, respectively). The differences between ages 10 and 14 years, and 10 and 16 years were significant. Girls' mean CDI scores did not differ over the three time points (7.1, 8.3, 7.2, $F(760,2)=2.85$, $p=0.058$). In the final model, prenatal maternal anxiety was a marginally significant ($p=0.08$) predictor of depressive symptoms in children from 10 to 16 years (Table 4-5).

Table 4-5 Prenatal maternal anxiety predicts depressive symptoms in children: Final model including interactions

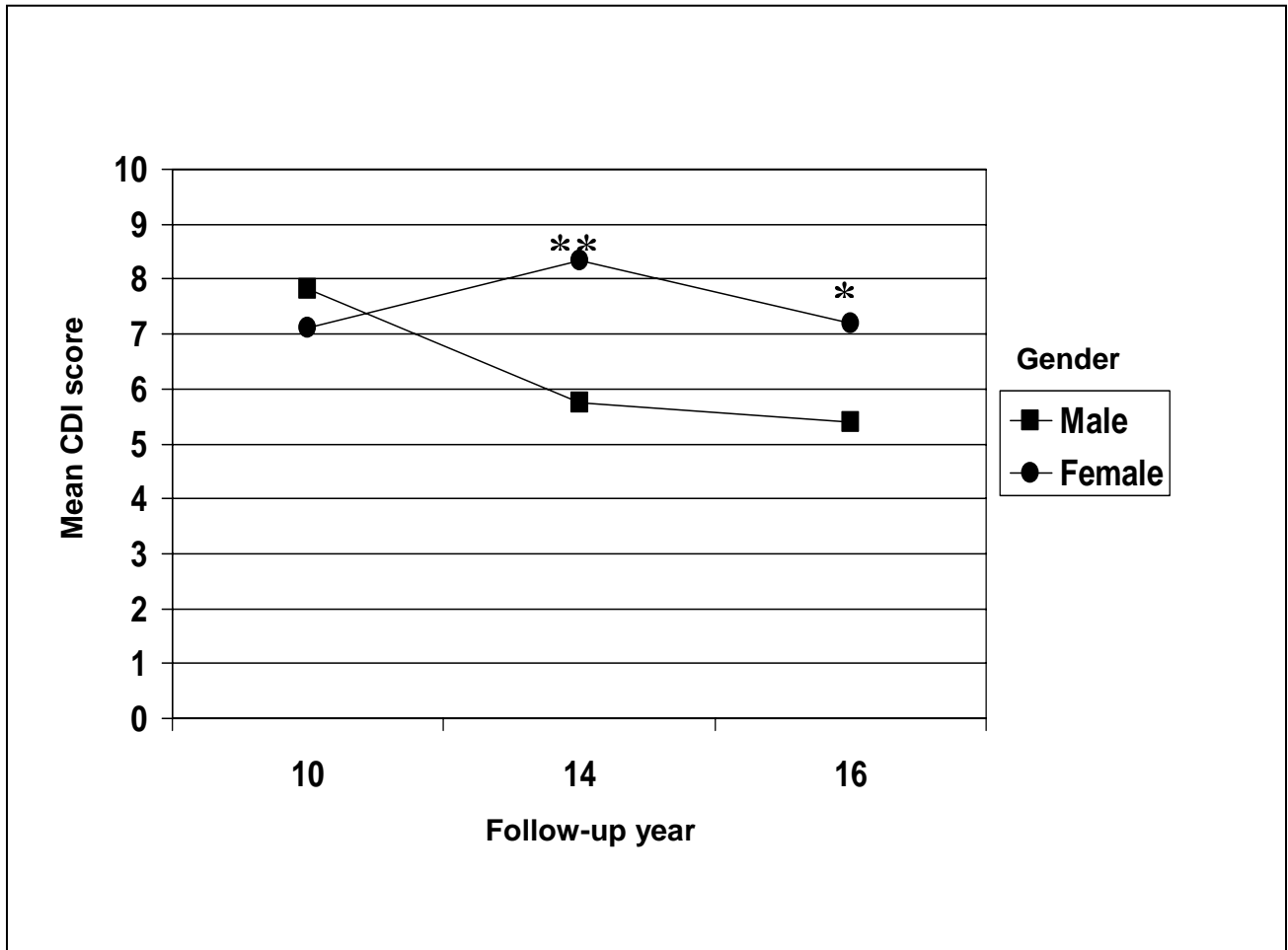|	β	p-value	95% CI of Estimate
Prenatal maternal anxiety	0.0050	0.080	-0.0005, -0.0106
Follow-up year	-0.0240	<0.001	-0.0330, -0.0151
Current maternal depressive symptoms	0.0043	<0.001	0.0022, 0.0064
Offspring gender (male)	0.3230	0.001	0.1403, 0.5057
Maternal education	-0.0534	0.013	-0.0955, -0.0112
Follow-up year * gender (male)	-0.0269	<0.001	-0.0395, -0.0143

