EXPOSURE TO PRE- AND POSTNATAL DEPRESSION AND ANXIETY SYMPTOM TRAJECTORIES: EFFECT ON ADOLESCENT PSYCHIATRIC OUTCOMES

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EXPOSURE TO PRE- AND POSTNATAL DEPRESSION AND ANXIETY

SYMPTOM TRAJECTORIES: EFFECT ON ADOLESCENT PSYCHIATRIC

OUTCOMES

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Exposure to maternal pre- and postnatal depression (PPND) and anxiety (PPNA) symptoms have been linked to a number of adverse outcomes in children. This research used growth mixture modeling (GMM) to examine individual-level PPND and PPNA symptom patterns in a sample of women and adolescents participating in a longitudinal study of maternal health practices. These trajectory groups were then used as exposure states for offspring in a series of analyses that examined whether symptom trajectory exposure was associated with age of onset of any psychiatric illness, the risk for Major Depressive Disorder (MDD), or the risk of Conduct Disorder (CD). Finally, path analysis was used to identify potential mechanisms associated with trajectory exposure and psychiatric illness.

The GMM analyses found distinct trajectories of PPND and PPNA symptoms. Two groups of stable PPND symptom patterns were identified: low and high. PPNA exposure had three stable symptom patterns: low, medium, and high. Examination of the co-occurrence of PPND and PPNA found that those in the high PPND trajectory were more likely to be in the medium or high PPNA symptom trajectories, compared to the low PPND individuals. PPND, PPNA, and co-occurring trajectory group exposure were not associated with age of onset of first psychiatric illness or with MDD. The risk of CD onset was not associated with PPND or co-

occurring trajectory exposure. However, males exposed to medium and high PPNA trajectories were at an increased risk of CD compared to low PPNA exposed males. Females exposed to medium or high PPNA trajectories were at a decreased risk of CD, compared to their low PPNA counterparts. Results of the path analysis suggested a direct path from PPNA to CD risk, moderated by gender. Furthermore, PPNA exposure predicted higher levels of emotionality, which predicted higher CD risk.

CD is responsible for serious morbidity among affected children and places a large burden on society as a result of increased service use and involvement in the juvenile justice system. The public health significance of identifying a strong risk factor for CD in males is that it provides a new potential target for primary prevention.

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PREFACE

I would like to acknowledge a number of people for their contributions to this work. First, many thanks go to my family, my partner, and my friends who supported me and kept me motivated when my energy waned. Special recognition goes to my partner, Jamek, who put up with me through Master's and Ph.D. programs and who patiently proof-read my papers throughout.

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1.0   INTRODUCTION

Psychiatric illness affects an estimated one in four people in their lifetime [1] . In the United States, approximately 21% of children under age 16 meet criteria for a psychiatric disorder [1]. Disorders arising in adolescents that persist or recur are associated with a longer duration, more relapses, and greater lifetime impairment [2]. There is a lack of longitudinal research addressing the etiology and course of mental illness [1]. Research evaluating risk factors for development of psychiatric illness, using appropriate longitudinal methods, has been advocated by the world's most respected health organizations [1, 3]. The effect of exposure to elevated anxiety and depression symptoms during pregnancy and early infancy on the later risk for the development of psychiatric disorders in offspring is one avenue underexplored.

Major depression and generalized anxiety disorder are two of the most common mental illnesses in community and health care settings [1, 4, 5]. Even in developed nations, these disorders often go untreated [5, 6]. This suggests that a substantial portion of children are exposed to symptoms of maternal depression and anxiety during a period of significant brain and emotional development [7]. In one well-conducted community-based study examining symptoms of depression and anxiety, Heron et al. reported that from 18 weeks gestation to 8 months postpartum, 24% of the women had elevated levels of depression symptoms and 27% had elevated levels of anxiety symptoms [8]. Negative aspects of maternal mood, such as depression and anxiety symptoms, have been linked to a number of adverse outcomes in children. For

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example, exposure to elevated maternal depression symptoms has been associated with poorer infant cognitive and social development [9, 10]. Exposure to general anxiety symptoms, although less well documented, may be related to difficult infant temperament [11, 12], poorer cognitive development [9], and feeding problems [13]. There is some suggestion that these exposures may increase the risk of psychiatric disorders later in life [14-17]. One of the first steps toward understanding the relationship between depression and anxiety symptoms and risk for psychiatric illness is to evaluate the nature of the exposure.

This document provides an overview of the current state of the literature, followed by research to address the link between exposure to maternal anxiety and depression symptoms during pregnancy and the postpartum and adolescent psychiatric illness. The literature review starts with an evaluation of studies examining the prevalence and patterns of pre- and postnatal depression symptoms, followed by the same for pre- and postnatal anxiety. Next, studies examining the co-occurrence of depression and anxiety symptoms during pregnancy and the postpartum are assessed. Finally, evidence for the potential mechanisms and effects of pregnancy-related depression and anxiety exposure on the risk of psychiatric illness in adolescent offspring are evaluated.

1.1   DEPRESSION DURING AND AFTER PREGNANCY

1.1.1   Prevalence

Estimates of the prevalence of probable clinical depression during pregnancy range from 9% [18, 19] to 46% [20]. Postnatal prevalence ranges from 3% [21] to 43% [22]. Variation in

these estimates can be traced to the use of different assessment techniques, diverse study populations, and varied assessment timing. Several assessment instruments have been used to identify probable clinical depression during this time period including: the Edinburgh Postnatal Depression Scale (EPDS) [23], the Center for Epidemiological Studies Depression scale (CES-D) [24], and the Beck Depression Inventory (BDI) [25]. The different questionnaires obtain different ranges of prevalence estimates. Furthermore, none of these scales assess clinical depression, which requires the presence of at least five specific symptoms causing significant impairment lasting for two or more weeks [26]. Instead these scales provide cutoff points for what is probable clinical depression. Thus, these scales provide only approximations of rates of clinical depression, which has more restrictive criteria. Only the EPDS was designed for specific use in pregnant populations. This may cause problems with assessment scales that have a large somatic component as normal body changes during pregnancy may mimic some of these symptoms. Studies using the EPDS [27-35] have estimated the prevalence of prenatal depression as between 9% [18] and 22% [36]. Postnatal estimates with the EPDS ranged between 5% [35, 37] and 24%. Studies using the BDI [19, 31, 35, 38, 39] have returned estimates during the prenatal period between 9% [19] and 20% [39] and postnatal rates of between 5.5% [35] and 30% [38]. Studies using the CES-D consistently identify higher estimates [20, 22, 40-44] ranging between 24% [43] and 46% prenatally [20] and between 8% [40] and 43% postnatally [22]. Complexity is also added by the time frame being assessed. [36]. While the BDI, the CES-D, and the EPDS all evaluate symptoms during the seven days prior to the assessment, studies sometimes change the time frame to "since you became pregnant". This is often the case with studies evaluating symptoms only at one time point. Even within a single instrument, studies have used varying cut points to distinguish probable clinical depression, making direct

comparisons difficult [31, 45]. The use of different cut points is often based upon the distribution of scores in the sample, and not on sensitivity or specificity information. This increases the chance of error in classifying probable clinical depression.

Population differences have also led to differences in prevalence estimates. A study by Lee et al., examining Hong Kong women, found one of the highest levels of depression symptoms during pregnancy and the postpartum (37.1%) [36]. This suggests there may be populations in which depression symptoms are more common, perhaps due to differences in cultural factors such as attitudes towards pregnancy and social support for childbearing women. However, it may also be due to the use of assessment methods not validated in these populations. Scales developed for use in one population may not be as valid or reliable when used in different cultures.

Other studies have examined populations with differing risk factors. Verkerk and colleagues reported on differences in prevalences of postpartum clinical depression between women with a personal or family history of clinical depression and those without [29]. The prevalence of depression in the first postpartum year was 25% in high-risk women and 6% in low-risk women. In a study of unwanted pregnancies, rates of elevated depression symptoms were approximately 30% [41] and nearly half of teens and disadvantaged women had high levels of depression symptoms during pregnancy [20]. Studies examining prevalence are observational in nature and recruitment methods may unwittingly lead to differences in the distribution of risk factors across the studies, particularly in samples recruiting volunteers. Women struggling with more risk factors for depression, such as low social support [36], lower socioeconomic status, or more psychiatric symptoms [29, 34, 36] may be less likely to volunteer to participate [46].

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1.1.2 Pattern

While individual prevalence estimates may vary between studies, the overall pattern of elevated depression symptoms across time is fairly consistent. Figure 1 presents the prevalence results over time found in various studies. Most studies examining changes in depression symptoms from pregnancy through the postpartum report a stable prevalence.

Figure 1: Findings of studies examining prevalence of depressive symptoms through pregnancy and the postpartum.

The most notable exceptions to this general pattern were the studies by Adewuya et al. (2005), Lee and colleagues (2007), and Sugawara et al. (1999). One possible reason for the differences in these findings was the use of scales not commonly used in pregnant populations. Lee and colleagues [36] utilized the Hospital Anxiety and Depression Scale (HADS) [47] in assessing depression, while Adewuya and Aflabi [34] and Sugawara et al. [48] used the Zung

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Self Rating Depression Scale (ZSDS) [49]. The two studies that used the ZSDS both have more variation in their measurements across time than the other studies, while the HADS is generally used in hospitalized patients to assess depression comorbid with other medical conditions. Furthermore, each of these studies includes an ethnically specific sample. Lee et al. focused on mothers in Hong Kong, Adewuya et al. examined pregnant women in Nigeria, and Sugawara and colleagues evaluated Japanese women. It may be that elevated depression symptoms are more common and less stable in these populations. Two other studies, O'Hara et al. [19] and Green [50], suggest an increase in the prevalence of elevated depression symptoms across this time period. However, the degree of change is slight and the studies only included two time periods, suggesting a steeper change than what may actually be occurring.

One significant limitation to these studies is that only the patterns of prevalence at the group level are presented. It is not possible to determine if the same women who have probable depression during the prenatal period are the ones who are depressed postnatally. Cross-sectional prevalence estimates do not inform about patterns of depression at the individual level. Analyses based on the group experience instead of the individual symptom patterns, assume that the different patterns of depression are equal in risk factors and importance. Instead, there may be different risk factors for certain patterns of symptoms. For example, if transient symptoms are characterized by more life stressors whereas consistent symptoms are related to a history of depression, there may be a need for different treatments for these groups. Moreover, transient depression may not have as detrimental an effect on child development as a more chronic course.

Very few studies have attempted to refine the identification of symptom patterns from repeated cross-sectional analyses. One method has been to trace new and existing cases across time. In 2004, Heron and colleagues reported on a large population-based study in Avon,

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England [8]. At 18 weeks gestation, 11% of the sample was classified as having probable depression. At 32 weeks gestation, 6% of this group was still depressed and 7.3% of the initially non-depressed group had reached probable depression symptom levels. When the sample is broken down into the different patterns of probable depression and not depressed at each of the four measurement points, 16 different symptom patterns are possible. In the total sample, 76% of the women did not experience probable depression throughout the study; 1.5% were depressed throughout; the majority of the remaining participants experienced one episode of elevated depression symptoms, although the time point varied. Another study, by Lee and colleagues, found a great deal of intra-individual variability in depression symptoms as well, although only 60% of their participants were free of elevated depression symptoms throughout [36]. Matthey et al. also found that 60% of their sample was depression-free, while 9% had probable depression throughout [31]. Each of these studies used scale-based cut points to establish their depression classification. While these studies are informative, they do not provide information on the risk factors or consequences of the different symptom patterns.

A few studies have performed stratified analyses based on different factors to evaluate their impact on prevalence patterns. As previously mentioned, the Verkerk et al. study stratified on risk of clinical depression and found that in the low-risk group, depression prevalence was low and steady, whereas in high-risk women, the prevalence was high and decreased over the postpartum period, although never to the level of the low-risk women [29]. Perren et al. stratified on existing psychopathology as measured by a global symptom checklist assessing psychiatric symptoms [37]. Not surprisingly, those with psychopathology had higher levels of depression symptoms and a more persistent course. It is unclear, however, whether the depression symptoms were included in the measure of psychopathology, thus confounding the two.

Two studies have statistically analyzed individual depression symptom patterns. In 1996, Fergusson and colleagues used a latent modeling strategy to evaluate individual-level patterns of symptoms and the probability of changes in diagnostic status from 18 weeks gestation through 32 weeks postpartum [28]. The study found the best model for the data defined three groups: one was a group of individuals who were not depressed at the initial assessment and remained non-depressed throughout; these "not-vulnerable" participants accounted for 57% of the sample. Another group of women (37%) were not depressed initially, but were "vulnerable" to developing depression. Furthermore, 6% were both "vulnerable" and depressed at the first assessment. Diagnostic status remained relatively stable over time with one exception. This analysis found that the period surrounding delivery was a time of increased instability for depression symptoms, specifically; there was an increased rate of remission following delivery, in contrast to the belief that there is an increased incidence following child birth, "postpartum depression". This is consistent with the majority of the prevalence studies in Figure 1. Unfortunately, no risk factors for membership in these trajectories were examined.

Mora et al. recently reported on a study of over 1,700 community-recruited women and found five trajectory patterns [51]. The majority of women (71%) had no depression during pregnancy and the postpartum, 7% had consistently elevated depression symptoms, 6% had elevated depression during pregnancy only, 9% had elevated symptoms early in the postpartum, and 7% had late postpartum symptoms only. This pattern differs from that found by Fergusson and colleagues who found only three patterns [28]. This may be due to differences in the modeling procedure. Fergusson et al. modeled the patterns of the probability of meeting criteria for probable depression (yes or no) over time, whereas Mora et al. modeled depression symptom levels over time [28, 51]. Furthermore, Mora et al. examined a number of risk factors associated

with trajectory group membership and found a number of risk factors including education, race, parity, recent alcohol use, and objective stress that differed among trajectory groups. As this is the first study to examine risk factors for depression symptom trajectory over time, it is important to replicate the results in a different population. One major limitation to the Mora study was the exclusion of anxiety as a factor of interest. While anxiety over pregnancy was assessed, general anxiety symptoms were not considered, nor was the possibility of confounding or interaction between depression and anxiety symptoms evaluated.

1.2 ANXIETY SYMPTOMS DURING AND AFTER PREGNANCY

1.2.1 Prevalence

Most studies reporting on prenatal and postnatal anxiety in pregnancy have used the State-Trait Anxiety Inventory (STAI) [52] to assess anxiety during pregnancy and the postpartum. The STAI is a measure of current anxiety symptoms with two components and a range of possible scores from 20-80. The first is state anxiety, which measures the transient situational-based stress. The second component is trait anxiety which measures a more stable "personality" type anxiety. Trait anxiety is significantly correlated with Generalized Anxiety Disorder (GAD), a condition of persistently high anxiety symptoms. However, use of the STAI as a diagnostic indicator of GAD lacks specificity, with high correlations with depression and social phobia [53]. While the use of a single measure for assessing anxiety symptoms should lead to more comparable estimates across studies, there are a number of factors that make this difficult. First, the timing of assessments varied across studies. Second, some studies used a cut-

point to classify anxious from non-anxious women. As no standard cut-point has been established for the STAI, the point of classification varied between studies, usually based upon the distribution in the sample. Other studies reported means as opposed to prevalence at different time points. This should make comparison easier except one study reported the mean for the entire STAI, while other studies reported the means for the State or the Trait subscales. This has led to general disagreement about the rates of elevated anxiety during pregnancy and the postpartum. Mean state anxiety during pregnancy ranged between 20.5 [54] and 35.1 [55]. During the postpartum, estimates ranged between 19.9 [16] and 33.68 [56]. Mean trait anxiety estimates ranged from 33.7 [57] to 44.2 [55] in pregnancy and 31.77 [58] to 40.7 [55] in the postpartum.

1.2.2 Pattern

The difference in reporting means or prevalence in longitudinal studies of anxiety has led to difficulties in comparing findings. Figure 2 presents the findings of longitudinal studies reporting elevated anxiety symptom levels in pregnancy and the postpartum. The chart on the left in Figure 2 presents prevalence estimates of elevated anxiety symptoms across time. Only two studies examine both pre- and postnatal course. They both found relatively stable prevalence of elevated anxiety symptoms across the time periods. However, the study by O'Connor et al. included only two time points and may appear more stable than it actually is [59]. Another study by Lee et al. supports the idea of stable symptoms in the prenatal period but found a much higher prevalence [36]. This may be an effect of the scale used in the study. Unlike the others, Lee and colleagues used the Hospital Anxiety and Depression Scale which assesses depression and anxiety symptoms during the prior month and was designed for use in a hospitalized population

[47]. In the postnatal period, several patterns are evident including increasing [35], decreasing [34], and stable rates of elevated symptoms [8].
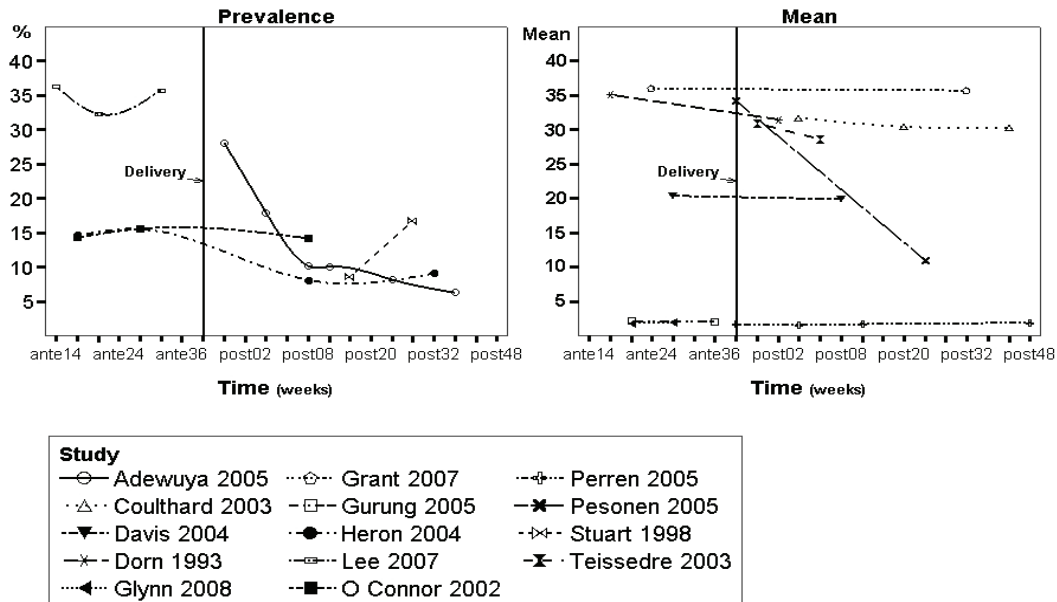
Figure 2: Findings of studies examining course of anxiety symptoms over pregnancy and the postpartum.

Studies of means over time have reported different levels of anxiety symptoms but a consistently stable pattern, except one. Pesonsen et al. reported a strong decrease through the postpartum [60]. This may be due to the use of the Perceived Stress Scale (PSS) [61] instead of the STAI. Not only does this make studies incomparable, there are subtle differences in the definition of stress versus anxiety. Stress tends to be viewed as events in an individual's life that challenge psychological and physical resources. Anxiety, on the other hand, is a psychological reaction to stressors. It is not clear how the PSS relates to levels of anxiety and it may not be a suitable proxy. The other studies all reported a stable or slightly decreasing mean across

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pregnancy and the postpartum. However, this must be interpreted with caution, as most of these studies included only two time points, potentially obscuring variation over time. Two studies did examine multiple time points and found stable estimates, strengthening confidence in the other studies' results [37, 62].