Figure 4-1 Mean depressive symptoms during late childhood and adolescence: Interaction between gender and follow-up year

Significant differences in mean CDI score between males and females are indicated:
* p<0.01 ** p<0.001

4.5   DISCUSSION

Maternal anxiety during pregnancy is a predictor of the level of depressive symptoms in late childhood and adolescence. This finding is consistent with the fetal programming hypothesis.

Our analyses confirmed that current maternal depressive symptoms are highly related to offspring depressive symptoms, as has been reported previously (Da Costa, Larouche, Drista, & Brender, 2000; Demyttenaere, Lenaerts, Nijs, & Van Assche, 1995; Beardslee, Versage, & Gladstone, 1998; Downey & Coyne, 1990; Gelfand & Teti, 1990). However, prenatal maternal anxiety remained a significant predictor of offspring depressive symptoms after controlling for current maternal depressive symptoms. Thus, the association between PMA and child depression cannot be simply explained by the high correlation between anxiety and depression. After controlling for maternal education and child gender, the relation between prenatal maternal anxiety and level of depressive symptoms in the offspring became marginally significant ($p<0.10$).

In an earlier manuscript we reported a significant interaction between gender and maternal major depressive disorder (MDD) in predicting MDD in the adolescent offspring (Hosseini, Day, Brooks, Wroble Biglan, Gorin, & Larkby, unpublished manuscript). In the present analysis of depressive symptoms, we have also found that girls of depressed mothers are at higher risk than would be expected from the independent effects of being female and having a mother with depressive symptoms. This disproportionately increased risk in girls of depressed mothers could be due, in part, to their increased sensitivity to family discord, a correlate of maternal depression (Davies & Windle, 1997; Fergusson, Horwood, & Lynskey, 1995).

Our finding of a significant interaction between follow-up year and gender is in accord with the literature that levels of depressive symptoms in boys and girls are similar prior to adolescence, and diverge beyond age 13 years (Twenge & Nolen-Hoeksema, 2002). Although many studies have reported that this divergence is due to an increase in symptoms among girls (e.g., Hankin & Abramson, 1999; Nolen-Hoeksema & Girgus, 1994), in our cohort the

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divergence is due to a significant decrease in depressive symptoms in the boys at the 14 and 16-year assessments. This difference in findings may be partially attributable to differences in study design. In a meta-analysis of 310 samples of children ages 8-16, Twenge & Nolen-Hoeksema (2002) found that testing effects due to repeated administration of the CDI in longitudinal studies resulted in lower CDI scores over time, as compared with results from cross-sectional studies using the CDI. They estimated that the magnitude of this longitudinal testing effect in the negative direction was equivalent to previously reported increases in girls' CDI scores during adolescence. Thus, any real increase in level of depressive symptoms in the girls would be offset by the testing effect, such that their level of depressive symptoms would appear constant during late childhood and adolescence. This is a potential explanation of why the levels of depressive symptoms in the girls appeared to be constant and those of males appeared to decrease in our longitudinal analyses.

There are several limitations to this report. We did not explore the effects of the timing of anxiety during pregnancy and, because anxiety and depressive symptoms in the mothers were very highly correlated, it was not possible to control for each separately. Furthermore, because our sample consists of lower socioeconomic status women, some of whom were substance users during pregnancy, our results may not be generalized to the population at large. Nevertheless, our study had several advantages. We had a large, racially-balanced cohort and a dataset that provided a wealth of variables. The study design allowed us to investigate the relation between a prenatal variable and a longitudinal outcome in the children several years later. The retention rate was high over the sixteen years (approximately 70%). Finally, a major advantage of our study over some others is our reliance upon child self-report of depressive symptoms, rather than parental report.