The studies presenting prevalence and means of anxiety symptoms over time, like the studies of depression symptoms, are limited in the conclusions that can be drawn from their results. If the prevalence studies by Adewuya and Aflabi [34] and Stuart et al. [35] are accurate and there is a variation in prevalence, how can the mean of the population be stable as the majority of those studies suggest? Mathematically, it is possible to have the same mean if the prevalence shifts. For example, Adewuya found a decrease in prevalence over time [34]. If those who scored above the cut-point had reduced anxiety over time, but those who had been below had an increase in anxiety symptoms while remaining below the cut-point, no change in mean would be detected. It is also possible that these studies are showing natural variation of anxiety symptoms in different populations. Stuart et al. [35] reported on a population in the U.S., while Adewuya studied Nigerian woman [34]. Finally, like the studies of depression symptoms, these studies utilize repeated cross-sectional assessment. This group-level measurement does not provide information on individual courses of anxiety symptoms. Those who are anxious early in pregnancy may not be the same women as those who are anxious in the postnatal period.

The final limitation is that these studies present group summary information only. They do not provide an assessment of changes at the individual level. Thus, it is not clear if the same women who are anxious prenatally are those who are anxious postnatally. This is similar to the limitation in the depression literature. Only one study provided descriptive information at the individual level. Heron et al. reported that 73% of the sample had no elevated anxiety, 2% had

consistently elevated anxiety, 10% of their sample were highly anxious at only one prenatal assessment, 4% at only one postnatal assessment, 4% were anxious only prenatally, and 1% were anxious only postnatally [8]. The remaining 6% were spread evenly across the remaining possible patterns. This study has yet to be replicated and no risk factors or effects of the different patterns were examined.

1.3 CO-OCCURRING SYMPTOMS DURING AND AFTER PREGNANCY

High co-occurrence between symptoms of anxiety and depression is widely recognized in the literature [5, 63]. However, there has been little work examining co-occurring anxiety and depression symptoms during pregnancy and the postpartum. Only two studies were identified that examined patterns of co-occurring symptoms over time. Lee et al. reported on the patterns of co-occurring depression and anxiety symptoms in an prenatal sample of pregnant women in Hong Kong [36]. Their results suggested a slightly "J-shaped" prevalence pattern, with 14% co-occurrence in the first trimester, 13% in the second, and 17% in the third trimester. Adewuya and Aflabi reported the pattern of co-occurrence in their sample of postnatal Nigerian women [34]. They found a generally decreasing prevalence of co-occurring elevated anxiety and depression symptoms over the postpartum: 10% one week post-delivery, 5% at one month, 7% at two months, 5% at three months, 4% at six months, and 3% by eight to nine months postpartum. No attempts have been made to replicate these findings. Furthermore, they report only on group-level data, limiting their usefulness. Without individual level data, it is unclear if the reduction in co-occurring symptoms is due to an amelioration of both depression and anxiety symptoms or a transition to a "purer" manifestation of anxiety or depression.

There are a number of challenges to studies examining depression and anxiety symptoms that arise as a result of the high co-occurrence of depression and anxiety symptoms. First, there is some evidence that the EPDS, the most commonly used scale for depression in this period, does not have good discriminate validity when it comes to anxiety symptoms. Coulthard and Harris found significant correlations between EPDS scores and STAI scores at every visit, with some correlations as high as 0.83 [62]. Stuart et al. found similar results of equal magnitude [35]. One Australian study examined the overlap of depression and anxiety symptoms in the EPDS by assessing depression using both the EPDS and the Depression and Anxiety Stress Scales (DASS) [64]. When they compared the proportion of women identified by these scales, they found that 12% of the 25% of women identified as "likely depressed" by the EPDS were classified as anxious by the DASS, but not depressed. Thus, it is difficult to discern if effects found based upon EPDS assessment are due to depression symptoms, anxiety symptoms, or both, which may be important toward guiding treatment decisions.

The high co-occurrence of symptoms also affects the ability to discern differential effects of anxiety and depression by over-controlling in standard regression models. If statistical analyses include both anxiety and depression, the two may mathematically cancel the effects of one another leaving the model significant but the individual effects not significant. This answers a different question than what is usually intended in such models. The high correlation changes the research question to: After controlling for the co-occurring effect of depression and anxiety, what additional effect does anxiety or depression alone exert? This may have an impact on the conclusions drawn by previous research, hiding potentially significant effects. However, most studies have only examined anxiety or depression, ignoring the co-occurrence of symptoms.

Such a study design does not address the possibility of effect modification due to co-occurring symptoms.

1.4   EFFECTS OF DEPRESSION AND ANXIETY SYMPTOMS

With at least 10% of children exposed to maternal depression and/or anxiety symptoms during the critical prenatal and postnatal periods, the consequences of such exposures are of great significance. During gestation, anxiety may trigger the psychological stress response in the mother, which may affect fetal development. After delivery, the impact of depression and anxiety symptoms operate through environmental mechanisms, such as interrupting the normal development of mother-child attachments.

1.4.1   Prenatal effects

During the prenatal period, alterations in maternal physiology can have profound effects on fetal development. Both clinical depression and anxiety disorders as well as elevated anxiety and depression symptoms have been linked to dysregulation of the hypothalamic pituitary adrenal (HPA) axis [65, 66]. The HPA axis is an integral part of the stress response system. In response to a stressor, the hypothalamus releases corticotrophin-releasing-factor (CRF), which starts a cascade of system-wide changes designed to prepare the body's response to danger. When CRF is released, it triggers the pituitary to produce adrenocorticotropin hormone (ACTH) which, in turn, triggers the adrenal gland to produce cortisol. Cortisol impacts both the brain and the body. In the brain, cortisol triggers activity in the amygdala, hippocampus, prefrontal cortex,

and the brainstem. In the rest of the body, HPA products increase heart rate, cause vasoconstriction, increased respiration rate, and decreased digestive motility [67, 68].

The HPA axis, when fully functional, has a negative feedback mechanism to regulate the stress response. Chronic stressors, however, can lead to system exhaustion and damage this regulatory mechanism, primarily at the hippocampus [65]. Symptoms of chronic stress include feelings of anxiety and depression. Furthermore, it has been suggested that some anxiety disorders, particularly generalized anxiety disorder, are a prodrome of depression signaling the start of HPA dysregulation [69].

During pregnancy, the HPA axis takes on additional biological importance. CRF plays an important part in ova implantation and maternal immune tolerance to the fetus [70]. Excess CRF can lead to pregnancy complications including intrauterine growth restriction, preeclampsia, and preterm labor [70]. Around mid-gestation, the placenta begins to release its own CRF into the mother's bloodstream at detectable levels, which continue to rise through the end of pregnancy. Cortisol also rises during this period and both cortisol and CRF readily pass the placental barrier [71].

It has been suggested that the combination of normal increases in CRF and cortisol, combined with the dysregulation of the maternal HPA axis associated with depression and anxiety, can have long lasting effects on the child's development. This fetal "programming" hypothesis suggests that alteration of physiology during development programs offspring to be more vulnerable to psychopathology later in life, particularly their own HPA dysregulation [72, 73]. Cortisol is fat soluble and readily crosses the placental barrier, particularly in late gestation [74]. Cortisol levels are also positively associated with levels of testosterone in amniotic fluid, independent of fetal sex, suggesting that stress exposure may cause a cascade of alterations in

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fetal hormone exposure [75]. Such alterations have been linked to delayed maturation levels of newborns [76]. Moreover, the HPA axis response involves alteration of blood flow and subsequently, fetal oxygenation and nutrition, which may cause developmental alterations [72]. In addition, DiPietro et al. found that fetuses have an independent stress response starting around 24 weeks gestation. Thus, they are susceptible to the mother's reaction as well as their own [77].

1.4.1.1 Prenatal depression symptoms

Evidence for the fetal programming hypothesis is growing. Prenatal depression symptoms are associated with adverse obstetrical outcomes including a three-fold increased risk of any pregnancy complication [78], a two-fold increase in the risk of the neonate being admitted to intensive care [79], and 2.5 times the risk of preeclampsia [80]. Elevated prenatal depression symptoms have also been consistently linked with low birthweight and neonates being small for their gestational age [81]. These adverse outcomes are all related to systems functionally affected by CRF and cortisol [81]. Howard et al. found a five-fold increase in the risk of a child suffering from sudden infant death syndrome when their mothers suffered elevated prenatal depression symptoms, but no significant association with postnatal exposure [82].

Hormonally, pregnant women with elevated depression symptoms tend to have higher levels of cortisol and norepinephrine, and lower dopamine [81, 83, 84]. Newborns of these mothers had similar differences in their neurotransmitter and hormone profile [81, 84]. Alterations in CRH, cortisol, norepinephrine, and dopamine have consistently been linked to affective disorders including depression and anxiety disorders, suggesting possible dysregulatory effects linked to prenatal depression symptom exposure [68, 81, 85-87].

Structural brain differences in infants exposed to elevated prenatal depression symptoms have also been detected. In a small study of infants less than 24 hours old, children of mothers

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with probable depression had significantly poorer motor scores, poorer ability to orient, more irritability, and less activity [81]. In a larger study, EEG activation was higher in the right frontal area in offspring of mothers with probable depression and the infants had poorer vagal tone, an indication of dysregulation of the autonomic nervous system [81, 88]. Frontal cortex abnormalities have also been linked to attention deficit hyperactivity disorder [89, 90] and clinical depression [91].

Alterations in neurotransmitter activities and structural brain differences in offspring exposed to elevated prenatal depression symptoms may lead to an increased risk of psychiatric illness in later life. However, studies examining behavioral outcomes in relation to prenatal depression symptom exposure are scarce and have had mixed results [92]. Diego et al. reported more fussing and crying behavior and less optimal scores on neurobehavioral assessments among infants exposed to prenatal depression symptoms [93]. In contrast, Perren et al. found no association between maternal depression symptoms throughout pregnancy and measures of infant difficulty or fussiness. Neither of these studies examined anxiety, although Perren and colleagues evaluated psychosocial stress, which was associated with infant difficulty [37]. Furthermore, these assessments were done in infants up to 18 months old. The relation to risk for psychopathology later in life is unclear.

Behavioral and emotional problems have been studied among older children as well. In preschool children, Mohan et al. found no association between elevated prenatal depression symptoms and behavior problems [92]. Similarly, O'Connor et al. reported that excessive prenatal depression symptoms (as measured by the EPDS) were not associated with four year olds' behavioral/emotional problems. However, elevated pre- and postnatal anxiety and postnatal depression symptoms were associated [94]. The use of regression modeling to control for anxiety

may have obscured an association in this study and their analysis did not model co-occurring symptoms. These results contradict a study by Luoma et al., which found higher externalizing problems among eight- and nine-year-old offspring exposed to prenatal depression symptoms [27]. However, anxiety was not evaluated or controlled. Associations may be confounded by the strong co-occurrence between depression and anxiety symptoms and there is no evaluation of the impact of co-occurring symptoms on risk. The contradiction in findings may also be due to the ages at which the children have been evaluated. Behavioral problems may be more evident in older children. For instance, Maki et al. reported an association (OR=1.6) between violent offences in male offspring and exposure to prenatal depression as reported by the mothers [95]. While the association was slight, it persisted 33 years after exposure. However, maternal depression was not evaluated using a standardized instrument, women were asked mid-gestation if they felt depressed. Use of repeated, standardized assessments would have strengthened the reliability of the results of this study.

These studies have shown mixed results with regard to the association between child psychological outcomes and prenatal symptoms of depression. While they provide indirect evidence of potential outcomes in later life, they did not use clinical diagnoses of psychiatric disorders. Many disorders have risks of onsets that increase following puberty, having highest incidence in adolescents and young adults. Anxiety disorders and depression become much more common starting in adolescence [96]. Thus, a failure to find behavioral effects earlier in life does not negate the possibility of effects later. None of these studies evaluated the impact of comorbidity and many of them may have statistically over-controlled due to co-occurring symptoms.

1.4.1.2 Prenatal anxiety symptoms

There is little research on the psychological effects of prenatal anxiety symptoms. As in depression, prenatal anxiety symptoms induce hormonal changes in the fetus, including increased levels of CRH, adrenocorticotropin-releasing hormone, and corticosterone [97]. Early in pregnancy, maternal anxiety levels have been associated with plasma cortisol levels, which are correlated with amniotic fluid cortisol levels [98]. The majority of research has focused on pregnancy complications with regards to anxiety symptoms, with results similar to the cortisol-related complications evidenced in depression, suggesting similar mechanisms behind anxiety and depression during pregnancy.

Only three studies were identified that examined behavioral/emotional outcomes in children exposed to prenatal anxiety symptoms. Davis et al. found prenatal anxiety symptoms were related to negative behavioral reactivity to novel stimulus in infants, after controlling for postnatal exposure [16]. O'Connor et al. reported on behavioral and emotional problems in four year olds exposed to prenatal anxiety and again when the children were six. They found significantly more problems in boys and girls exposed to prenatal anxiety after controlling for prenatal depression symptoms and postnatal mood at four years [59], and again at six years [99]. The effect of exposure to prenatal anxiety symptoms on the risk of psychiatric illness in adolescents has not been explored. There is indirect evidence that general stress during pregnancy is related to adverse psychiatric outcome. However, these studies do not distinguish between depression and anxiety effects so their results can only indirectly support the hypothesis that psychiatric illness is related to prenatal anxiety exposure [97, 100, 101].

1.4.2   Postnatal effects

Exposure to maternal depression and anxiety symptoms during the postnatal period may not have the direct biological effects of prenatal exposure; however it is still a critical period of development. During the postnatal period, infants and mothers bond and the early emotional experience of the type of bonding sets up attachment patterns that may stay with children throughout their lives [102]. Evidence that attachment styles may increase the risk of psychiatric illness in later life has been demonstrated in schizophrenia [103], personality disorders [104], substance abuse [105], depression [106], eating disorders [107, 108], and psychopathology in children and adolescents [109, 110]. Moreover, different attachment patterns have been linked to higher levels of infant cortisol secretion in a reciprocal relationship potentially leading to HPA dysregulation [111].

1.4.2.1 Postnatal depression symptoms

Depression and depressive symptoms in the postnatal period have received a great deal of attention in recent years. Numerous studies have linked postnatal depression and related symptoms with adverse outcomes in children [112, 113]. One study by Murray et al. found that mothers suffering from elevated postpartum depression symptoms had different communication styles with their infants than non-depressed mothers, including less focus on the infant and more negative affect [114]. This disruption of mother-infant interactions may impair bonding and form part of the mechanism through which postnatal depression may increase risk of later psychiatric illness.

Several studies have examined behavioral and emotional problems in offspring of postpartum depressed mothers. As early as 1985, research showed an association between behavior problems and postnatal depression symptoms [115]. This study found that brief periods of elevated postpartum depression symptoms were associated with significant behavior problems in three year olds. Moehler et al. found higher fear and behavioral inhibition in 14-month-old infants of mothers with probable clinical depression [116]. Gao et al. found more internalizing disorders in symptom-exposed two year olds, but no increased risk of externalizing disorders [117]. This would be consistent with the findings in younger children with greater fear response. However, neither of these studies controlled for prenatal exposures or other comorbid disorders, leading to ambiguity when interpreting the results.

Luoma and colleagues examined both pre- and postnatal depression symptom exposure [27]. While they found that postnatal depression symptoms were linked to lower social competence in children, it was prenatal exposure that was associated with total problem behaviors. One concern with these studies is the potential for biased reporting. Depressed mothers may pay more attention to negative events or interpret behavior as more negative than non-depressed parents. This hypothesis was confirmed in a study by Najman et al. who found mothers with elevated depression and anxiety symptoms reported more negative behaviors than healthy mothers and more negative behaviors than the children themselves [118]. Only one study was identified that attempted to externally validate these reports. Sinclair and Murray found that teachers' reports of child disturbance were associated with the child's exposure to clinical postpartum depression [119].

Not all studies have found a positive association between postnatal depression and child behavioral problems. Caplan et al. found that currently clinically depressed mothers had 4 year

olds with more behavioral problems, but it was current depression not postnatal depression that was associated with these problems [15]. Philipps and O'Hara also found no association between behavior problems in 4½ year olds and their exposure to clinical postnatal depression. However, problems were associated with later episodes of maternal depression [120].

A few studies have been performed with older children and adolescents focusing on the effects of clinical levels of maternal depression. At the biological level, Halligan et al. found that there were higher and more variable levels of cortisol in adolescents exposed to postnatal clinical depression [121]. A recent study by Pawlby and colleagues found increased psychopathology in 11 year olds exposed to postpartum depression, as diagnosed by clinical interview [122]. Similarly, Hay et al. found an increased risk of violence at age 11 in children exposed to postpartum clinical depression. This was independent of subsequent exposure to maternal depression and results were confirmed by teacher's reports [123]. Finally, Halligan et al. found an increased risk of depression and anxiety in adolescents exposed to postnatal clinical depression, even after controlling for later exposure [124].

While depression during the postnatal period has received more attention than prenatal depression, it has suffered from substantial methodological problems. The majority of studies have not controlled for the prenatal effects of depression. Given the repeated findings that those suffering postnatal depression likely experienced prenatal depression, differentiating the effects of pre- versus postnatal depression is difficult. One exception is a study by Diego et al. in 2005, which examined infants of women who experienced elevated prenatal depression symptoms, postnatal depression symptoms, both, and neither [125]. Infants exposed to prenatal or pre- and postnatal probable depression expressed a difference in stress reactions, more fussiness, and less time awake and alert. Only infants exposed to both pre- and postnatal probable depression were

more active than children not exposed to depression. To date, no study identified has examined the risk factors related to exposure to the most frequently experienced trajectories of depression symptoms and their subsequent relation to the development of psychiatric disorders.

1.4.2.2 Postnatal anxiety symptoms

The psychiatric effect of exposure to postnatal anxiety has been the subject of very little research. Only three studies were identified exploring these outcomes, two of which utilized the same cohort of subjects. In 1991, Barnett and colleagues reported on the association between postnatal anxiety symptoms and behavior problems in children, as measured by the Child Behavior Checklist [126]. They found that five year olds of highly anxious mothers were less active and socially competent. In boys, there was also an association with anxiety and being more immature, delinquent, and schizoid. These results were only found among mother's ratings, however, and were not confirmed by teacher's reports. As the children in this study were between five and six, it may be that teachers of this age group were not able to detect differences that might be more marked at home. Anxious mothers may be more biased in their reporting of negative behaviors. This study had several limitations. First, depression was not assessed. Second, prenatal exposure to anxiety symptoms was not examined. The highly anxious mothers in this study were randomly allocated to treatment or standard care, and while there was a reduction in anxiety symptoms displayed by mothers in the intervention group, this did not translate into differential outcomes in their children. It may be that the intervention did not reduce anxiety enough to be effective in helping child outcomes or, the results may have occurred due to prenatal exposure, which was not assessed. Other possibilities include biased results due to unassessed confounding factors, such as drug use and paternal psychiatric status.

In a population-based study of over 6,000 women in England, O'Connor and colleagues reported on the effects of exposure to postnatal anxiety symptoms with regard to emotional and behavioral problems in four year olds [59] and again in six to seven year olds [99]. This study was the only one identified that evaluated anxiety and depression symptoms during both the prenatal and postnatal periods. In four year olds, the risk of emotional problems was 50% higher in boys and girls exposed to postnatal anxiety, independent of prenatal anxiety and depression symptoms, and postnatal depression symptoms [59]. Exposed girls were at a 45% increased risk of conduct problems after controlling for depression throughout pregnancy and the postpartum and prenatal anxiety. By age six, the increased risk for emotional problems in boys was 60%. However, there was no longer an association in girls [99]. The risk of conduct problems in exposed girls at age six had strengthened to a two-fold increased risk. In such an analysis, controlling for co-occurring symptoms and prenatal exposure was only possible due to the large sample size. The study also controlled for a large number of potential confounders including substance use, obstetric factors, socio-economic status, tobacco use, etc. These results suggest that postnatal anxiety exposure increases the risk of behavioral and emotional problems in children in excess of the risks associated with prenatal anxiety exposure and exposure to pre- or postnatal depression. Thus, the total risk associated with exposure to both pre- and postnatal anxiety and depression is likely higher. These findings have not been replicated however, and as exposure was assessed at individual time points, they do not represent the risk associated with common exposure patterns, only the risk associated with having been exposed at some point during the prenatal period, postnatal period or both.