The mean CDI scores for the children were within the normal range (Kovacs, 1981; 1992). However, the fact that there is a significant effect of PMA on the level of depressive symptoms, even below the range of clinical significance, is important. Moderate and non-diagnostic levels of depressive symptoms in childhood can negatively affect academic and social performance (Nolen-Hoeksema, Girgus, & Seligman, 1992; Susman, Dorn, & Chrousos, 1991). Non-clinical levels of depressive symptoms and the resultant psychosocial impairments persist into adulthood (Rohde, Lewinsohn, & Seeley, 1991; Nolen-Hoeksema et al., 1992) and are risk factors for subsequent Major Depressive and Substance Use Disorders (Angst & Merikangas, 1997; Fergusson, Horwood, Ridder, & Beautrais, 2005; Lewinsohn, Solomon, Seeley, & Zeiss, 2000). Thus, an increased rate of depressive symptoms may have important implications for long-term prognosis.

In conclusion, trait anxiety in pregnant women predicted depressive symptom levels in their children from 10 to 16 years of age. This relation remained significant after controlling for current maternal depressive symptoms. Prevention efforts aimed at improving the psychological well-being in expectant mothers may be important for reducing the risk of subsequent mental health problems in their offspring. Maternal education and female gender are also risk factors that should be considered when assessing a child's risk for developing depression.

5.0   SUMMARY/CONCLUSIONS

5.1   OVERVIEW OF MANUSCRIPTS 1, 2, AND 3

Initially, the overarching hypothesis of this dissertation was that exposure to prenatal maternal anxiety (PMA) would predict major depressive disorder (MDD) in 16-year-old adolescent offspring.   In order to explore this hypothesis, it was crucial to establish the potential confounders of this relation.   In a first step, Manuscript 1, entitled "Trait anxiety in pregnant women predicts offspring birth outcomes," we established the significant covariates of PMA, and examined prediction of adverse birth outcomes by PMA.   In regression models, trait anxiety measured at the 7th gestational month and shortly after delivery predicted lower birthweight and shorter birth length, controlling for confounds. Anxiety reported shortly after delivery was associated with shortened gestational age, controlling for confounds.   Further, Manuscript 1 described PMA severity and duration as they related to birth outcomes.   At the 4th and 7th gestational month assessments, the relation of birthweight and birth length to maternal trait anxiety was only significant for severe anxiety.   Women whose anxiety reached severe levels for at least two of the three assessments were significantly more likely to deliver offspring of lower birthweight and shorter birth length than those women who reported severe anxiety at none or one of the assessments.   Additionally, offspring of women who experienced severe anxiety during three assessments had shorter mean gestational age compared to offspring of women who did not report severe anxiety at any assessment.   Thus, we concluded in Manuscript 1 that

women who report chronic, severe trait anxiety are at the highest risk of having shorter gestations and delivering smaller babies. These findings confirmed that there were at least short term effects of PMA on children's physical outcomes; this encouraged us to explore the potential lasting effects of PMA on development of psychiatric/psychological outcomes, namely major depression and depressive symptoms in the offspring.

Next, in Manuscript 2, entitled "Covariates of major depressive disorder in mid-adolescence," the significant covariates of MDD in adolescent offspring were determined bivariately and the strongest predictors and correlates were established in a multivariate logistic regression model. The lifetime prevalence of MDD among the 16-year-old adolescents was 13 %. Female gender, history of severe childhood maltreatment, and maternal diagnosis of MDD independently increased the odds of MDD in adolescents. There was a significant interaction between offspring gender and maternal MDD. We concluded that these risk factors, especially girls whose mothers had MDD, should prompt early screening and intervention in children. These results pointed to the potential confounders which we would need to consider for Manuscript 3.

Preliminary analyses for Manuscript 3 revealed that there was no significant bivariate association between PMA at any of the three prenatal assessments and MDD in the 16-year-old offspring, nor were there any significant bivariate associations between MDD and any of the covariates of PMA. Thus, the outcome of interest was changed. The outcomes explored in Manuscript 3 were depressive symptoms over the 10-, 14-, and 16-year assessments. The paper was entitled "The relation between maternal anxiety during pregnancy and level of depressive symptoms in late childhood and adolescence of offspring." There were two advantages of using this new outcome: 1) The full range of depressive symptoms was explored, and 2) All three

assessments during late childhood and adolescence were used. Drawing on the richness of our longitudinal data allowed us a fuller picture of the longitudinal course of depression and depressive symptoms in the children than would a diagnosis of MDD, which simply measured lifetime prevalence. The theory supporting this new overarching hypothesis essentially remained the same: fetal programming due to PMA exposure makes the offspring more liable to developing depressive symptoms.