1.5   SUMMARY

Evidence is suggestive that pre- and postnatal depression and anxiety symptoms are associated with later mental illness in offspring. However, the research is sparse and inconsistent and no studies have used clinical diagnosis of psychiatric disorders as their end point. The evidence suggests that this remains an important area for further research.

Several common weaknesses were evident throughout the literature evaluating the effects of exposure to pre- and postnatal depression and anxiety symptoms on the later risk of psychiatric problems in offspring. First, there is limited research on prenatal depression and anxiety, and on postnatal anxiety. No studies have evaluated prenatal depression, prenatal anxiety, or postnatal anxiety exposure and the risk of psychiatric outcomes in adolescents.

Second, studies that have evaluated the patterns of maternal symptoms over time have examined group-level changes only. Only one study evaluated individual level trajectories of depression symptoms and no studies have examined patterns of anxiety symptoms or of co-occurring depression and anxiety symptoms. Furthermore, most studies examining outcomes of maternal depression and anxiety symptom exposure have looked at exposure at a certain time point, instead of investigating exposure patterns over time and evaluating the effects of these patterns on the risk of psychiatric illness. Methods for statistically controlling for exposure during other periods may over-control for confounding and obscure important outcomes that result from a cumulative exposure. Evaluating commonly-occurring patterns of depression and anxiety experienced by pregnant women eliminates the need to statistically control for pre- versus postnatal exposures, while providing an understanding of the effects of the most common experiences of symptoms on the risk of psychiatric illness in offspring.

Third, most studies have not examined co-occurring anxiety and depression symptoms. Those that have examined co-occurring symptoms have provided descriptive patterns only. Studies that include both anxiety and depression together in regression models do not model co-occurrence, which might have additive or multiplicative effects. While these studies may help isolate specific timing effects, they do not represent the more naturalistic exposure scenarios and their effects.

Finally, none of these studies have evaluated the pathways involved between exposure to maternal depression and anxiety symptoms and psychiatric illness in the offspring. Understanding of these pathways is essential to identifying potential targets for interventions. Without an understanding of the process, prevention of the long-term consequences of this exposure will be more difficult.

The following research was designed to address these weaknesses. The first paper evaluates the most common patterns of symptoms of anxiety, depression, and co-occurrence experienced by mothers during the pre- and postnatal periods. It also evaluates risk factors associated with these trajectories. The second paper evaluates the association between the trajectories and the risk of later psychiatric illnesses in the adolescent offspring. The third paper examines theorized mechanisms between the psychiatric outcome, Conduct Disorder, and exposure to symptom trajectories, specifically anxiety symptoms.

2.0 PAPERS

2.1 PAPER 1: TRAJECTORIES OF MATERNAL DEPRESSION AND ANXIETY SYMPTOMS ACROSS PREGNANCY AND THE POSTPARTUM

2.1.1 Abstract

Background: Depression and anxiety symptoms during pregnancy and the postpartum are associated with negative outcomes in women and children. However, few studies have examined individual-level patterns of depression and anxiety symptoms.

Methods: Growth Mixture Modeling was used to examine trajectories of depression and anxiety symptoms from the first trimester of pregnancy through 18 months postpartum. Depression and anxiety trajectory group membership was then examined in relation to combined symptom patterns and trajectory correlates.

Results: Trajectories of depression and anxiety symptoms were stable over time. Evaluation of depression trajectories revealed two groups: low and high. Three anxiety groups were identified: low, medium, and high. Depression and anxiety trajectories were highly correlated with each other. Women in the high depression trajectory smoked more cigarettes and had lower social support. Education and social support were negatively associated with being in the higher anxiety trajectory. Social support was the only correlate of the combined symptoms trajectories.

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Conclusions: Symptoms of depression and anxiety are stable across pregnancy and the postpartum. Therefore, early screening can detect women at risk during both periods. Women experiencing elevated depression symptoms are likely to experience elevated anxiety. Low social support is associated with higher symptom levels and may provide an avenue for clinical intervention.

2.1.2   Introduction

Elevated symptoms of depression and anxiety over the course of pregnancy and the postpartum have been linked to adverse outcomes in mothers [127, 128] and children [9, 10, 13, 14, 97, 129, 130]. A substantial portion of women and children are exposed to these symptoms. In the antenatal period, approximately 19% of women will experience antenatal depression [8], which is associated with prenatal, birth, and postnatal complications [81]. In the postpartum, clinical depression affects approximately 13% of women [8, 131] and is linked to significantly lower health-related quality of life in mothers [127] and delays in cognitive and motor development in exposed children [9, 14, 42]. Clinically significant anxiety during pregnancy affects an estimated 22% of women and is related to an increased risk of perinatal and delivery complications [132], as well as higher rates of behavioral/emotional problems in the offspring [99]. Postnatal anxiety, although less studied than postnatal depression, is a topic of growing interest. Estimates from a community sample found that 13% of women experienced elevated postnatal anxiety symptoms, similar to postnatal depression symptoms [8]. Effects of postnatal anxiety are less well understood, but some research suggests it may be related to more difficult infant temperament [133-135] and impaired mother-child interactions [136].

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While it has been established that depression and anxiety symptoms during and after pregnancy can have negative consequences, there are a number of gaps in current knowledge. First, the study of course of symptoms over time has yielded conflicting results, varying by population, assessment timing, and symptom measure. One of the earliest studies of postpartum depression found an increase from 9% to 12% in the prevalence of elevated symptoms between the second trimester and nine weeks postpartum in a community-based sample [19]. By contrast, a study in Japan found no change in the estimated 12% prevalence between the antenatal and postnatal period in a community sample of primiparous women [137]. However, both of these studies utilized only two time points, which are not enough time points to observe variation over time.

Two studies reported prevalence estimates of elevated depression symptoms at multiple antenatal and postnatal time points in the general population. Matthey and colleagues found that the initial 12.3% antenatal prevalence decreased to 8% at six weeks postpartum, but increased back to 12.4% by one year [31]. Another study found a decrease in postnatal depression symptoms from the antenatal to the postnatal period from 11.4% at 18 weeks gestation to 13.1% at 32 weeks gestation, to 8.9% and 7.9% at eight weeks and eight months postpartum, respectively [8]. A community-based study in the United States, which examined depression symptom patterns in the postpartum only, found a decrease between 14 and 30 weeks postpartum (23.3% to 18.7%) [35]. This finding is similar to the Heron et al. [8] study with respect to pattern, but the prevalence estimates are over twice that of Heron et al.'s results. A community-based study of Nigerian women found a very different postpartum pattern. Depression at one week postpartum was almost 20%, decreased by half at four weeks, increased again by 12 weeks (~15%), then decreased to 8.1% by 36 weeks postpartum [34]. The differing results of these

studies may be indicative of differences in assessment timing, instruments used, and the populations studied.

Studies examining anxiety symptoms over time are sparse. Three studies were identified examining the course of anxiety symptoms during pregnancy and the postpartum, only one of which assessed both time periods. Heron and colleagues studied a community-based sample of women and found a steady antenatal prevalence, 14.6% at 18 weeks and 15.6% at 32 weeks gestation [8]. This decreased to 8.1% at eight weeks postpartum and remained steady by eight months. The two studies focusing on postnatal anxiety found conflicting results. The Nigerian study found a decrease between one week postpartum (28.1%) and 36 weeks postpartum (6.3%), which leveled off between eight and 12 weeks (~10%) in a community sample [34]. The third study of community-based women found a twofold increase in anxiety symptom prevalence between 14 and 30 weeks postpartum (8.7 to 16.8%) [35]. These conflicting results, as well as the lack of antenatal studies, demonstrate the need for further research on the pattern of anxiety symptoms.

The second limitation of the current literature is the use of repeated cross-sectional measurements to describe patterns over time. While this allows for a basic overview of the general prevalence patterns of symptoms, it does not permit the evaluation of symptom patterns at an individual level. This design cannot establish if those with elevated postnatal anxiety or depression symptoms are the same women who had elevated antenatal symptoms. While the Heron study in the United Kingdom provides some information on what percentage of women go on to develop symptoms at each phase [8], only two studies have statistically evaluated intra-individual symptom changes [28, 51].

In 1996, Fergusson and colleagues evaluated patterns of depression symptoms and the probability of changes in diagnostic status from 18 weeks gestation through 32 weeks postpartum in a non-clinical sample [28]. The study found that the best model for the data defined three trajectories: one consistently non-depressed group accounting for 57% of the sample, another group of women who were not depressed initially, but were "vulnerable" to developing depression (37%), and a third who were depressed at the first assessment and remained so (6%). Recently, Mora et al. reported on a study of over 1,700 community-recruited women and found five trajectory patterns [51]. The majority of women (71%) had no depression during pregnancy and the postpartum, 7% had consistently elevated depression symptoms, 6% had elevated depression during pregnancy only, 9% had elevated symptoms early in the postpartum, and 7% had late postpartum symptoms only. The different findings across studies might be explained by differences in population and assessment timing so additional research is needed to identify the source of the inconsistencies.

The third limitation of the existing literature is that the patterns of both depression and anxiety symptoms have rarely been examined in tandem despite the frequent co-occurrence of these symptoms. One study of Nigerian postpartum community-sampled women found that up to 9.8% of their sample had comorbid depression and anxiety [34]. This was similar to the 7% reported in an Australian study of community-sampled women [64]. Without examining the patterns of individual or co-occurring symptoms, it is impossible to tell if risk factors are the same for the individual and co-occurring trajectories.

The goals of the present study were to improve upon the existing research by utilizing recent advancements in statistical methods for longitudinal designs. First, individual trajectories of maternal depression and anxiety symptoms across pregnancy and the postpartum were

analyzed using growth mixture modeling (GMM) [138, 139]. GMM permits the identification of different latent classes of individuals' symptom patterns over time. Second, symptom trajectories were examined in tandem to determine if anxiety and depression symptom patterns were interdependent. Third, correlates of individual trajectory group (depression or anxiety) membership were assessed. Finally, correlates of the co-occurring trajectory patterns (depression and anxiety) were assessed to determine if correlates associated with combined group membership were different than the individual symptom trajectories.

2.1.3   Methods

2.1.3.1 Participants and Procedures

From 1982 to 1985, adult, English-speaking women were recruited through a hospital-based outpatient prenatal clinic during their fourth or fifth month of pregnancy (N. Day, P.I. [140, 141]). Initial refusal for participation was 15%. The first interview was administered to 1,360 women as part of two longitudinal studies on the effects of prenatal alcohol and marijuana exposure on offspring development. The alcohol cohort included all women who drank on average at least three alcoholic drinks per week and a random selection of one-third of those who drank less or abstained. The marijuana cohort included all women who smoked two or more joints per month and a random sample of those who used less. The sampling was done with replacement so women could be chosen for one or both cohorts. Twenty-six percent of this sample abstained from alcohol and drug use in their first trimester.

This analysis combines the alcohol and marijuana cohorts because both studies were conducted simultaneously with the same protocol and instruments. Assessments included in this analysis were the 1st and 2nd trimester, delivery, and 8 and 18 months postpartum. Each phase of

assessment included measures examining psychological status, drug use, social support, and demographics. A medical records review after delivery obtained data on pregnancy, labor, and delivery complications.

The combined cohorts consisted of 829 women who were selected for the study. By delivery, this was reduced to 763; 21 had moved, 16 were missed, 8 refused the delivery assessment, 2 were multiple births, 18 were lost to maternal or infant death, and 1 infant was placed for permanent adoption and could not be followed. This report is the first step in a larger project examining whether symptom trajectories in mothers predict psychiatric illness in their offspring. Therefore, only women whose children had psychiatric diagnostic assessments at age 16 were included in this analysis. This left 577 individuals (76% of the birth cohort) available for analysis. Women excluded from this analysis (n=186) were more likely to be Caucasian (58% in the excluded group versus 45% in the included group) and to have given birth to a male child (58% in the excluded group versus 48% in the included group), and less likely to have used marijuana prior to pregnancy than were the women included in the analysis (38% in the excluded group versus 42% in the included group). There were no differences in any other covariates (Table 1 lists included covariates), including depression and anxiety score.

Written informed consent was obtained from all participants and the study was conducted according to the University of Pittsburgh's Institutional Review Board and Magee-Womens Hospital's Research Review and Human Experimentation Committee.

2.1.3.2 Measures

The two main outcome variables were depression and anxiety. Depression symptoms were measured at each phase using the *Center for Epidemiological Studies Depression Scale* (CES-D) [24]. The CES-D is a 20-item scale with a 4-point Likert response scale measuring

frequency of depression symptoms (e.g., "I felt sad": rarely/none of the time, some/a little of the time, occasionally/a moderate amount of the time, and most/all of the time). At the first trimester measurement, depression was framed with the statement "Since you've been pregnant": subsequent assessments did not specify a time criteria. Possible scores range from 0 to 60 with higher scores indicating more symptoms, a cut-point of 16 is usually used to indicate probable clinical depression. The CES-D has been used frequently in studies of pregnant women [22, 40] and has strong psychometric properties in clinical and general populations [24, 142].

Anxiety was measured at each phase using a study-specific, modified version of the trait scale of Spielberger's *State-Trait Anxiety Inventory* (STAI) [143]. The modified scale was originally published as the *State-Trait Personality Inventory* (STPI) [144]. The STPI is almost identical to the more recognized STAI trait short form. Two questions have slight wording changes and one question asks conceptually the same question with a clearer wording. The more substantial wording change was deemed necessary due to the lower education of the majority of the participants. Trait anxiety (T-anxiety) assesses a person's propensity to react to threatening stimuli with anxiety [145]. It can be thought of as a measure of the susceptibility to state anxiety, which is the acute experience of anxiety. The trait scale consists of questions such as "I feel at ease," with a 4-point Likert response scale ranging from almost never to almost always. Scores ranged from 10 to 40. The STAI has excellent psychometric properties and has been used repeatedly in studies of pregnant and postpartum women [56, 146, 147]. The Cronbach's alpha for this sample at baseline was .87.

Potential risk factors were determined based upon established risk factors for postnatal depression and anxiety [14, 20, 128, 131, 132]. Variables included: race (white/black), maternal age, education, marital status (yes/no), work status (employed or student/none), and family

income, all of which were assessed at the first trimester assessment. Number and type of pregnancy, labor, and delivery complications were abstracted from medical records shortly after delivery. Social support was measured in the first trimester using questions designed by the Human Population Laboratory, such as "Is there one special person that you feel very close to… someone you can talk to about your most private feelings?" [148]. Stressors were assessed with a modified version of the PERI Life Events Scale [149]. This scale asks about the occurrence of a number of common life events and how stressful they were to the respondent. Examples include "Had trouble with a boss" and "Became engaged". Information on life stressors was not collected until the delivery assessment.

Drug use was assessed using measures specifically designed for this study. A detailed description of the measures and their reliability is published elsewhere [150, 151]. Substances assessed included alcohol, cigarettes, marijuana, cocaine, and other illicit drugs. Data on pre-pregnancy and current substance use were collected for all substances except cigarette use, for which only current use was collected. Both quantity and frequency of use were ascertained and converted into average daily drinks and joints for alcohol and marijuana, respectively. Cocaine and other illicit drugs were measured dichotomously. Cigarette use was categorized for this analysis into less than one, 1 – 19, and 20 or more cigarettes per day, based on the baseline distribution. In all analyses, data from the earliest available assessment was used. For most variables, this was the first trimester assessment. However, pre-pregnancy drug use was available and therefore was used as a predictive covariate.

2.1.3.3 Statistical Procedures

Trajectory analysis was performed using the GMM function of Mplus [152]. GMM allows for the identification of subgroups of similar individuals from among the sampled, more

heterogeneous, group. In this way, it is more informative than traditional growth modeling, which provides a single growth curve for the entire sample and assumes the homogeneity of individuals [3]. In this analysis, two sets of trajectories (i.e., latent classes) were examined: trajectories characterized by depression symptoms over time and trajectories characterized by anxiety symptoms over time.

The depression and anxiety trajectory models were identified separately. The first step was to identify the optimal number of trajectory groups for each symptom set. This was done by consecutively modeling an increasing number of groups until non-convergence was reached, then evaluating several fit criteria, including: the Bayesian Information Criteria (BIC), the sample size adjusted BIC, the Akaike Information Criteria (AIC), entropy, and the Lo, Mendell, and Rubin statistic. The a priori criterion for best fit was the model with the most ideal indicators on the fit indices. In case of a tie, the most parsimonious model was selected [153]. After the number of groups was determined, the shape of each trajectory was examined. To determine trajectory shape, parameters from intercept only through a quadratic growth curve were tested for significant contribution to the model.

Once the trajectory models were established, participants were classified into their most likely trajectory based upon the posterior probability. Group membership for depression and anxiety symptom trajectories were then cross-tabulated to determine combined trajectory memberships. While joint trajectories allowing for correlation among trajectory variables (depression and anxiety) is possible in Mplus, the high correlation between depression and anxiety trajectory membership prevented the identification of this joint trajectory, necessitating the use of cross-tabulation of trajectory membership instead of the modeling of a joint trajectory.

The final step in the analyses was to analyze correlates of trajectory group membership. To determine if risk factors for trajectories were different for depression groups, anxiety groups, and the combined trajectory groups, each set was modeled separately. Logistic regression, ordinal regression, and multinomial regression models were used to evaluate correlates of trajectory membership depending upon how many trajectories were identified in the symptom models. For each outcome (depression, anxiety, or combined symptom trajectory), univariate Chi-square and one-way ANOVA tests were run first on risk factors and correlates. Variables were retained in the regression model if the significance was less than 0.1 in the univariate model. The more conservative cut-point of .1 instead of .05 for keeping variables in the model helps ensure that important potential confounding variables are kept in the model regardless of their individual significance level.

2.1.4   Results

2.1.4.1 Descriptive Statistics

The average age of the 577 women in this analysis was 22.9 years (SD=3.9), about half were Caucasian (45%), the rest African American (see Table 1). At the first trimester assessment, a third of the sample was married (32%), 26% were employed and/or attending school, the mean family income was $345 a month at baseline (1982-1985), and the average completed education was 11.8 years (SD=1.37). On a scale of zero to four (four being the highest level of support), the mean social support score was 3.3 (SD=0.6). Depression scores were high in the sample when compared to the traditional CES-D cut-point of 16; the mean CES-D score was 21.1 (SD=8.7). The average trait anxiety score was 17.8 (SD=4.8). Approximately half of the sample (52.3%) smoked less than a cigarette per day, a third (32.6%) smoked between 1 and

19 cigarettes daily, and 15% smoked a pack or more per day. The average pre-pregnancy alcohol use was 1.2 (SD=2.1) drinks a day and the average pre-pregnancy marijuana use was 0.8 (SD=2.1) joints per day. Eleven percent of the sample reported using cocaine prior to pregnancy and 30% reported other illicit drug use prior to pregnancy.

At the delivery assessment, the average number of stressful life events reported was 1.7 (SD=1.8). There were a large number of medical complications related to pregnancy in the sample. Sixty-four percent of women experienced pregnancy complications which included any disorders during pregnancy, such as poor weight gain, infection, or diabetes; 44% experienced complications of labor such as placental conditions, infection, or toxemia; and 81% had delivery complications or conditions such as anesthesia use, prolapsed cord, cesarean section, or breech delivery.

2.1.4.2 Depression Trajectories

Models for two through four latent classes were fit to identify homogenous subgroups of depression symptom patterns across the five assessments (1st and 2nd trimester, delivery, and 8 months and 18 months postpartum). Models specifying five latent classes universally failed to converge. One of the strengths of GMM is the ability to manage unequal assessment intervals by either specifying the intervals on a fixed scale, freely estimating the time interval, or a combination of the two. The first three assessments were at regular intervals (1st through 3rd trimester), while the final two assessment intervals (8 months and 18 months postpartum) varied. Several models were tested both allowing for free estimation and fixing the estimates on a three month scale. Parameter estimates of intercept, slope growth term, and quadratic growth term were tested for each model. There was no evidence of quadratic growth, based upon the z-test for

Table 1: Descriptive statistics for the sample and by symptom trajectory membership.

Variable		Sample (n=577)	Depression Trajectory		Anxiety Trajectory		
			Low	High	Low	Medium	High
		Mean (±SD)	(n=91)	(n=463)	(n=65)	(n= 288)	(n=201)
Age (years)[1]		22.9 (±3.9)	23.2 (±0.5)	22.9 (±0.2)	23.5 (±0.5)	23.0 (±0.2)	22.7 (±0.3)
% Caucasian[1]		45.4	43.2	45.9	37.8	49.2	39.2**
% Married[1]		32.1	35.8	31.3	43.5	32.4**	27.8**
% Working/Attending School[1]		26.0	30.5	25.1	33.3	25.8	23.9
Monthly income[1]		$345 (±$291)	$411 (±34) **	$331 (±13)	$434 (±39)***	$348 (±18)	$313 (±19)***
Education (years) [1]		11.8 (±1.37)	12.1 (±0.2)*	11.8 (±0.1)	12.3 (±0.2)***	11.8 (±0.1)	11.7 (±0.1)***
Social support score[1]		3.3 (±0.6)	3.5 (±0.1)***	3.2 (±0.0)	3.6 (±0.1) ***	3.4 (±0.0) ***	3.1 (±0.1)***
Depression[1]		21.1 (±8.7)	11.5 (±0.5)***	22.9 (±0.4)	13.2 (±0.7)***	18.7 (±0.4)***	25.9 (±0.6)***
Anxiety[1]		17.8 (±4.8)	13.7 (±0.3)***	18.6 (±0.2)	12.7 (±0.2)***	15.8 (±0.1)***	22.3 (±0.3)***
Daily cigarettes[1]	< 1	52.3	63.2**	50.2	52.2	53.5	50.7
	1 - 19	32.6	29.5	33.2	34.8	33.4	30.6
	20+	15.1	7.4**	16.6	13.0	13.0	33.4
Alcohol use[2] (ave. drinks/day)		1.2 (±2.1)	1.0 (±0.3)	1.3 (±0.1)	0.8 (±0.2)	1.3 (±0.1)	1.3 (±0.1)
Marijuana use[2] (ave. joints/day)		0.8 (±2.1)	0.8 (±0.4)*	0.8 (±0.1)	0.7 (±0.2)	0.9 (±0.2)	0.7 (±0.1)
% Using Cocaine[2]		11.4	7.4	12.2	5.8	12.7	11.5
% Using other illicit drugs[2]		30.3	23.2	31.7	20.3	31.8	31.6
# Life events[3]		1.7 (±1.8)	1.4 (±0.2) **	1.8 (± 0.1)	1.5 (±0.2)	1.7 (±0.1)	1.8 (±0.1)
% Pregnancy Complications[3]		63.6	61.6	64.1	56.5	63.5	66.0
% Labor Complications[3]		43.9	40	44.7	37.7	43.5	46.6
% Delivery Complications[3]		81.3	75.8	82.4	79.7	80.3	83.8

Notes: 1. Measured at baseline, 2. Pre-pregnancy use, measured at baseline, 3. Measured at delivery assessment.

*Univariate significant difference between symptom groups, p<.10, **significant difference between symptom groups, p<.05,
    ***Significant difference between symptom groups, p<.01

parameter differences of zero. Growth-factor variances and covariances, as well as class-specific variances and covariances, were freely estimated. The best fit model was a two group solution that fixed the first and second trimesters and delivery. The 18 month postpartum assessment was also fixed using a three month interval scale, while allowing the eight month follow-up interval to be estimated freely. Table 2 presents fit indices for the depression models.

Table 2: Depression model fit indices.

Model		AIC	BIC	BIC (ss)	Entropy	Lo –Mendell-Rubin p-value
# of classes	Fixed time points*					
2	1-3	17483.3	17561.7	17504.6	0.592	0.002
2	1-3,5	17486.1	**17551.5**	**17503.9**	0.512	0.173
2	1-5	17517.0	17569.3	17531.2	0.590	0.422
3	1-3	17486.4	17564.8	17507.7	0.683	0.065
3	1-3,5	17492.6	17579.8	17516.3	0.297	0.634
3	1-5	17488.3	17562.4	17508.4	0.701	**0.000**
4	1-3,5	**17475.7**	17628.2	17517.1	**0.728**	0.965
4	1-5	17486.6	17573.7	17510.2	0.626	0.045

Notes: Abbreviations AIC, Akaike Information Criteria, Bayesian Information Criteria, BIC (ss), Sample size adjusted BIC. Bold indicates the best fit statistic. *1=First trimester, 2=Second trimester, 3=Delivery, 4=8 months postpartum, 5=18 months postpartum.

The two-group trajectory pattern suggests a low and a high symptom group that had a minor decrease in symptoms over the five assessment points (see Figure 1). Approximately 17% (n=95) of the sample were classified into the low symptom group whereas 84% were in the high symptom group (n=482). White and colleagues have reported that a mean classification probability of each group greater than 0.7 is sufficient for standard parametric statistics to be

used to test differences in trajectory groups without concern for classification error [154]. The classification mean was 0.69 for the low symptom group and 0.81 for the high symptom group.
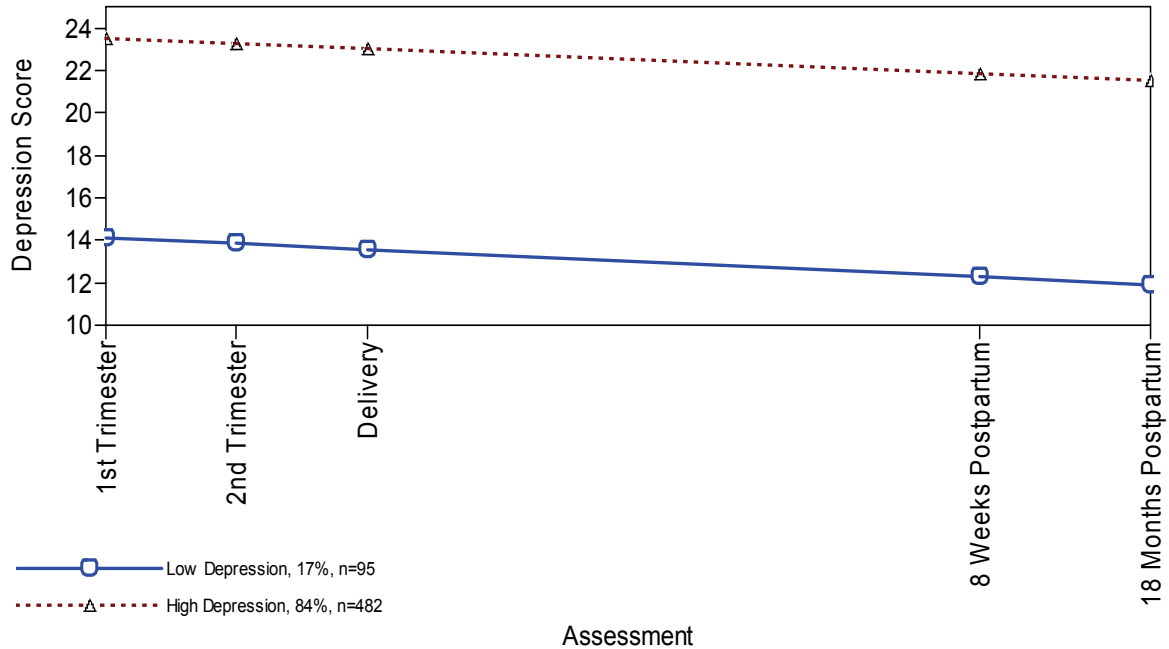
Figure 3: Depression trajectories.

T-tests and Chi-square analyses were used to examine the univariate relationships between trajectory group membership and possible correlates. Table 1 presents descriptive statistics and univariate associations for the depression trajectory groups. Tests of the logistic regression model assumptions indicated that there was a linearity problem with the relationship of social support to the logit (log[p]-log[1-p], where p is the probability of event occurrence). Social support was squared to linearize the relationship. Table 3 presents the final multivariate logistic regression model results. The final model included income, education, social support, cigarette smoking, pre-pregnancy marijuana use, and stressful life events (Table 1). Low social support and cigarette smoking were significantly associated with high depression trajectory membership

after controlling for maternal education, income, stressful life events, and pre- pregnancy marijuana use. For each point increase in squared social support score, the probability of being in the high depression trajectory decreased 15% (OR=0.85, CI=0.78-0.92, p<.001). Cigarette smoking was also indicative of depression trajectory; women in the high depression trajectory were two times more likely to smoke more than a pack per day (OR=2.89, CI=1.2-6.8, p=.02).

Table 3: Multivariate logistic regression results for explanatory variables of depression symptom trajectory membership.

Variable		β	SD	Wald	p-value	OR	95% CI
Constant		6.016	1.348	19.91	<.001	77.06	--
Social support squared		-.165	.040	17.48	<.001	0.85	.78-.90
Cigarette Smoking	<1/ day	Ref.	--	6.55	.038	--	--
	1-19	.347	.266	1.70	.192	1.42	.84-2.39
	20+	1.06	.435	5.93	.015	2.90	1.23-6.81
Education		-.070	.088	0.62	.432	0.93	.79-1.11
Income		-.072	.039	3.40	.067	0.93	.86-1.00
Stressful life events		.124	.075	2.72	.099	1.13	.98-1.32
Pre-pregnancy marijuana		-.039	.050	0.60	.439	0.96	.87-1.06

Model fit: -2 Log likelihood=461.47, Nagelkerke R^2 =.114

2.1.4.3 Anxiety Trajectories

Anxiety symptom trajectories were modeled in the same fashion as the depression symptom trajectories. Similar to the depression trajectories, the best fitting model was the model that fixed all but the eighth month assessment (Table 4). The optimum solution was a three group trajectory model (low, medium, and high symptoms) with a quadratic growth pattern in the high symptom group. Twelve percent (n=69) of the sample were classified into the low anxiety symptom trajectory, 52% (n=299) were in the medium symptom group, and 36% (n=209) were in the high group (Figure 2). Overall, symptoms decreased a small amount over time, particularly

among the high symptom group. The classification mean was 0.7 for the low group, 0.79 for the medium group, and .87 for the high symptom group.

Table 4: Anxiety model fit indices

Model		AIC	BIC	BIC (ss)	Entropy	Lo –Mendell-Rubin p-value
# of classes	Fixed time points*					
2	1-3	13924.875	**14025.105**	13952.089	0.556	0.015
2	1-3,5	17486.099	17551.466	17503.847	0.512	0.173
2	1-5	13969.726	14056.883	13993.391	0.539	**0.000**
3	1-3	13922.363	14044.383	13955.494	0.586	1.000
3	1-3,5	**13915.248**	14028.552	**13946.013**	**0.596**	0.098
3	1-5	13951.296	14055.884	13979.694	0.595	0.086
4	1-3,5	13942.042	14059.704	13973.990	0.559	0.334
4	1-5	14030.748	14117.905	14054.413	0.583	0.434
5	1-5	14034.679	14130.552	14060.711	0.569	0.731

Notes: Abbreviations AIC, Akaike Information Criteria, Bayesian Information Criteria, BIC (ss), Sample size adjusted BIC. Bold indicates the best fit statistic. *1=First trimester, 2=Second trimester, 3=Delivery, 4=8 months postpartum, 5=18 months postpartum.
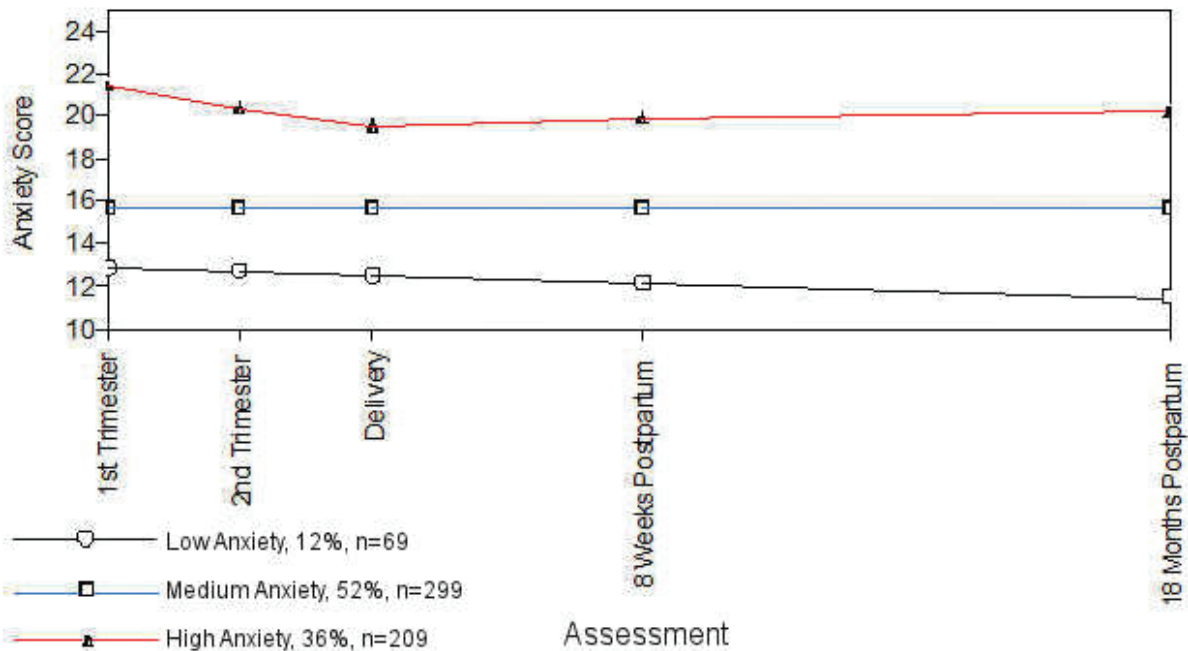
Figure 4: Anxiety trajectories.

ANOVA and Chi-square tests were used to evaluate univariate associations among the potential correlates of anxiety symptom trajectory membership. Race, marital status, income, education, and social support showed associations of p less than 0.1 and were retained in the final model (Table 1). Ordinal regression was used to model the multivariate associations between correlates and anxiety trajectory membership. Ordinal regression has fewer restrictions on normality and variability of the error terms than other types of regression [155]. The assumption for ordinal regression is that the relationship between the covariates and the outcome does not depend on the outcome category, also known as the test of parallel lines. For the ordinal regression, two potential link functions were evaluated: the logit and complementary log-log link. The logit link function (i.e., the proportional odds model) fitted the data best and passed the assumption of parallel lines (χ^2=7.69, df=5, p=.174).

Table 5 presents the results of the ordinal regression model. Both threshold values were significantly different from zero; the threshold is analogous to the intercept in a standard linear regression, only for multiple categories. Only two covariates significantly contributed to the model, social support and education. Both social support score and maternal education were significantly protective against being classified in the higher anxiety groups, after controlling for maternal race, marital status, and income at baseline.

2.1.4.4 Combined Trajectory Groups

Membership in the two depression trajectories and three anxiety trajectories can be cross-tabulated into six groups: low depression and low anxiety (7.8%), low depression and medium anxiety (8.1%), low depression and high anxiety (0.7%), high depression and low anxiety (4.3%), high depression and medium anxiety (43.7%), and high depression and anxiety (35.5%).

Table 5: Multivariate ordinal regression results for explanatory variables of anxiety symptom trajectory membership.

Variable		β	SD	Wald	p-value	95% CI
Anxiety Threshold	Medium Trajectory	-7.132	.918	60.30	<.001	-8.93 – -5.33
	High Trajectory	-4.357	.883	24.33	<.001	-6.09 – -2.63
Education		-.151	.063	5.82	.016	-.27 – -.03
Social support		-.995	.156	40.83	<.001	-1.3 – -.69
Race		.145	.183	.63	.426	-.21 – .58
Income		-.028	.031	.79	.374	-.09 – .03
Marital status		.180	.201	.80	.371	-.21 – .58

Model Fit: -2 log likelihood χ^2= 64.04, df=5,p<.001; Pearson χ^2= 724.66, df=721, p=.455; Nagelkerke pseudo R^2 =.126

Five of the six possible trajectory combinations contained over 1% of the sample. There were only four individuals in the low depression/high anxiety group. Due to the small number of women in this group, these women were excluded as outliers for the purpose of evaluating correlates. Evaluation of the joint trajectory group characteristics showed a strong positive association between experiencing depression and anxiety symptoms during pregnancy and the postpartum (Fisher's exact=124.67, p<.001). Ordinal analysis showed that anxiety trajectory membership was significantly predicted by depression trajectory (Somers' d=.60, p<.001) and vice versa (Somers' d=.28, p<.001).

To examine correlates of joint trajectory group membership, multinomial logistic regression was used. Univariate ANOVA and Chi-square analyses suggested including education, average monthly income, and social support as potential correlates. Tests of regression model assumptions indicated that there was a problem with the linearity assumption of some variables in some, but not all, of the trajectory groups. This prevented correction of the problem because any solution to one group would cause problems in the groups where there was a linear relationship. We have to rely upon the robustness of the regression method, but

acknowledge that estimates may not be precise. Multinomial logistic regression relies on an overall significance test for each variable's contribution to the model, which is interpreted prior to examining each category-specific association. In the final multivariate model (Table 6), only social support significantly contributed to the overall model (Likelihood χ^2=52.63, p<.001). Social support was protective against membership in: 1) the low depression/medium anxiety group (OR=.32, CI=.12-.89, p=.028) compared to the low/low group, 2) the high depression/medium anxiety trajectory (OR=.23, CI=.1-.55, p<.001) compared to the low/low group, and 3) the high depression/high anxiety trajectory (OR=.11, CI=.05-.27, p<.001) compared to the low/low group. However, social support did not significantly distinguish the high depression/low anxiety trajectory from the low/low group.

2.1.5 Discussion

Elevated symptoms of depression were common in this sample. The mean depression score at baseline for the entire sample was 21.1, well over the traditional 16-point cut off, which correlates with an elevated risk for clinical depression. These higher rates are consistent with other studies of pregnant women from urban disadvantaged populations [156-159], as well as studies with African Americans, who comprise over half of this sample [158-161]. The majority of this sample was in the high depression trajectory (83.5%). Contrary to the high depression findings in this study, a recent study examining trajectories of depression symptoms in a study by Mora et al. found that the majority of women were in a consistently non-elevated depression symptom trajectory [51]. This inconsistency may be due to the differences in populations sampled. The Mora study included over 1,700 women recruited from a variety of health centers,

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Table 6: Multinomial regression results for explanatory variables of joint symptom trajectory membership.