Based on Manuscripts 1 and 2 which determined the significant covariates of PMA and MDD, respectively, we determined which variables needed to be considered as potential confounders in exploring the relation between PMA and depressive symptoms in Manuscript 3. We additionally confirmed that history of childhood maltreatment, and the other bivariately significant covariates established in Manuscript 2, were not confounders of the relation. However, based upon the findings in Manuscript 2 of a significant interaction between gender and maternal depression (i.e., MDD) and upon the fact that maternal depression was a confounder of the relation, we controlled for both gender and current maternal depressive symptoms in Manuscript 3. Furthermore, several correlates of PMA in Manuscript 1 were also correlates of depressive symptoms in children (including race, maternal education, and prenatal cigarette and alcohol use).

In Manuscript 3 we found the following: 1) Maternal anxiety and level of depressive symptoms were highly correlated across the follow-up assessments. 2) Boys' levels of self-reported depressive symptoms significantly decreased at the 14 and 16-year assessments, as compared with the 10-year assessment; girls' level of symptoms did not significantly change over time. 3) Prenatal maternal anxiety significantly predicted depressive symptoms in offspring from age 10 to 16 years, controlling for the follow-up year. 4) After controlling for current

maternal depressive symptoms, prenatal maternal anxiety remained an independent significant predictor of depressive symptoms in offspring. 5) Additionally controlling for child gender and prenatal maternal educational status rendered the relation between prenatal maternal anxiety and child depressive symptoms marginally significant (p=0.09). 6) There was a significant statistical interaction between gender and follow-up year in predicting depressive symptom level in offspring from age 10 to 16 years. We concluded that maternal anxiety during pregnancy has lasting effects on the level of depression of offspring into late childhood and adolescence. Thus, clinicians should aim prevention efforts at improving psychological health and reducing anxiety in women during the prenatal period, and continue depression screening in women throughout their offspring's childhood and adolescence.

5.2   FETAL PROGRAMMING BY PRENATAL MATERNAL ANXIETY

Traditionally, familial risk of depression has been thought to be primarily conferred through either genetic inheritance, or through environmental effects of exposure to post-natal maternal depression, as the child is growing up. Our results indicate that an additional mechanism, fetal programming by maternal anxiety, plays an important role in development of depressive symptoms.

Formation of the hypothalamus, pituitary, and adrenal glands occurs throughout gestation, with fetal HPA activity beginning at midgestation (Gitau, Fisk, Teixeira, Cameron, & Glover, 2001). Thus, it may be susceptible to the ill effects of elevated stress and anxiety levels in pregnant women. The potential mechanisms for modification of the fetal HPA-axis were discussed in greater detail in the introductory section and in Manuscript 3. Additionally, the

prefrontal cortex has been implicated as one of the potentially susceptible parts of the fetal brain because it is responsible for organizing and integrating brain signals involved in behavioral/emotional regulation in children and adults (Grossman, Churchill, McKinney, Kodish, Otte, & Greenough, 2003; Ladd, Huot, Thrivikraman, Nemeroff, Meaney, & Plotsky, 2000).

5.3   TIMING OF EXPOSURE TO PRENATAL MATERNAL ANXIETY

Because the literature has already established that prenatal anxiety/stress negatively impacts birth outcome, we did not want to simply duplicate others' findings. Rather, we were interested in using our measure of PMA at the two assessments during pregnancy and the one at delivery to determine which assessment(s) were best in predicting birth outcome, and whether at each of these assessments, trait anxiety was a stronger predictor than either depression or trait anger in the pregnant women. Furthermore, we used all three assessments of maternal anxiety in order to determine the effects of duration of anxiety. Despite our findings in Manuscript 1 that anxiety measured at the 2nd and 3rd assessments were significant predictors of birth outcome, we selected the 1st assessment of PMA as our predictor of depressive symptoms in children. Our justification for doing so was discussed in Manuscript 3.

A consequence of our choice to only use the 1st assessment of PMA is that we are limited in our ability to make conclusions about gestational periods for which the fetus is more susceptible to the modifying effects of PMA. Even if we were to treat our measure of trait anxiety as one of state anxiety, as we did for Manuscript 1, then we would be limited by the 1 ½ month range of the first assessment. Although many women were first assessed during their 4th

gestational month (n=516), many were first assessed at their 4 ½ month (n=245), and a substantial number came in as late as their 5 ½ month of pregnancy (n=76).   Thus, this assessment generally represented mid-gestation.