Joint Trajectory Group*	Variable		β	SD	Wald	p-value	OR	95% CI
Low Depression & Medium Anxiety	Intercept		3.78	1.88	4.07	.044	--	--
	Social Support		-1.13	.51	4.81	.028	.32	.12-.89
	Not Married		.68	.44	2.34	.126	1.97	.83-4.70
	Cigarettes•	1-19	-.46	.47	.94	.333	.63	.25-1.60
		20+	-.11	.86	.02	.895	.90	.16-4.85
High Depression & Low Anxiety	Intercept		0.97	2.30	.17	.675	--	--
	Social Support		-.60	.63	.90	.343	.55	.16-1.88
	Not Married		.31	.52	.37	.542	1.37	.50-3.76
	Cigarettes•	1-19	.43	.56	.58	.445	1.54	.51-4.64
		20+	1.70	.80	4.46	.035	1.54	1.13-26.31
High Depression & Medium Anxiety	Intercept		6.40	1.61	15.92	<.001	--	--
	Social Support		-1.46	.44	11.14	.001	.23	.10-.55
	Not Married		.54	.34	2.52	.112	1.71	.88-3.32
	Cigarettes•	1-19	.16	.36	.19	.661	1.17	.58-2.36
		20+	.97	.65	2.25	.134	2.64	.74-9.35
High Depression & High Anxiety	Intercept		8.45	1.62	27.19	<.001	--	--
	Social Support		-2.20	.44	24.43	<.001	.11	.05-.27
	Not Married		.69	.35	3.78	.052	1.99	1.00-4.00
	Cigarettes•	1-19	.03	.38	.01	.930	1.03	.50-2.16
		20+	1.26	.66	3.71	.054	3.53	.98-12.74

Notes: Only social support contributed to overall model significance (Likelihood χ^2=52.63, p<.001). Marital status and cigarette smoking were retained as potential confounders but should not be interpreted at the category level. *Comparison trajectory is low depression/low anxiety. • Reference is less than one cigarette per day.

whereas this sample focused on one prenatal clinic [51]. The Mora study also included a large number of Hispanics, a group not represented in this sample. The differences may also be due to the larger sample in that study, which would enable the identification of more rare trajectories. The overall variability of CES-D scores was higher in the Mora study, suggesting that both of these explanations are viable. Furthermore, that study modeled only one prenatal assessment and three postpartum assessments, whereas this study modeled two prenatal assessment points, delivery, and two postpartum assessments.

Mean anxiety for the sample at baseline was 17.8 with a standard deviation of 4.8. The majority of the participants were in the medium (51.8%) or high (36.2%) anxiety trajectories. No studies were identified that examined trajectories of anxiety over time in pregnant women, so comparison with other findings is impossible at this time.

The GMM analysis of symptom trajectories suggests that symptoms are fairly stable across pregnancy and the postpartum period. The two depression trajectories and three anxiety trajectories were linear across the time period with little decrease over time. While the slopes of these lines were significantly different from zero, in absolute magnitude they represented only small point decreases in symptom scores, not clinically significant change. The findings of stability have an important implication for clinical practice. These results suggest that screening for elevated depression and anxiety symptoms should start early in pregnancy. Women showing elevated symptoms at their first prenatal visit are likely to continue to show elevated symptoms throughout pregnancy and the postpartum. Early identification can enable earlier treatment to improve the mothers' quality of life and possibly prevent negative consequences of exposure on the children.

Depression and anxiety trajectories, while highly correlated, had different associated factors. Only the depression trajectories were associated with smoking status. Women in the high depression trajectory were almost three times more likely to smoke a pack or more of cigarettes per day than their low depression counterparts. Educational status was associated only with the anxiety trajectories. As years of education increased, the risk of being in the medium and high anxiety trajectories decreased in a linear fashion. Social support was consistently protective against both elevated depression and anxiety trajectories. This is consistent with a large body of research that suggests that social support plays a critical role in the experience of depression and anxiety symptoms in pregnant women [162-165]. Clinicians may want to consider ways of increasing women's social support networks as a potential way of helping pregnant women with elevated depression and anxiety symptoms.

Analyses of the combined trajectory patterns showed that the majority of women experiencing elevated depression symptoms also experienced elevated levels of anxiety. This is not surprising given the high co-occurrence of these symptoms in depression and anxiety disorders, as well as suggestions that elevations in the two symptoms share a similar pathway and may be two manifestations of the same underlying disorder [1, 8, 35, 36, 53, 65, 166]. One implication of the co-occurrence of these symptoms is that the children exposed to depression during early development are also being exposed to elevated anxiety levels, yet we identified no study that examined the combined effect of the two symptom types on offspring.

Analysis of the correlates of the joint trajectory found that only social support was associated with group membership. Social support was protective against being in the high symptom combination groups. The fact that cigarette smoking and education, while significant in the individual trajectories, were not significant in the combined trajectory analysis is not

surprising as they were only predictive of one of the two types of symptom trajectories. This again emphasizes the importance of social support for pregnant women.

The use of the CES-D in low socioeconomic and minority populations has been criticized from the standpoint that it may be capturing the increased life stress associated with poverty and having a minority status rather than actual depression. This is difficult to determine because life stressors and discrimination are also contributing factors to depression [167]. Furthermore, the use of other depression symptom scales finds similar results in these populations [168]. There is also concern over the use of the trait scale of the STAI. Admittedly, this is not the ideal measure for assessing anxiety symptoms, as it does not measure acute symptoms and it is expected to be stable over time. However, trait anxiety is a measure of how prone individuals are to becoming anxious in response to stressful stimuli. Therefore, the two types of measures are highly correlated and trait anxiety can be considered an inexact proxy for state anxiety.

An additional limitation is that this study had no measurements of risk factors prior to pregnancy, except for pre-pregnancy drug use. Therefore, the evaluation of associations was confined to correlations only. However, the trajectory correlates identified in this analysis can help clinicians identify additional factors to consider for care. Another concern is the postpartum assessment timing. The first postpartum assessment was not until the 8th month after delivery. An earlier assessment period would have been helpful in confirming the stability of the trajectory patterns. This should be considered in future study designs.

There is some concern over the generalizability of these results, as women were recruited based upon their substance use. However, over a quarter of the women in this sample used no alcohol or other illicit drugs during pregnancy and results of the multivariate analyses showed that pre-pregnancy use of alcohol, marijuana, cocaine, and other substances was not associated

with depression or anxiety trajectories. To further assess this, a secondary analysis was performed and found that average prenatal alcohol and marijuana use, and any drug use during pregnancy were not significantly associated with depression and anxiety symptom trajectories ($p>.05$, results not shown), mitigating this concern.

Despite these limitations, this is the first study to examine trajectories of both anxiety and depression symptoms at the individual level over pregnancy and the postpartum, as well as factors associated with trajectory membership. Additionally, the sample was recruited from a low socioeconomic sample and had a large proportion of African American participants, who are often underrepresented in research settings. While race was not significantly associated with depression or anxiety symptom patterns, it was important to be able to examine potential differences between ethnic groups.

This analysis is the first step toward a better understanding of depression and anxiety symptoms during pregnancy and the postpartum. Previous research suggests that exposure to elevated symptoms is problematic, both for the mother's well-being and for children who may experience biological alterations during prenatal development [99, 169-171], as well as impaired mother-infant bonding [131, 169, 172-174]. Only two studies have examined depression trajectories previously, neither of which examined outcomes, and no one has examined anxiety trajectories. Thus, the potential consequences of exposure to these symptom trajectories are unknown. Using these trajectories as the exposure measure, instead of a single cross-sectional assessment, may provide a better understanding of the risk for negative outcomes in children.

These results suggest that clinicians should screen early in pregnancy for depression and anxiety and thereby identify women who are at risk for elevated depression and anxiety symptoms throughout pregnancy and the postpartum. Social support is an important factor in

women's experience of these symptoms and may be an avenue for intervention and symptom reduction. Finally, future research should focus on the joint and specific effects of exposure to depression and anxiety trajectories on children in order to better understand these mechanisms and find ways to ameliorate negative consequences.

2.2 PAPER 2: THE RISK FOR PSYCHIATRIC ILLNESS IN ADOLESCENTS RESULTING FROM EXPOSURE TO PRE- AND POSTNATAL MATERNAL DEPRESSION AND ANXIETY SYMPTOMS

2.2.1 Abstract

Background: Up to 25% of children may be exposed to elevated levels of pre- or postnatal depression symptoms (PPND) and/or pre- and postnatal anxiety symptoms (PPNA). Exposure to prenatal maternal anxiety and depression symptoms may affect fetal development, making offspring more vulnerable to psychopathology later in life. Postnatal exposure to maternal depression and anxiety symptoms may disrupt the development of healthy attachment patterns in children, increasing the risk for later psychiatric disorders.

Methods: A previous study by the authors utilized Growth Mixture Modeling to identify the most common trajectories of PPND and PPNA symptoms, as well as the combination of these trajectories. These trajectory groups were used as the exposures of interest for survival analyses examining the time until onset of psychiatric illness among adolescents. A secondary analysis used logistic regression to determine if PPND and/or PPNA exposure predicted the risk of Major Depression (MDD) and Conduct Disorder (CD), specifically.

Results: Exposure to PPND, PPNA, or combined symptom trajectories did not significantly increase the risk of onset of "any" psychiatric disorders among adolescents. Major Depression was not significantly associated with PPND, PPNA, or combined symptom trajectories. The occurrence of CD was significantly higher among males exposed to high and

medium anxiety symptom trajectories than among their low exposure counterparts. Females exposed to medium and high anxiety trajectories were significantly less likely to have met CD criteria than females with low exposure. There was no association with PPND or combined symptom trajectories and the risk for CD in adolescents.

Conclusions: Exposure to PPND and PPNA did not increase the risk of non-specific psychiatric illness. However, CD risk was significantly related to PPNA exposure. This is the first study to examine the effect of PPNA exposure on the risk of psychiatric illnesses. These results point toward new directions for investigation into the etiology of CD with a novel target for prevention.

2.2.2 Introduction

Community-based prevalence studies have shown that up to 25% of children are exposed to elevated levels of pre- or postnatal depression (PPND), with similar exposure levels for pre- and postnatal anxiety symptoms (PPNA) [8]. Exposure to PPND and PPNA has been hypothesized to increase the risk for psychiatric illness in exposed children. During the prenatal period, exposure to high maternal anxiety and depression symptoms may lead to elevated levels of stress hormones crossing the placental barrier and affecting fetal development, making offspring more vulnerable to psychopathology later in life [66, 72, 73, 175]. During the postnatal period, infants and mothers form emotional attachment patterns that stay with children throughout their lives [102, 176]. Exposure to maternal depression and anxiety symptoms during this period may disrupt the development of healthy attachment patterns [54, 176]. Negative attachment styles, in turn, are associated with a number of specific psychiatric illnesses including: personality disorders [104], substance abuse [105], depression [106], and eating

disorders [107, 108], as well as nonspecific psychopathology in children and adolescents [109, 110, 177, 178].

2.2.2.1 Prenatal Exposure

Studies testing the link between prenatal anxiety and depression and subsequent mental illness in humans are limited. To date, there are a several studies linking prenatal stress, anxiety, and depression exposure to infant fussiness and difficult temperament in infants and young children [54, 133, 179-181], and several studies have examined psychopathology specifically [18, 59, 99, 129, 182, 183]. Each of these studies found at least partial support for exposure to elevated prenatal depression or anxiety symptoms in community-sampled women contributing to the risk of children developing emotional or behavioral problems.

The Avon Longitudinal Study of Parents and Children (ALSPAC), a large prospective cohort study in England, examined the effects of prenatal anxiety symptom exposure on children at 4 [59] and 6.75 years of age [99]. In 4-year-olds, prenatal anxiety symptoms (either at 18 or 32 weeks of pregnancy) were associated with more emotional problems in girls and boys, more conduct problems in girls, and more hyperactivity/attention problems in boys, even after controlling for postnatal anxiety and depression [59]. These findings persisted at the 6.75-year assessment, with the additional finding that antenatal anxiety predicted conduct problems and hyperactivity/attention problems in both boys and girls by 6.75 years [99]. Similarly, Luoma and colleagues [27] found that elevated third trimester depression symptoms were associated with higher total problem scores on the Child Behavior Checklist [CBCL, [184]], specifically with more externalizing disorders, in a community-based sample of physically healthy mothers and their 8- and 9-year-old children. This association was independent of immediate postnatal and later maternal depression symptoms.

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Leech et al. [182] examined a number of predictors of high depression and anxiety symptoms in the 10-year-old children of a sample of generally healthy women of low-socioeconomic status who were recruited during pregnancy. Consistent with the other studies' findings, higher prenatal depression symptom exposure was associated with the children's combined depression and anxiety symptoms at 10, even after controlling for the mother's later depression and anxiety (18 months, 3 years, and 6 years postpartum). Prenatal anxiety also significantly predicted the children's combined depression and anxiety symptoms at age 10, but only in bivariate analyses.

Only two studies have examined prenatal depression and anxiety symptoms in relation to psychiatric diagnoses, as opposed to symptoms. In a retrospective study of high school students and their parents [129], adolescent psychiatric diagnoses of Major Depressive Disorder (MDD), any of several Anxiety Disorders, and Disruptive Behavior Disorders (DBD) were obtained using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS, [185]). Maternal emotional health (combined anxiety and depression symptoms) predicted the occurrence of MDD and DBD, but not anxiety disorders. Likewise, a prospective study of a community-based sample of pregnant women by Pawlby et al [186] found a four-fold increase in the risk of MDD in 16-year-old adolescents exposed to maternal depression, as diagnosed by their primary care provider during the second or third trimester. However, this association became non-significant when the number of subsequent maternal depressive episodes was included in the model.

2.2.2.2 Postnatal Exposure

While the psychiatric impact of prenatal depression and anxiety symptoms has been examined by a limited number of studies, the postnatal period has received more attention in

recent years, at least with respect to postnatal depressive symptoms. Several systematic reviews and meta-analyses have been performed on studies examining the effects of postnatal (postpartum) depression [187-189]. Evidence suggests that postnatal depression impairs early mother-child interactions [187] and is linked to difficult infant temperament [188, 189]. Difficult temperament and negative mother-child interactions, in turn, have been linked to subsequent child behavioral and emotional problems [190-196]. Postnatal anxiety has been the subject of fewer studies. However, growing evidence is suggestive of similar effects as those of postnatal depression on difficult infant temperament [133-135] and mother-child interactions [197].

There have been a number of studies examining postnatal depression effects on behavioral and emotional problems in children. In a meta-analysis, Beck [14] summarized nine studies and found a small effect size for the relationship between postnatal depression and cognitive and behavioral development. Unfortunately, the two outcomes were grouped in Beck's analysis, so the effect size on behavioral outcomes alone is not available. In a systematic review, Grace, Evindar, and Stewart [198] also reported an effect of postnatal depression on child behavioral outcomes, although they warn that their findings may not be specific to exposure during the immediate postnatal period but rather reflect the effects of chronic maternal depression on child behavior.

Fewer studies have examined the effect of postnatal anxiety exposure on psychiatric outcomes. Barnett and colleagues [126] reported that 5-year-olds of community-sampled mothers with high anxiety symptoms were less active and socially competent than low anxiety exposed boys. High symptom exposed boys were more immature, delinquent, and schizoid than their unexposed counterparts. Similarly, results from the ALSPAC study found that the risk of emotional problems was 50% greater in 4-year-olds exposed to higher postnatal anxiety

symptoms, and exposed girls were at a 45% increased risk of conduct problems, independent of prenatal depression and anxiety symptoms and postnatal depression symptoms [59]. At age 6, the increased risk for emotional problems in boys was 60%, but there was no longer an association in girls [99]. Furthermore, the risk of conduct problems in exposed girls at 6 years had strengthened to double the risk of unexposed girls.

Thus, there is some evidence to support the hypothesis that PPND and PPNA symptoms may increase the risk for mental illness in exposed children. However, several challenges exist when studying depression and anxiety symptoms in the pre- and postnatal periods and the impact on offspring, which these studies have not addressed. First, prenatal depression and anxiety symptoms usually precede postnatal symptoms [8, 28]. This correlation makes it difficult to isolate the effects of prenatal exposure from postnatal exposure without very large samples. Research that has examined postpartum depression effects, in particular, typically does not consider the impact of prenatal depression. Furthermore, attempts to isolate the relative effects of pre- and postnatal symptoms may not represent the true risk to exposed children. If most children who are exposed to prenatal symptoms also experience postnatal exposure, then the combined effects would better represent the typical exposure. None of the studies identified have looked at the combined effects of pre- and postnatal exposure.

The second challenge is that PPND and PPNA usually co-occur [8, 34, 199], and this co-occurrence makes statistical analyses complicated. Most studies have evaluated only anxiety or depression symptoms, not both. The few that did examine both often found that adding the co-occurring symptoms greatly diminished or negated the primary association. However, this may not represent the true association as the combined exposure may have an additive or

multiplicative effect on the children's risk. None of the studies examined the risk associated with the interaction of depression and anxiety symptoms.

These challenges lead to the question of how best to evaluate the psychiatric effect of the maternal symptom exposures that these children are experiencing. This study attempts to address this question by utilizing trajectory analysis for longitudinal data. The purpose is to determine if commonly occurring patterns of PPND and PPNA increase the risk of psychiatric illness onset in children by age 16. Specifically, Growth Mixture Modeling (GMM) [139] was used to identify the most common symptom patterns that women experienced in the peripartum period and classify the children by their exposure trajectory. These trajectory groups were then treated as the exposure status for a survival analysis that examined time until onset of psychiatric illness. Additionally, we examined the relationship between depression and anxiety trajectory exposure on MDD and Conduct Disorder (CD), the two most frequent diagnoses in the sample. We hypothesized that exposure to either PPND or PPNA would increase the risk of earlier onset of psychiatric illness in offspring and that combined exposure would convey greater risk than either exposure alone. We also hypothesized that PPND and PPNA would increase the risk of MDD and CD, specifically.

2.2.3   Methods

2.2.3.1 Participants

This report is a secondary data analysis utilizing data from the Maternal Health Practices and Child Development (MHPCD) project (N. Day, P.I. [140, 141]). The MHPCD project is a combination of two longitudinal cohorts of adult, English-speaking women recruited from one prenatal, hospital-based clinic. Between 1982 and 1985, 1360 women were screened for

participation during their fourth or fifth prenatal month. The first cohort of women was selected based upon their prenatal alcohol consumption. Subject selection included all women who drank three or more drinks per week and a randomly selected comparison group of those who drank less or abstained. The second cohort, recruited concurrently, was selected based upon their marijuana use. The cohort included all women who smoked two or more joints per month during their first trimester, and a random selection of women who used less or abstained. Sampling was done with replacement, so women could participate in one or both cohorts. This sampling scheme allowed for a continuum of women to be recruited, from those who used no substances during pregnancy to those who used heavily during this time. Aside from the selection criteria, the cohorts followed the same protocol and are combined for these analyses.

The MHPCD project has completed 10 assessments: 1st trimester baseline (assessed at the 4th or 5th month of pregnancy); 2nd trimester (assessed at the 7th prenatal month), delivery, 8 and 18 months postpartum, and 3, 6, 10, 14, and 16 years postpartum. A 22-year follow-up assessment is in progress. A total of 829 women were recruited at baseline. At delivery, the sample size was 763 (21 had moved away, 16 were missed, 8 refused the delivery assessment, 2 were multiple births, 18 experienced maternal or infant death, and 1 infant was placed for adoption). Follow-up rates for each phase subsequent to birth ranged between 76% and 88% with a mean of 82%.

These analyses focus on psychiatric diagnoses in the children; therefore, only mother-child pairs who had completed the child psychiatric assessment at the 16-year-assessment were eligible for this analysis. Of the 592 participants included in the 16-year phase of the MHPCD project, 577 (76% of the birth cohort) had completed child psychiatric assessments. Women excluded from the analysis due to missing data (n=186) were more likely to be Caucasian (58%

of the excluded group versus 45% of the included group), but otherwise did not differ by demographic variables. Children who were lost to follow-up were more likely to be male (58% of the excluded group versus 48% of the included group), and were less likely to have been prenatally exposed to marijuana (38% of the excluded group versus 42% of the included group).