5.4   LOW BIRTH WEIGHT AND ADVERSE BIRTH OUTCOMES AS MARKERS OF DYSREGULATED HPA AXIS

There is evidence that birth weight impacts on child and adult health (e. g., Clark, Hindmarsh, Sheill, Law, Honour, & Barker, 1996; Phillips & Jones, 2006).   Adjusting for sex and current weight, both high and low birth weight babies have elevated urinary cortisol in childhood, presumably reflecting lasting effects of an adverse fetal environment (Clark et al., 1996). Although low birth weight, preterm delivery, and other pregnancy complications have been shown by some authors to predict MDD in adolescents and adults (e. g., Jablensky, Morgan, Zubrick, Bower, & Yellachich, 2005; Patton, Coffey, Carlin, Olsson, & Morley, 2004), we found no such association in our cohort.

We hypothesized a significant relation between adverse birth outcomes (including lower birth weight, low birth weight, shortened gestational length, preterm delivery, and small for gestational age) and depression in the offspring. We found significant associations between child depressive symptoms at age 10 and the following birth outcomes: small size for gestational age; low birth weight. Low birth weight significantly mediated the relation between prenatal maternal anxiety and age 10 depressive symptoms in children (results not included in

Manuscripts). However, none of the birth outcomes was associated with either MDD diagnosis, or depressive symptoms at ages 14 or 16 years.

A potential explanation for our inability to detect a relation between birth outcome and longitudinal depressive symptoms, is that our cohort of adolescents generally had healthy birth outcomes (mean birth weight= 3.19 kg, SD=0.58; 11% were low birthweight (< 2.5 kg); mean gestational age=39.7 weeks, SD=2.2; 9 % were preterm (< 37 gestation weeks); 10% were small for gestational age).

5.5   CHILDHOOD MALTREATMENT

In Manuscript 2, we report our findings that history of childhood maltreatment significantly predicts a lifetime diagnosis of MDD in 16-year-old adolescents. Although our childhood maltreatment findings are consistent with the literature, their interpretation is limited by several factors. First of all, our assessment did not include information about the timing or duration of childhood maltreatment. Furthermore, in order to understand better the mechanisms of experiencing childhood maltreatment, a next step would be to explore the specific categories of maltreatment (i.e., emotional neglect and abuse; physical neglect and abuse; and sexual abuse). Finally, because we do not have information on who the abuser/neglectful caretaker was, we cannot assume that the mechanism is poor parenting.

The proposed biological mechanism for the overarching hypothesis of this dissertation may encompass the effects of childhood maltreatment as well. As the HPA axis is susceptible to modification by stresses even after birth, it has been suggested that HPA-axis dysregulation may be the etiological link between childhood maltreatment and subsequent mood and anxiety

disorders (Kendall-Tacket, 2000; Shea, Walsh, MacMillan, & Steiner, 2004; Teicher, Andersen, Polcari, Anderson, Navalta, & Kim, 2003).

5.6   PMA → DEPRESSION RELATION

The vast majority of cases of MDD in our cohort had an onset at age 11 years or later (mean age=13.8 years, SD=2.5, range: "earlier than I can remember" to 17 years). Because we would expect depressive symptoms to be elevated beginning around 10 years of age in some children, it was appropriate that we began measuring depressive symptoms at this age. The dual finding of a non-significant association of PMA with MDD and a significant association between PMA and depressive symptoms in children 10 to 16 years old may be explained by the effects of PMA being chronic and generally sub-threshold for clinical depression.   This is not surprising considering the dimensional nature of the STPI measure of trait anxiety as including sub-clinical anxiety. Although the effects of PMA in our cohort are not strong enough to predict MDD, this does not render their effects on child depressive symptoms trivial.

5.7   CLINICAL IMPORTANCE OF SUB-THRESHOLD DEPRESSIVE SYMPTOMS

Many groups (e.g., Angst & Merikangas, 1997; Fergusson, Horwood, Ridder, & Beautrais, 2005; Lewinsohn, Solomon, Seeley, & Zeiss, 2000) have lent support to the idea that major depression, as defined by DSM-IV, is a categorical diagnosis imposed on a continuum of depressive symptoms of varying severity and duration. During the past few years, these researchers have

been particularly interested in examining "sub-threshold depression." In the study by Lewinsohn et al. (2000), the authors found that increasing depressive symptoms (i.e., higher CES-D score) predicted worse psychosocial dysfunction and higher incidence of both, major depressive and substance use disorders. Thus, Lewinsohn's group concluded that even non-diagnosable levels of depression are risk factors for poor prognosis. Fergusson et al. (2005) longitudinally followed a community sample of adolescents in order to determine the association between extent of depressive symptoms (no symptoms, sub-threshold, major depression) in late adolescence and outcomes at age 25. After adjusting for confounding variables, the adolescents' extent of depression significantly predicted major depression, number of depressive symptoms, suicidal ideations and treatment for anxiety-related disorders. This study essentially found that those subjects with sub-threshold depression had a similar prognosis as those with MDD. This lends support to the idea that MDD patients are not a discrete group which differs from those not meeting DSM-IV criteria.

Angst & Merikangas (1997) found that the prevalence of threshold and sub-threshold categories of depression were similar and that many subjects with depression met the criteria for multiple depressive subtypes (including major depression, recurrent brief depression, minor depression, and dysthymia) over a 15-year period. Furthermore, they found that sub-threshold depression is associated with a large increase in the risk of the subsequent development of MDD over time. Their findings suggest that brief recurrence of even low-level depression may have important implications for long-term prognosis. In light of these authors' findings, our results for depressive symptoms from ages 10 to 16 years have clinical relevance.

5.8   PUBLIC HEALTH IMPLICATIONS

Several key factors for preventing depression in children and adolescents are indicated. Our findings that anxiety in pregnant women affected birth outcomes and depressive symptoms in offspring point to the need for reducing anxiety in these women. Studies are called for which assess whether prenatal care that addresses the psychological well-being of pregnant women would result in improved birth outcomes. Anxious women should be identified early in or even prior to pregnancy and targeted for anxiety reduction. Furthermore, in multivariate models, lower maternal education significantly predicted both shortened birth length and higher depressive symptoms in offspring; this is a relatively easily identifiable indicator of risk which could be used more extensively by clinicians.

Prevention of abuse and neglect during a child's development is also a key factor in reducing their risk of MDD, not to mention the various other improvements in a child's life which would result from such prevention. Once childhood maltreatment is detected, however, early intervention targeted at these children may lower rates of MDD in adolescence.

Finally, ensuring the psychological health of mothers throughout their children's development is expected to greatly decrease the risk of depression. Olson and colleagues (2006) recently implemented a brief depression screening of mothers at well-child visits. They found that such a program was feasible, not time-consuming, and that it added significant value in detecting potentially depressed women. Many of the mothers were open to discussion about the impact of their mental health on their child, and furthermore, some mothers received referrals from the pediatricians. Thus, we would recommend maternal screening for depression by pediatricians beginning in early childhood, so that the mother may be referred for the appropriate

care. Finally, it has been shown that interventions such as group cognitive therapy are effective in preventing depression in adolescent offspring of depressed parents (Clarke et al., 2002).

5.9   FUTURE DIRECTIONS

Based our current findings, future research could be taken in several directions. Importantly, our study controlled for the effects of maternal depression concurrent with those measurements in the children at ages 10, 14, and 16 years. However, there may be additional effects of post-natal depression in early infancy which predispose the children to behavioral/emotional problems (O'Connor, Heron, & Glover, 2002). Thus, future studies could control for such early post-natal depression in mothers. A second direction is that our cohort of children could be followed into adulthood to see if the effects of prenatal maternal anxiety on depressive symptoms last into adulthood, and whether a relation with MDD emerges.

Third, new studies could incorporate measures of maternal state anxiety at several points throughout pregnancy. As it is known that brain development continues throughout gestation, and that many developmental processes occur at precise times (Nowakowski & Hayes, 2002), identifying periods when the fetus is especially sensitive to the harmful effects of maternal anxiety is beneficial: 1) It has implications for prevention in highly anxious pregnant women, and 2) It may also hold the potential of revealing which developmental processes of early brain development were disturbed. Finally, as in another recent study, measuring cortisol in the children (and even later in adulthood) could provide insight into whether HPA-axis is

dysregulated in prenatal anxiety-exposed children (O'Connor, Ben-Shlomo, Heron, Golding,

Adams, & Glover, 2005).

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