2.2.3.2 Measures

The purpose of this report was to examine the effect of the children's exposure to the mothers' depression and anxiety symptoms from the first trimester through 18 months postpartum (1st and 2nd trimester, delivery, 8 and 18 months postpartum). Determining the children's exposure status was done in two steps. First, maternal symptoms of depression and anxiety were collected at each of the assessments. Depression symptoms were measured using the *Center for Epidemiological Studies Depression Scale* (CES-D)[24]. The CES-D is a 20-item scale with a 4-point Likert response scale measuring frequency of depression symptoms. Scores range from 0 to 60 with higher scores indicating more symptoms. The CES-D has been widely used, including in studies of pregnant women [22, 40], and has strong psychometric properties in clinical and general populations [Cronbach's α = .85 and 0.9, respectively; [24, 142]].

Anxiety was measured using a modified version of the trait scale of Spielberger's *State-Trait Anxiety Inventory-Short Form* (STAI) [200]. The modified scale was originally published as the *State-Trait Personality Inventory* (STPI) [201]. The STPI is almost identical to the more recognized STAI trait short form. Two questions have slight wording changes and one question asks conceptually the same question with a clearer wording, which was deemed more appropriate for a sample with low educational attainment. Trait anxiety (T-anxiety) assesses a person's overall anxiety susceptibility, as opposed to temporary levels of situational anxiety and it has been repeatedly used to measure anxiety symptoms in pregnant and postpartum women [56, 146,

147]. The trait scale consists of questions such as "I feel at ease," with a 4-point Likert response scale. Scores ranged from 10 to 40 [143]. The Cronbach's alpha for the baseline combined alcohol and marijuana cohorts in the MHPCD sample was .87.

The second step in determining the children's exposure was to use growth mixture modeling (GMM) to evaluate the presence of distinct subgroups of symptom patterns across the five assessments. GMM, using Mplus statistical software, allows for the identification of subgroups of similar individuals from within the sample and provides growth curves for each group [3]. Separate trajectory groups were modeled for maternal depression symptoms and for anxiety symptoms over time. A detailed description of the modeling procedures used to obtain trajectory group exposures is reported elsewhere [202]. In brief, separate models of two through four latent classes were fit to identify trajectories of depression and anxiety symptoms (1st, 2nd, and 3rd trimester, 8 and 18 months postpartum). Both depression and anxiety models tested parameter estimates of intercept, slope growth term, and quadratic growth term and allowed free estimation of growth-factor and class-specific variances and covariances. Trajectory group membership was determined by the posterior probability scores provided by Mplus.

For depression, the best model was a two-group solution of a low and a high trajectory with stable symptoms. Seventeen percent (n=95) of the sample were classified into the low symptom group and 84% were in the high symptom group (n=482). The best model of anxiety symptoms was a three-group trajectory model. Twelve percent (n=69) of the sample was classified as low anxiety with stable symptoms, 52% (n=299) were in the medium symptom group with stable symptoms, and 36% (n=209) were in a high group, which experienced a slight decrease in anxiety score early on in pregnancy, but remained high and stabilized over time [202].

To examine the effect of a combined exposure, the depression and anxiety trajectories were cross-tabulated into six groups: 1) low depression and low anxiety (7.8%), 2) low depression and medium anxiety (8.1%), 3) low depression and high anxiety (0.7%), 4) high depression and low anxiety (4.3%), 5) high depression and medium anxiety (43.7%), and 6) high depression and anxiety (35.5%). As there were only four individuals in the low depression/high anxiety group, this exposure pattern was excluded as an outlier for analyses utilizing combined trajectory groups as an exposure measure [202].

The primary outcome of interest in the current analysis was the time until onset of any psychiatric disorder. A secondary analysis focused on the occurrence of the two most common psychiatric disorders in the adolescents, MDD and CD. Maternal and child psychiatric diagnoses and time of onset were assessed using the computerized Diagnostic Interview Schedule (DIS-IV) [203], which was administered as an oral interview to the mothers and the offspring at the age 16 assessment. The DIS-IV is a structured diagnostic interview assessing psychiatric illness according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition [204]. The interview assessed the current (12-month) and lifetime prevalence of a number of disorders, including: Generalized Anxiety Disorder (GAD), Posttraumatic Stress Disorder (PTSD), Depression, Dysthmia, Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, Hyperactivity Disorder, Separation Anxiety, Oppositional Disorder, Conduct Disorder, Antisocial Personality Disorder (for those > age 15), Alcohol Dependence and Abuse, and Drug Dependence and Abuse. The DIS-IV is a well-established, widely used interview [205, 206]. All analyses used lifetime diagnoses.

Covariates included in these analyses were determined based upon previous research into risk factors for maternal depression and anxiety and for adolescent psychiatric illness.

Demographic variables included: child's gender, maternal race (Caucasian/African American), maternal age at baseline, maternal education at baseline, and family income (averaged across the assessments). Child's social environment included mother's marital status and child's primary custodian. Marital status across the study period was categorized as married throughout the study, single throughout the study, or divorced during the study. Only three mothers became married during the study period and did not also report a divorce, so they were classified as married. Child's custodial status was categorized as consistently living with the mother (at each phase) or inconsistently living with the mother. Information on the number of pregnancy, delivery, and labor complications was collected from the medical records shortly after delivery. These complications were categorized according to common obstetrical complication schemes as guidelines [207-209]. Maternal CD and Antisocial Personality Disorder (APD) were assessed using the same DIS-IV procedure used for the offspring. Maternal drug use was assessed using measures specifically designed for this study. A detailed description of the measures and reliability is published elsewhere [150, 151]. Substances assessed at each phase were alcohol, marijuana, tobacco, cocaine, and other illicit drugs. Both quantity and frequency of use were ascertained and converted into an average daily drinks or joints for alcohol and marijuana, respectively. Cocaine and other illicit drugs were measured dichotomously. Cigarette use was assessed at every phase and was categorized based on the distribution as less than one, $1 - 19$, and 20 or more cigarettes per day. For these analyses, maternal substance use was broken into two time frames, prenatal use and postnatal use. Prenatal alcohol and marijuana use were averaged across the three prenatal assessments (1st trimester, 2nd trimester, delivery), while cocaine and other illicit drug use was categorized as any or none during this period. Postnatal use was calculated similarly for all of the post-delivery assessments through the age 16 assessment.

To examine the effect of different coding methods for substance use, prenatal use of alcohol, marijuana, and other illicit drugs were also categorized in no use, 1st trimester only, or 1st through 3rd trimester use. Treating substance use as a categorical variable, instead of averaging across the prenatal period, had no effect on the association between depression and anxiety trajectories and psychiatric illness, so the average coding was retained.

2.2.3.3 Statistical Methods

To evaluate whether exposure to certain trajectories of maternal depression and anxiety symptoms from pregnancy through the postpartum is related to the risk for an earlier onset of "any" psychiatric illness in children, survival analysis using Cox regression was performed. Separate models were tested for depression trajectories, anxiety trajectories, and the combined trajectory groups, and were regressed on the time of earliest psychiatric illness onset, using SPSS, version 15 [210]. Interaction effects between exposure and child gender were tested for each model, as there is evidence that the effects of exposure differ between males and females [59, 94, 99]; only significant interactions (p<.05) were retained in the final model. In addition, logistic regression was used to determine if trajectory group exposure (3 models of exposure: depression trajectories, anxiety trajectories, combined trajectory groups) predicted the occurrence of the two most common diagnoses in the sample, MDD and CD, individually. Interaction effects were also tested in these analyses and retained if significant (p<.05). For all of these analyses, potential covariates were evaluated using t-tests (adjusted for unequal variance when necessary) and Chi-square. If covariates were associated with the occurrence of a psychiatric disorder (for the Cox regressions) or MDD or CD (for the logistic regressions) at p<.10, they were included in the multivariate model.

2.2.4   Results

2.2.4.1 Sample Characteristics

As seen in Table 7, the MHPCD subsample included in these analyses is almost equally split by child gender (53% males) and maternal race (45% Caucasian, 55% African American). At baseline, the mothers were on average 22.9 years of age (SD=3.9), and had completed 11.8 years of education (SD=1.4). The mean family income over the study period (beginning in 1982) was $595 per month with a wide variation among individuals (SD=$440). Only a minority of mothers were married throughout the entire study period (12%), most were divorced (57%) or single throughout the study (31%). Almost 20% of the children in this sample had an unstable custodial arrangement, living with their mothers on an inconsistent basis. There were a large number of pregnancy (64%), labor (44%), and delivery complications (82%). However, complications included minor events such as infection without implication and previous pregnancy losses, so the occurrence of a complication does not itself signify significant medical morbidity.

The MHPCD study's primary objective was to evaluate the effects of maternal prenatal substance use on children, thus the rates of substance use among the mothers are higher than in the general population. Mean prenatal alcohol use during pregnancy was .29 drinks per day (SD=.84). Average daily marijuana use was .25 joints per day (SD=.67). Over 95% of the sample reported no prenatal cocaine use and 88% reported no other illicit substance use during pregnancy. Twenty-six percent of the sample abstained from alcohol, marijuana, and other illicit drugs in the first trimester. Approximately half of the mothers smoked less than one cigarette per

Table 7: Descriptive statistics for the total sample and by diagnosis status.

Variable		Total Sample (n=577)	Any Diagnosis (n=184)	No Diagnosis (n=393)	p-value
Gender	Males	52.5%	57%	50%	.079
	Females	47.5%	43%	50%	
Maternal Race	Caucasian	45%	51%	43%	.106
	African American	55%	50%	57%	
Maternal Age[1]		22.93	22.89	22.96	.841
Maternal Education[1]		11.82	11.66	11.90	.047
Monthly Family Income[2]		$595	$543	$619	.054
Mother's Marital Status[2]	Single	31%	32%	30%	.289
	Married	12%	9%	13%	
	Divorced	57%	59%	57%	
Lives with Mother[3]	Consistently	81%	81%	81%	.956
	Inconsistently	19%	19%	19%	
Pregnancy Complications[4]	No	36%	36%	37%	.858
	Yes	64%	64%	63%	
Labor Complications[4]	No	56%	58%	55%	.542
	Yes	44%	42%	45%	
Delivery Complications[4]	No	19%	19%	19%	.920
	Yes	82%	82%	81%	
Prenatal Alcohol Exposure[5]		.29	.34	.26	.320
Prenatal Marijuana Exposure[5]		.25	.22	.32	.086
Prenatal Cocaine Exposure[5]	Any	4%	4%	4%	.994
	None	96%	96%	96%	
Prenatal Drug Exposure[5]	Any	13%	13%	12%	.982
	None	88%	88%	88%	

Table 7 continued

Prenatal Tobacco Exposure[5]	<1 per day	49%	43%	51%	.232
	1-19 daily	30%	33%	28%	
	20+ daily	22%	23%	21%	
Maternal Alcohol Use[3]		.91	1.06	.85	.067
Maternal Marijuana Use[3]		.23	.32	.22	.051
Maternal Cocaine Use[3]	Any	20%	24%	18%	.086
	None	80%	76%	82%	
Maternal Drug Use[3]	Any	25%	32%	22%	.010
	None	75%	69%	78%	
Depression Trajectory	Low	17%	13%	18%	.129
	High	84%	87%	82%	
Anxiety Trajectory	Low	12%	12%	12%	.966
	Medium	52%	51%	52%	
	High	36%	37%	36%	
Combined Trajectory Group	Low Depression & Low Anxiety	8%	7%	8%	.691
	Low Depression & Medium Anxiety	4%	5%	4%	
	High Depression & Low Anxiety	44%	45%	44%	
	High Depression & Medium Anxiety	8%	7%	9%	
	High Depression & High Anxiety	36%	37%	35%	

[1]Measured at baseline, [2] Averaged or tabulated across three prenatal and seven post-pregnancy (8 months, 18 months, 3, 6, 10, 14, and 16 years) assessments, [3] Averaged or tabulated over seven post-pregnancy assessments, [4]Measured at delivery, [5] Average or tabulation of three pregnancy assessments.

day or abstained during pregnancy, while 30% smoked an average of between one and 19 cigarettes per day, and 22% exceeded a pack a day on average during pregnancy. Maternal postpartum alcohol use was on average .91 drinks per day (SD=1.29). Postpartum maternal marijuana use was on average .23 joints per day (SD=.57). Eighty percent of mothers reported no post-pregnancy cocaine use and 75% reported no other illicit drug use after pregnancy.

High depression symptom status was common in this sample, with 84% of mothers being classified in the high symptom trajectory. The mean baseline CES-D depression score in the high depression symptom trajectory was 22.92 (SD=.37), whereas the mean of the low trajectory was 11.45 (SD=.47). The three trajectory groups identified by GMM showed that at least moderately elevated anxiety was common in these mothers. Only 12% of the sample was classified as low anxiety with a mean baseline trait anxiety score of 12.7 (SD=.24). Over half were classified as being in the medium anxiety trajectory (mean baseline anxiety score = 15.8, SD= .14), and over a third were classified as high anxiety (mean baseline anxiety score = 22.4, SD= .3).

Examination of the combined trajectory groups indicated that depression and anxiety trajectory group memberships were highly correlated; 80% of the mothers in this sample were in either the High Depression & Low anxiety group (44%) or the High Depression and High Anxiety group (36%).

Psychiatric illnesses were diagnosed in 32% of the children in this sample. The mean age of first illness onset was 11 years (SD = 4 years). The two most common diagnoses were MDD (14%) and CD (12%), followed by Post Traumatic Stress Disorder (6%). All other disorders had a prevalence of 5% or less in this sample.

2.2.4.2 Age of Onset

Three survival analyses were performed using Cox proportional-hazard regression, one for depression trajectory exposure, one for anxiety trajectory exposure, and the third for the combined trajectory group. Evaluation of sample characteristics stratified by psychiatric diagnosis status indicated that child gender, maternal education, monthly family income, prenatal marijuana exposure, and all postnatal maternal substance use (alcohol, marijuana, cocaine, and other) were potentially associated with the child having a psychiatric diagnosis by age 16 (p<.10). These characteristics were therefore included in each multivariate survival model as potential confounders (Table 7). Interaction effects between exposure trajectory and child's gender were tested for each of the three models. None significantly contributed to the model (as tested by the -2 Log Likelihood Chi-square, p<.05) and were dropped. Graphical examination of the proportional-hazards assumption suggested that all covariates in the models met the assumption.

Table 8 presents the results of the Cox regression model for the separate depression and anxiety trajectory exposures. There was no significant association between depression symptom trajectory exposure and the age of first psychiatric illness onset (Wald $\chi^2(1)$ =.92, p=.337), after controlling for other covariates. Similarly, there was no significant association between anxiety trajectory exposure and age of psychiatric illness onset (Wald $\chi^2(2)$ = .44, p=.802). Given the lack of findings in the individual models, it is not surprising that the combined trajectory group model also produced null results (Wald $\chi^2(4)$ =2.13, p=.713; results not shown). The only covariate that significantly predicted earlier onset of psychiatric illness was mother's postnatal drug use, which approached significance in the PPND model (Wald $\chi^2(1)$ =3.63, p=.057) and

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Table 8: Cox regression model results for depression and anxiety trajectory exposure.

Variable		Parameter Estimate	Standard Error	Wald	Significance	Hazard Ratio	95% Confidence Interval
Depression Trajectory Exposure[1]							
Depression Trajectory	High[3]	.213	.222	.923	.337	1.24	.80-1.9
Gender	Males[4]	-.199	.152	1.71	.191	.82	.61-1.1
Maternal Education		-.074	.061	1.503	.220	.93	.82-1.1
Monthly Family Income		.000	.000	1.805	.179	1.00	1.0-1.0
Prenatal Marijuana Use		-.021	.137	.023	.880	.98	.75-1.3
Maternal Alcohol Use		.058	.055	1.115	.291	1.06	.95-1.2
Maternal Marijuana Use		.152	.157	.944	.331	1.17	.86-1.6
Maternal Cocaine Use	Yes[5]	.021	.207	.010	.919	1.02	.68-1.5
Maternal Drug Use	Yes[5]	.337	.177	3.625	.057	1.40	.99-2.0
Anxiety Trajectory Exposure[2]							
Anxiety Trajectory	Low	Reference		.441	.802		
	Medium	-.151	.241	.392	.531	.86	.54 – 1.38
	High	-.159	.252	.396	.529	.85	.52 – 1.40
Gender	Males [4]	-.199	.153	1.703	.192	.82	.61 – 1.11
Maternal Education		-.079	.060	1.697	.193	.92	.82 – 1.04
Monthly Family Income		.000	.000	2.248	.134	1.0	1.0 – 1.0
Prenatal Marijuana Use		-.018	.138	.017	.896	.98	.75 – 1.29
Maternal Alcohol Use		.058	.054	1.125	.289	1.06	.95 – 1.18
Maternal Marijuana Use		.153	.158	.938	.333	1.17	.86 – 1.59
Maternal Cocaine Use	Yes[5]	.038	.208	.034	.855	1.04	.69 – 1.56
Maternal Drug Use	Yes[5]	.350	.178	3.886	.049	1.42	1.01 – 2.01

[1]Omnibus Model Test: -2 Log likelihood = 2230.89, Chi-square = 20.394, df = 9, p = .016.
[2] Omnibus Model Test: -2 Log likelihood = 2231.43, Chi-square = 20.134, df =10, p = .028.
[3] Reference = low trajectory, [4] Reference = Females, [5] Reference = no use.

reached significance in the PPNA model (Wald $\chi^2(1)$ =3.89, p=.049, HR=1.42, CI=1.01-2.01). Gender, maternal education, family income, prenatal marijuana exposure, postnatal maternal alcohol, marijuana, and cocaine use did not significantly predict age of onset.

2.2.4.3 Major Depression

Logistic regression was used to determine if the occurrence of MDD was predicted by each of the symptom trajectory groups. Separate models were created for each of the exposure types (depression, anxiety, and combined trajectories). Tests of logistic regression assumptions indicated that all assumptions were met except for a small cluster of outliers in the residuals. This was present in each of the three models. There was no evidence of error in the data for these individuals and therefore they were retained in the final multivariate model. A sensitivity analysis was also performed removing these cases from the data set. The results regarding the main exposures of interest did not change substantially. However, maternal age reached significance in the anxiety and combined trajectory models, although the odds-ratio changed little from the original results (results not shown).

Covariates tested for inclusion in the MDD model were the same as those considered for the age of onset survival analyses (Table 7). To be included in the multivariate model, covariates had to be significantly associated with the occurrence of MDD at p<.10. This meant that child gender, maternal age at baseline, and maternal education at baseline were included in the final multivariate model. Interaction effects between gender and trajectory membership were tested in each model. None of them significantly contributed to the model (p<.05) and were not included in the final model.

Table 9: Logistic regression results of Major Depressive Disorder predicted by depression and anxiety trajectory groups.

Variable		Parameter Estimate	Standard Error	Wald	Significance	Odds Ratio	95% Confidence Interval
Depression Trajectory Exposure[1]							
Depression Trajectory	Low	Reference	--	--	--	--	--
	High	-.064	.336	.036	.849	.94	.49 – 1.81
Gender	Females	Reference	--	--	--	--	--
	Males	-1.221	.285	18.331	<.001	.30	.17 - .52
Maternal Age		-.055	.035	2.445	.118	.95	.88 – 1.01
Maternal Education		-.143	.100	2.058	.151	.87	.71 – 1.05
Anxiety Trajectory Exposure[2]							
Anxiety Trajectory	Low	Reference	--	2.777	.250	--	--
	Medium	-.616	.380	2.629	.105	.54	.26 – 1.14
	High	-.372	.388	.922	.337	.69	.32 – 1.47
Gender	Females	Reference	--	--	--	--	--
	Males	-1.221	.286	18.222	<.001	.30	.17 - .52
Maternal Age		-.056	.035	2.515	.113	.95	.88 – 1.01
Maternal Education		-.149	.100	2.230	.135	.86	.71 – 1.05

[1]Model Fit Statistics for Depression Trajectory: Model Chi-Square =28.73, p<.001, Nagelkerke R^2=.089
[2] Model Fit Statistics for Anxiety Trajectory: Model Chi-Square =31.37, p<.001, Nagelkerke R^2=.097

Table 9 presents the results of the logistic regression models for each of the depression and anxiety trajectory exposures. None of the three main exposures of interest, depression trajectory, anxiety trajectory, or combined trajectories (not shown), were significantly associated with the occurrence of MDD (OR=0.94, p=.849, CI=.49-1.81; Wald $\chi^2(2)$ = 2.777, p=.25; and Wald $\chi^2(4)$ =2.932, p=.569, respectively).

Gender was the only covariate significant in the three models: males were 70% less likely to have an MDD diagnosis than females (Wald $\chi^2(1)$ =18.33, p<.001, OR=.30, CI=.17 - .52, regardless of model). Maternal age and education did not significantly predict MDD after controlling for the other covariates.

2.2.4.4 Conduct Disorder

The logistic regression analyses for CD were performed in the same manner as for MDD, with the addition of including maternal CD and APD as covariates. Tests of logistic regression assumptions indicated that maternal alcohol use violated the linearity assumption required for the appropriate modeling of this variable in the regression. Correction of this problem would have differed for each model leading to difficulty in interpretation; therefore it was corrected only in the anxiety model where it might impact the primary results of interest. Since the depression and combined trajectories were not even closely associated with CD, it is unlikely that correcting the linearity problem would change the results. Correction was performed by squaring mean maternal alcohol consumption. Similar to the MDD models, a cluster of outlying residuals was detected. This was present in each of the three models and there was no evidence of error in the data for these individuals so they were retained in the final multivariate model. A sensitivity analysis without these outliers made little difference in the depression and combined trajectory

findings. In the anxiety model, the odds-ratios associated with CD and anxiety trajectory increased markedly. However, due to the reduction in sample size, the odds-ratio estimates have less precision and are not reported.

Covariates included in the multivariate CD models were child gender, maternal CD or APD, and maternal alcohol use. Interaction effects of gender by trajectory exposure were tested for all three models (depression trajectory, anxiety trajectory, and combined trajectory group). The interaction effect was significant only for the anxiety trajectory model ($\chi^2(2) = 7.865$, p=.020). Neither depression trajectory exposure nor combined trajectory group exposure predicted the occurrence of CD by age 16 (Table 10, combined trajectory results not shown). However, anxiety trajectory exposure was significantly associated with the occurrence of CD. Females exposed to medium levels of maternal anxiety between pregnancy and 18 months postpartum were 84% less likely to have met criteria for CD by age 16 than those exposed to the low trajectory symptoms (OR=.16, p=.007, CI=.04 - .60). Females exposed to the high anxiety trajectory were even less likely to meet CD criteria (OR=.10, p=.002, CI=.02 - .43). By contrast, males exposed to medium levels of anxiety were eleven times more likely to meet CD criteria than those exposed to low levels (OR=11.63, p=.022, CI=1.43 – 94.91) and males exposed to the high anxiety trajectory were almost 19 times more likely to meet CD criteria (OR=18.76, p=.007, CI= 2.26 – 155.89). Neither postnatal maternal alcohol use nor maternal CD and APD predicted child CD in this sample.

Table 10: Logistic regression results of Conduct Disorder predicted by depression and anxiety trajectory groups.

Variable		Parameter Estimate	Standard Error	Wald	Significance	Odds Ratio	95% CI
Depression Trajectory Exposure[1]							
Depression Trajectory	Low	Reference	--	--	--	--	--
	High	.165	.384	.184	.668	1.179	.556 – 2.502
Gender	Females	Reference	--	--	--	--	--
	Males	.706	.279	6.422	.011	2.026	1.173 – 3.496
Maternal Alcohol Use		.245	.082	8.886	.003	1.278	1.088 – 1.501
Mother's CD or APD	No	Reference	--	--	--	--	--
	Yes	-.147	.467	.098	.754	.864	.346 – 2.156
Anxiety Trajectory Exposure[2]							
Anxiety Trajectory		--	--	12.160	.002	--	--
Anxiety /Gender Interaction				7.865	.020		
Females	Low	Reference	--	--	--	--	--
	Medium	-1.864	.686	7.380	.007	.155	.040 - .595
	High	-2.313	.743	9.690	.002	.099	.023 - .425
Males	Low	Reference	--	--	--	--	--
	Medium	2.454	1.071	5.248	.022	11.631	1.425 – 94.909
	High	2.932	1.080	7.363	.007	18.757	2.257 – 155.889
Gender	Females	Reference	--	--	--	--	--
	Males	-1.352	.864	2.448	.118	.259	.048 – 1.407
Mother's CD or APD	No	Reference	--	--	--	--	--
	Yes	-1.363	1.034	1.737	.187	.256	.034 – 1.942
Maternal Alcohol Use (squared)		-.049	.064	.575	.448	.952	.839 – 1.080

[1]Model Fit Statistics for Depression Trajectory: Model Chi-Square = 13.40, p = .009, Nagelkerke R^2=.05
[2]Model Fit Statistics for Anxiety trajectory: Model Chi-Square = 20.25, p = .005, Nagelkerke R^2=.095

2.2.5 Discussion

2.2.5.1 Age of Onset

Three types of exposures were evaluated in this analysis: PPND, which consisted of a stable high trajectory and a stable low symptom trajectory; PPNA, which consisted of stable high, medium, and low symptom trajectories; and a combined symptom trajectory group, which consisted of the cross-tabulation of the PPND and PPNA trajectories. No association was found between the PPND, PPNA, or combined trajectory group membership and the age of any psychiatric illness onset in the 16-year-old children in this sample. This suggests that exposure to PPND, PPNA, and combined PPND and PPNA symptoms is not related to an earlier or later illness onset when defined as any illness. There a several possible explanations for this finding. First, there may be no link between the PPND, PPNA, or combined exposure and later child psychiatric illness. Most of the previous studies that found significant associations between PPND and PPNA exposure have examined younger children and examined behavioral and emotional problems, not clinical diagnoses [14, 94, 182]. It may be that exposure to PPND and PPNA symptoms increases problems in younger children but these problems are either time-limited or do not translate into clinical level disorders. Another more likely interpretation is that PPND and PPNA exposure only increases the risk for certain psychiatric illnesses and examining the outcome dichotomously obscures this association. The findings of anxiety exposure influencing the risk of CD in this sample support this interpretation.

Other considerations are the age at which diagnoses were assessed. It may be that age 16 is too young to determine the impact of PPND and PPNA exposure. While late adolescence is a time of increasing incidence for psychiatric illness, the peak incidence is in early adulthood

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[211]. Future research should extend the outcome to older ages to determine if this is the case. Finally, this research focuses on the experience of PPND and PPNA symptoms, not diagnoses. Meeting clinical criteria for depression and anxiety diagnoses require specific combinations of symptoms lasting for a specified duration that cause significant impairment. The use of symptom criteria may not represent a high enough level of maternal functional impairment, which may be necessary for PPND or PPNA to increase the risk of psychiatric illnesses in the exposed children.

The hypothesis that combined PPND and PPNA exposure would increase the risk of earlier diagnosis of any psychiatric illness was not supported. With no association between PPND or PPNA and age of onset, this is not surprising. Even without the individual trajectories displaying a significant association, it is possible that there could be an effect of combined exposure related to an increase in the severity of maternal symptoms and their impact on functioning. However, this was not supported.

2.2.5.2 Major Depression

No association was found between PPND or PPNA and the risk of MDD occurrence in this sample. With regard to PPND exposure, this was inconsistent with previous literature that overall suggests that there is an association with depression symptoms and MDD [129, 186]. Beyond the possibilities discussed with regard to age of onset results, there are a few additional considerations. The first is in the exposure measure of the PPND trajectory. The majority (84%) of women in this study were classified as being in the high depression trajectory. This seems unreasonably high. However, elevated depression symptoms were frequent in this sample of women. The mean CES-D score for women classified in the high depression trajectory was 23, well above the traditional 16-point cut-off for probable depression. Furthermore, this is not the first study to find high scores on the CES-D in low socioeconomic samples, as well as in samples

with a high proportion of African American women [156, 160, 161]. Still, there is concern that the use of the CES-D might provide a high rate of false positives [212], and this might be obscuring an association between PPND exposure and psychiatric illness. To test this possibility, an alternative modeling strategy was employed, using a dichotomous CES-D classification with a more stringent cut-point of greater than 23. This was modeled across the same five time points and logistic regression modeling was done the same way as in the primary analyses. While the distribution of women in the trajectories differed with the high depression group, encompassing only 15% of the sample, the results of the regression analyses were the same (results not shown) in that no association was found between depression trajectory and MDD diagnosis. It may be that there is no association between PPND and MDD occurrence. While previous literature has some support for an association, few studies have used a diagnostic outcome, and in studies that use a symptom measure of exposure like the CES-D, the effect sizes were small at best [14, 198].

With regard to PPNA exposure, there is less evidence to suggest a specific association with MDD. The ALSPAC study results found a link between emotional problems and anxiety exposure, but their outcome was not a diagnostic measure and the children were only 4 and 6.75 years of age [59, 94, 99]. Future research should utilize clinical outcomes in older children and young adults to verify the null association found in our study.

2.2.5.3 Conduct Disorder

The findings of no association between PPND and CD are not surprising. No studies were identified that looked specifically at CD and exposure to PPND. While there was some suggestion of more DBDs in exposed children reported in one study [129], the exposure measure was a combination of maternal depression and anxiety symptoms in the prenatal period only.

Thus, the study might be picking up on the association related to anxiety exposure. This is an area of research that requires more work to confirm or refute our findings.

The significant association between PPNA and CD is of particular interest, not only because of the strength of the association but also given the differential effect in males and females. High PPNA exposure was strongly protective against CD diagnosis in girls, but was a strong risk factor for boys. This gender difference is not without precedence. The primary characteristics of CD include repetitive and persistent patterns of maladaptive, antisocial behaviors that violate the rights of others and are age-inappropriate [213, 214]. CD is far more commonly diagnosed in boys and there is suggestion of a biological vulnerability as these behaviors are more common among males of every culture and every age [214]. PPNA exposure may increase this biological vulnerability in boys while reducing it in girls. During the prenatal period, male fetuses begin producing large amounts of androgens, particularly testosterone. Anxiety may be associated with increased stress, and elevated stress hormones, such as cortisol, have been correlated with higher levels of circulating testosterone crossing the placental barrier [75, 98]. Testosterone has been proposed to have differential effects on the fetus depending on gender. In males, the testosterone boost may impact the hypothalamic pituitary adrenal (HPA) axis, the stress response system, by promoting an aggressive "fight" response to stress instead of "flight".

The reduction of CD risk in exposed females may result from the same mechanisms that increase the risk in males. Increased cortisol may promote an increase in testosterone crossing the placenta. In females, this does not trigger additional testosterone production by the fetus, instead, testosterone suppresses estrogen production. This, in turn, may alter the HPA axis to promote the "flight" response in females instead of the "fight" response [214]. This would

reduce overt aggression in females, a large component of CD diagnosis. These hypotheses are still preliminary, however, and more research is needed to verify that prenatal anxiety has a differential effect on HPA axis function in males and females. While PPNA appears to protect against CD in this sample, it must be kept in mind that the effect of PPNA on other disorders is not yet known. Only MDD and CD had a high enough prevalence in this sample by age 16 to evaluate the individual disorders. Future studies should consider the risk of anxiety disorders among exposed females, which may be elevated as a result of altered HPA activity and estrogen suppression [215].

2.2.5.4 Conclusion

The study design used in this research provides a number of unique contributions to the literature. The use of individual-level trajectory patterns across both the pre- and postnatal period allows for the evaluation of the effect of commonly occurring patterns of symptoms and may be a more realistic exposure than a single time point assessment. Furthermore, by examining both anxiety and depression trajectories, we were able to examine the impact of co-occurring symptom patterns on psychiatric illness risk. To date, very few studies on PPND have used psychiatric diagnoses in adolescents as an endpoint and no other studies have been identified that examined the effect on PPNA on psychiatric illnesses.

A potential limitation of this research is the generalizability of these findings. Women in this sample were recruited based upon their first trimester substance use. However, over one quarter of this sample used no alcohol or other illicit drugs during pregnancy. In addition, results of prior analyses showed that pre-pregnancy use of alcohol, marijuana, cocaine, and other substances was not associated with depression or anxiety trajectories [202]. Furthermore, average alcohol and marijuana use, and any other illicit drug use during pregnancy were not

significantly associated with depression and anxiety symptom trajectories, mitigating this concern. Nevertheless, further replication in other samples is in order.

The strong association found between PPNA exposure and the risk of CD in males is an important avenue for future research. CD is significantly impairing to individuals, their families, and society. It is associated with poor family and peer relationships, school disruption and truancy, conflicts with authority, and criminal and aggressive behavior. Furthermore, it is also a precursor to antisocial personality disorder [213, 216]. Current treatment programs for CD have small treatment effects at best and identifying risk factors is essential for reducing the morbidity among adolescents, their families, and society [217, 218]. Developing interventions for pregnant women with high levels of anxiety may represent a novel approach to prevent the onset of CD in offspring.

2.3   PAPER 3: FROM PRE- AND POSTNATAL ANXIETY EXPOSURE TO CONDUCT DISORDER: A PATH ANALYSIS OF POTENTIAL MECHANISMS

2.3.1   Abstract

Background: Previous research into maternal pre- and postnatal anxiety (PPNA) exposure suggests that trajectories of elevated PPNA symptoms are associated with an increased risk for conduct disorder (CD) in exposed male offspring and a decreased risk for CD in exposed females. The purpose of this study is to examine potential mechanisms for this relationship.

Methods: Path analysis was used to examine five potential pathways between PPNA exposure and CD. The path model included the following hypothesized pathways: 1) a direct path between PPNA and CD, moderated by gender 2) a path involving PPNA predicting risk of child abuse, which would predict CD risk, 3) PPNA predicting negative parenting styles, which would increase CD risk, 4) PPNA affecting child temperament, thereby increasing the risk of CD, and 5) PPNA predicting lower IQ, which would predict a higher risk of CD.

Results: Two of the hypothesized pathways were confirmed. PPNA exposure predicted CD risk directly, with a significant moderation by gender. Medium and high PPNA-exposed males were at greater risk for CD than their low-exposure counterparts. Medium and high PPNA-exposed females were at a decreased risk for CD compared to the low-exposure group. PPNA also predicted alterations in child temperament. High PPNA exposure predicted higher levels of emotionality in offspring, which predicted an increased risk of CD. PPNA exposure

also predicted lower caregiver warmth, lower child IQ, and higher child activity ratings. However, these did not correspond to an increased risk of CD.

Conclusions: PPNA exposure significantly increased the risk of a number of adverse outcomes including CD in males, higher child temperament ratings of emotionality and activity, lower child IQ, and less caregiver warmth. This study provides a starting point for examining the effects of PPNA exposure on children and has implications for intervention targets.

2.3.2   Introduction

Conduct Disorder (CD) is a childhood psychiatric disorder characterized by chronic seriously deviant and antisocial behavior, including aggression to people and animals, property destruction and theft, serious violation of rules, and deceitfulness [26]. CD is associated with significant morbidity and stress for diagnosed children and their families, as well as for society. One estimate suggests that every child with CD costs society an additional $70,000 over a 7-year period related to increased services use and juvenile justice system involvement [219].

Primary prevention of CD is important for cost savings and reduction of the associated morbidity but requires an understanding of the etiology of the disorder. Recently, a new risk factor for the development of CD has been under investigation: exposure to maternal pre- and postnatal anxiety symptoms (PPNA). In a study using growth mixture modeling (GMM) to evaluate the most common individual-level trajectories of anxiety across the pre- and postnatal period, PPNA symptom exposure was significantly associated with the risk of CD in 16-year-old adolescents [220]. In males, the risk of CD in the medium PPNA exposure group was eleven times higher than for those in the low exposure group. Males in the high exposure group had an 18-fold increased risk of CD compared to the low exposure group. In females, the association

was reversed. Females exposed to medium levels of PPNA were 84% less likely to meet CD criteria compared to their low-exposure counterparts and females exposed to high PPNA levels were at an 90% reduced risk of CD compared to the low exposure group [220].

To date, PPNA is an underdeveloped area of study. No other research has been identified that examines PPNA exposure and the subsequent risk of CD. Most studies focused on the effects of postnatal depression exposure and excluded the impact of anxiety. Those that have examined pre- or postnatal anxiety exposure have focused on outcomes such as temperament [57, 133, 135] and behavioral/emotional problems in early childhood [59, 99].

In order to evaluate the role of PPNA on CD, it was necessary to identify first the known factors related to the development of CD and consider which of them might be related to PPNA exposure. This was followed by a path analysis to explore possible mechanisms through which PPNA exposure might alter the risk of CD. Burke and colleagues [221] reviewed 10 years of research on the etiological mechanisms of CD. This was used as a framework for the current theoretical path model. Major factors implicated in the development of CD include: child biology (e.g., hormones, neurotransmitters, and structural neurology), child abuse, parenting style, child intelligence, and child temperament [221]. There is evidence that each of these factors may be impacted by PPNA exposure.

During the prenatal period, alterations in child biology may be a result of excessive maternal Hypothalamic-Pituitary-Adrenal (HPA) axis activity, part of the "fight or flight mechanism" implicated in anxiety disorders [175]. Cortisol, a stress-induced hormone released by the HPA axis, readily crosses the placental barrier and is implicated in changes in fetal hormone production [76, 84]. Therefore, there may be a direct biological explanation for the link

between PPNA and CD risk. Furthermore, cortisol has a differential effect on male and female fetuses as a result of an increase in testosterone provoked by cortisol exposure [75, 98].

Parental anxiety and stress increase the risk of child abuse in the family, thereby increasing the risk of CD. Maternal anxiety has been directly linked to child abuse in several studies [222, 223]. It is possible that PPNA increases the risk of child abuse, which would increase the risk for CD, although this does not explain the differential effects of PPNA on male and female offspring.

Maternal parenting style is hypothesized to be impacted by maternal anxiety [224, 225], although few studies have examined this during the pre- or postnatal period [136, 199]. For example, mothers with clinically diagnosed anxiety disorders are more prone to catastrophizing, or overreacting to negative events [226]. Additionally, Woodruff-Borden et al. [227] reported that clinically anxious mothers were more withdrawn and disengaged during observed mother-child interactions than were non-clinically anxious women. Studies thus far have focused on mothers with a clinically diagnosed anxiety disorder, and it is unclear if symptoms of anxiety would produce the same effects as anxiety that meets clinical severity and duration criteria.

No studies have specifically examined the relationship between anxiety in the prenatal period and later child IQ, although one related study examined objective stress ratings in the prenatal period and child IQ in 5.5-year-olds [228] and found lower IQ scores in children exposed to high maternal stress in-utero compared to children exposed to medium and low levels of maternal stress. Only one study has examined postnatal anxiety exposure and an intelligence-related outcome. Galler et al. [134] found that scores on a national high school entrance exam, administered to children at age 11, were significantly lower among children exposed to elevated

maternal postnatal anxiety symptoms compared to children with exposure to lower levels of anxiety symptoms.

Alterations in child temperament as a result of PPNA symptom exposure have been examined with mixed results. Almost all studies in this area have examined temperament in infants. In a study of three-month-olds, Coplan et al. [133] found that maternal postnatal anxiety symptoms were associated with higher activity levels, more distress to limitations, and lower soothability. In contrast, Diener and colleagues [57] found no association between postnatal maternal anxiety symptoms and infant temperament. Similarly, studies in four-month-olds have had conflicting results. McMahon et al. [135] found that postnatal anxiety symptom exposure was associated with higher ratings of infant difficultness, while Davis et al. [54] found no association between postnatal anxiety symptoms and child temperament. Davis did, however, find an association between exposure to prenatal anxiety symptoms and negative behavioral reactivity to novelty in four-month-olds. Studies of postnatal anxiety symptom exposure and temperament in older infants are similarly conflicting, with no more substantial evidence pointing toward or against an association [229]. Some of these differences result from the fact that exposure assessments were performed at different times (e.g., 1-week postpartum, 6-months postpartum, etc.) and outcomes were measured using different instruments.

Thus, considering each of these factors, there is evidence that PPNA may operate through any one or all of these mechanisms (child biology, child abuse, parenting, IQ, and temperament) to affect the risk of CD in offspring. Identifying the most relevant paths will allow for better targeting of prevention activities, while enabling the identification of other important effects of PPNA exposure.

The path analysis in this report examined the following hypothesized pathways: 1) a direct path between PPNA and CD, moderated by gender 2) a path involving PPNA predicting risk of child abuse, which would predict CD risk, 3) PPNA predicting negative parenting styles, which would increase CD risk, 4) PPNA affecting child temperament, thereby increasing the risk of CD, and 5) PPNA predicting lower IQ, which would predict a higher risk of CD.

2.3.3 Methods

2.3.3.1 Participants

This analysis used data from the Maternal Health Practices and Child Development (MHPCD) project (N. Day, P.I. [140, 141]). The MHPCD project consists of two longitudinal cohorts of adult, English-speaking women recruited from a prenatal, hospital-based clinic. Between 1982 and 1984, the MHPCD project screened 1360 women in their fourth or fifth prenatal month for participation in the two cohorts. One cohort was selected based upon their prenatal alcohol consumption and included all women who drank three or more drinks per week in the first trimester and a random selection of those who drank less or abstained [140]. The second cohort was selected based on marijuana use and included all women who smoked two or more joints per month during their first trimester, and a random selection of women who smoked less or abstained [141]. This allowed for a continuum of women to be recruited, from those who used no substances during pregnancy to those who used heavily during this time. The sampling strategy was with replacement, so women could participate in one or both cohorts. Twenty-six percent of the women in this analysis completely abstained from alcohol, marijuana, and other illicit drugs during their first trimester. Except for selection criteria, the cohorts followed the same protocol and were combined for these analyses.

This study used data from the 10 completed MHPCD assessments: 1st trimester (baseline, assessed at the 4th or 5th month of pregnancy); 2nd trimester (assessed at the 7th prenatal month), delivery, 8 and 18 months postpartum, and 3, 6, 10, 14, and 16 years postpartum. For the baseline assessment, 829 women were recruited. By delivery, the sample size was 763 (21 had moved away, 16 were missed, 8 refused the delivery assessment, 2 were multiple births, 18 experienced maternal or infant death, and 1 infant was placed for adoption). Follow-up rates for each phase ranged between 76% and 88% with a mean of 82% of the delivery cohort.

The outcome of interest for these analyses is CD in the children, therefore, only mother-child pairs who had completed the child psychiatric assessment at the 16-year assessment were eligible for this analysis. Five hundred ninety-two participants completed the 16-year phase of the MHPCD project, 577 (76% of the birth cohort) of these had complete child psychiatric assessment data. Baseline maternal depression and anxiety were not different between those with age 16 follow-up and those without. Women excluded from the analysis (or lost to follow-up, n=186) were more likely to be Caucasian (58% in the excluded group versus 45% in the included group), but otherwise did not differ by demographics. Children lost to follow-up were more likely to be male (59% in the excluded group versus 48% in the included group) and less likely to have been exposed to marijuana in the prenatal period (38% in the excluded group versus 42% in the included group) than those included in this analysis. Excluded children had lower IQ scores and were less likely to rate their primary caregiver as overprotective in their parenting style, but they did not significantly differ from included children on any other covariates included in this analysis.

2.3.3.2 Measures

The children's PPNA exposure status was determined in two steps. First, maternal anxiety symptoms were measured at each phase (1st and 2nd trimester, delivery, 8 and 18 months postpartum) using a version of the trait scale of Spielberger's *State-Trait Anxiety Inventory-Short Form* (STAI) [143]. The modified scale was originally part of the *State-Trait Personality Inventory* (STPI) [201], and is almost identical to the STAI trait short form. Two questions have slight wording changes and one asked the same conceptual question with a clearer wording deemed more appropriate for a sample with a lower education level. The trait anxiety scale used a 4-point Likert scale and consisted of questions such as "I feel at nervous and reckless" and "I worry too much over stuff that really doesn't matter". Scores ranged from 10 to 40. The STAI has excellent psychometric properties (Cronbach's α= .86, [143]) and has been used to measure anxiety symptoms repeatedly in pregnant and postpartum women [56, 146, 147]. The reliability of the STPI is comparable to the STAI (Cronbach's α= .87 at baseline for the combined alcohol and marijuana cohorts).

A second step used GMM to determine if there were distinct subgroups of mothers experiencing similar anxiety symptom patterns across the five assessments (1st and 2nd trimester, delivery, 8 and 18 months postpartum). In an earlier publication, we reported that the best fitting model of anxiety symptoms was a three-group trajectory model [202]. Of the 577 participants, 12% (n=69) were classified as having low anxiety with stable STPI-t scores, 52% (n=299) were in the medium symptom group with stable anxiety scores, and 36% (n=209) were in a high group that experienced a slight decrease in anxiety scores early on, stabilized and remained higher than the other two groups over time [202]. Women in each trajectory group had significantly different baseline anxiety scores, mean low anxiety STPI score was 12.73 (CI=12.24 - 13.21), mean

medium trajectory STPI score was 15.76 (CI=15.48 – 16.05), and mean high anxiety trajectory STPI score at baseline was 22.22 (CI=21.59 - 22.85). These three trajectory groups were the PPNA exposures for the path analysis.

The primary outcome of interest in the current study was the risk for CD. Psychiatric diagnoses for a number of disorders, including CD, were assessed using the computerized Diagnostic Interview Schedule (DIS-IV) [203]. The DIS-IV is a structured diagnostic interview assessing psychiatric illness according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition [204]. The interview assessed the current (12-month) and lifetime prevalence of a number of disorders, including CD. All assessments were audio-taped and a random selection from each assessor was verified for quality control purposes. Test-retest reliability of the DIS-IV CD diagnostic criteria is not available at this time. Reliability of the DIS-III has been examined in substance-using individuals where CD diagnosis was found to have a fair test-retest reliability (kappa=0.54) [230].

Retrospective reports of childhood abuse were assessed by child's self-report at age 16 using the Childhood Trauma Questionnaire (CTQ) [231]. Children reported on the frequency of experiencing emotional neglect, emotional abuse, physical neglect, physical abuse, and sexual abuse while growing up. For example, a question assessing physical neglect asks "I didn't have enough to eat," with responses ranging on a 5-point Likert scale from "never true" to "very often true". Possible scores range between 5 and 25 for each subtype and a total score is also provided. The CTQ has established reliability (test-retest ranged between .79 to .86 for a 4-month retest [232]). For these analyses, the continuous total CTQ score was utilized. The CTQ also provides a deception scale that indicates a respondent's tendency to idealize his/her childhood. A large number of the participants scored positive on this scale so a sensitivity analysis was run without

these individuals. The results remained consistent with the full sample, so the total sample results are reported.

Parenting style was measured using the Parental Bonding Instrument (PBI) [233], which is a measure of parenting style specifically designed to examine characteristics of parenting that might contribute to later psychological problems. The PBI assess three general parenting dimensions: lack of warmth, authoritarianism, and over-protectiveness. The adolescents indicated how accurate each statement is regarding their primary maternal caregiver. Statements include "Helped me as much as I needed" and "Seemed emotionally cold to me", which are rated on a 4-point Likert scale ranging from "very like" to "very unlike". The PBI has an acceptable test-retest reliability (r=.63-.76) and a number of studies supporting its validity (see Parker (1989) for a thorough review [234]). In the MHPCD study, the PBI was rated by the children at age 16. Although this is the same assessment period as the outcome, it should be noted that: 1) PBI assesses parenting style across the child's lifetime, 2) PBI ratings have been demonstrated to be stable over long periods of time [234, 235], and 3) studies have shown that the PBI score is not vulnerable to bias by current psychiatric illness [234]. For the SEM, three composite scores for each subscale were used: scores ranged from 11-44 for the lack of warmth summary score, 5-20 for the authoritarianism summary score, and 6-24 for the over-protectiveness summary score. Higher scores indicate more negative parental styles on the lack of warmth, authoritarianism and over-protectiveness factors.

Child IQ was measured by specially trained assessors at age 6 using the Stanford-Binet Intelligence Scale (SBIS), fourth edition, which measures fluid reasoning, knowledge, quantitative reasoning, visual-spatial processing, and working memory, yielding an age-standardized composite score [236]. The reported internal consistency at age 6 is .92 (sd=3.2

93

points) [236]. For this analysis, the age-standardized composite score was used to determine if PPNA was related to IQ and, in turn, CD risk.

Child temperament was measured by mother's report using the Emotionality, Activity, and Shyness Temperament Survey (EAS) [237]. The EAS was designed to measure three underlying facets of childhood temperament: emotionality, activity, and shyness. These behavioral characteristics are stable ways in which people relate to their environment. In addition to the three temperament styles that the EAS was designed to measure, it has also been validated to provide information on a fourth temperament style, sociability [238]. The MHPCD study collected information on the four factor structure of the EAS at 18 months, 3 years, 6 years, and 10 years of age. Because the number of parameter estimates in an SEM is limited by sample size, a single EAS assessment was selected for inclusion in the SEM. EAS temperament has been demonstrated to be stable after age three [238], so selection was based on the assessment with the most complete data, which was the age 6 assessment.

Two papers have already examined the relations of potential confounders for the relationship between PPNA and CD in this sample [202, 220]. Baseline demographic characteristics including maternal age, marital status, and employment status were not associated with anxiety trajectory in this sample, nor were the occurrence of pregnancy, labor, or delivery complications [202]. The occurrence of CD in this sample was not associated with baseline maternal income or education, child's prenatal exposure to cigarettes, cocaine, marijuana, or other illicit drugs [220]. Prenatal exposure to alcohol was related to CD. However, one-way between-subjects analysis of variance (ANOVA) results showed no association between prenatal alcohol exposure and anxiety trajectory ($F(1,576) = 1.69$, p=.194, η^2=.003). Therefore, it was not a confounder. Similarly, maternal CD and Antisocial Personality Disorder (APD), while

associated with child CD, were not associated with maternal PPNA trajectory ($F(1,553) = .253$, $p=.615$, $\eta^2<.001$). The other major concern for confounding is pre- and postnatal depression exposure. Previous examination of depression trajectories found no significant association between pre- and postnatal depression trajectory exposures and the risk of CD in this sample [220]. Furthermore, when categories were combined (e.g. high depression & low anxiety, high depression & high anxiety, etc.), there was no association between trajectories and the risk of CD.

2.3.3.3 Path Analysis

Path analysis was performed using Mplus [152] to evaluate potential mechanisms between maternal anxiety trajectory and the risk of CD. A theoretical model was conceptualized based on previous research into attributes contributing to the development of CD, as summarized by Burke et al. [221]. Five main pathways from anxiety trajectory to CD were proposed (Figure 5):

1. The prediction of CD by anxiety trajectory groups is moderated by child gender.

2. There is a significant prediction of parenting style by anxiety, which in turn predicts CD.

3. Anxiety trajectory exposure predicts the risk of child abuse, which increases the risk of CD.

4. Anxiety trajectory influences temperament development, which predicts an increased risk for CD.

5. Anxiety trajectory negatively predicts IQ, which increases CD risk.

Based on previous findings of an interaction between gender and PPNA on CD risk [220], each pathway between PPNA and the intermediary variable was examined for potential moderation by gender using appropriate regression techniques and a PPNA by gender interaction. None of these tests indicated a significant difference by gender. Therefore, only the direct path was modeled with a gender by PPNA interaction.

Model estimation for parameters was performed using the Mplus WLSMV estimation method. The WLSMV is a weighted least square method with a mean- and variance-adjusted chi-square test statistic [152]. To evaluate overall model fit, we examined the comparative fit index (CFI), over .95 indicates good fit [239]; Tucker-Lewis Index (TLI), over .90 is considered good fit [239]; Root Mean Square Error of Approximation (RMSEA), less than .06 is considered the minimum for good fit [239]; and a Weighted Root Mean Square Residual (WRMR) of greater than .90 is classified as a good fit [240].
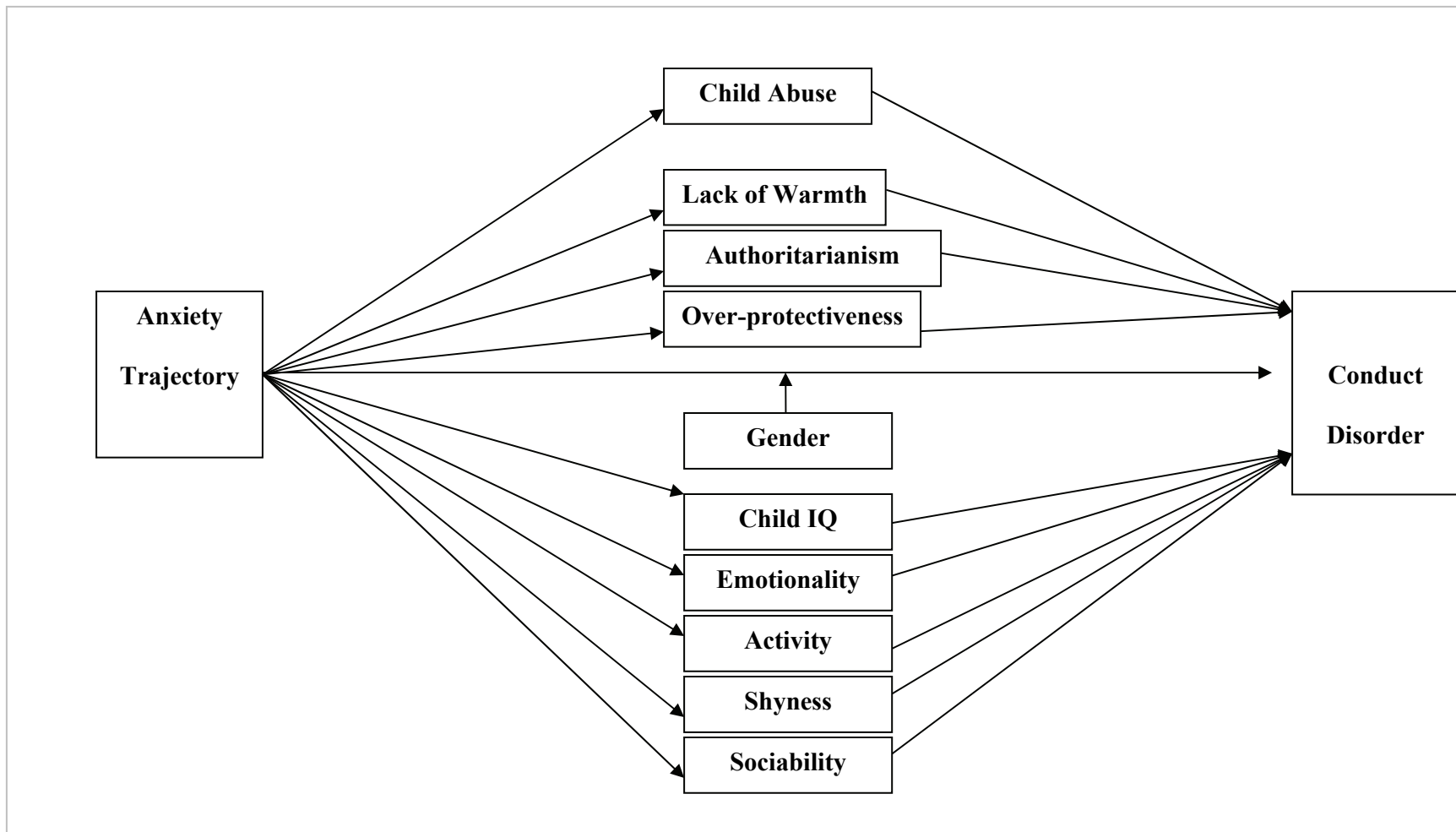
Figure 5: Potential mechanisms of the impact of maternal anxiety trajectory exposure on the risk for Conduct Disorder in offspring.

2.3.4 Results

2.3.4.1 Sample Characteristics

Mothers in this sample were, on average, 22.9 years of age at recruitment; about half were Caucasian (45%), and half African American (55%), 52.5% of the offspring were female and 47.5% were male (Table 11). About 12% of the children met diagnostic criteria for CD by age 16. Twelve percent of the children in this sample were exposed to the low PPNA trajectory, 52% to the medium, and 36% to the high level.

Anxiety trajectory was significantly correlated with child abuse, parental authoritarianism, child IQ, child emotionality, and child activity level. CD diagnosis was significantly correlated with gender, child abuse, parental lack of warmth, and child emotionality. The correlation matrix for variables included in the path analysis can be found in Table 12.

Table 13 presents the results of an uncontrolled logistic regression of CD on anxiety by child's gender. Females exposed to the medium and high anxiety trajectories were at a reduced risk of CD compared to girls exposed to low maternal anxiety trajectories. Males exposed to medium and high anxiety trajectories were at significantly higher risk for CD than males in the low exposure group.

Table 11: Sample characteristics.

Variable		Total Sample		Low Anxiety	Medium Anxiety	High Anxiety	p-value*
		(n=577)		12% (n=69)	51.8% (n=299)	36.3% (n=209)	
		Mean / % (sd)	Range				
Gender	Males	47.5%		50.7%	49.5%	43.5%	.353
	Females	52.5%		49.3%	50.5%	56.5%	
Conduct Disorder (CD) (age 16) [1]	Yes	11.6%		15.9%	11.5%	10.6%	.481
	No	87.5%		88.1%	94.5%	89.4%	
Child Abuse Score (age 16) [2]		35.0 (10.57)	25-96	33.61	34.28	36.55	.033
Parenting Style (age 16) [3]	Lack of Warmth	17.98 (6.53)	11-44	16.30	17.99	18.54	.049
	Authoritarianism	10.72 (3.3)	5-20	10.49	10.44	11.21	.032
	Overprotectiveness	11.07 (3.75)	6-24	10.41	10.93	11.51	.068
Child IQ (age 6) [4]		91.81 (13.95)	55-131	96.77	92.72	88.94	<.001
Child Temperament (age 6) [5]	Emotionality	2.76 (0.71)	1-5	2.58	2.74	2.85	.023
	Activity	3.89 (0.59)	2-5	4.08	3.92	3.78	.001
	Shyness	2.57 (0.61)	1-5	2.48	2.57	2.61	.888
	Sociability	3.53 (0.58)	1-5	3.52	3.54	3.52	.349

*p-value is for ANOVA for continuous variables and Chi-Square for categorical comparisons.

[1] CD was measured using the Diagnostic Interview Schedule, version IV [203].

[2] Abuse was measured by the Childhood Trauma Questionnaire [231].

[3] Parenting style was measured using the Parental Bonding Instrument [233].

[4] Child IQ was measured with the Stanford-Binet Intelligence Scale [236].

[5] Child temperament was measured using the Emotionality, Activity, and Shyness Temperament Survey [237].

Table 12: Correlation matrix for all variables in the conceptual model of anxiety trajectory exposure and risk of conduct disorder (CD).

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. CD	1.00											
2. Medium Anxiety	-.006	1.00										
3. High Anxiety	-.027	-.782*	1.00									
4. Gender	.090*	.042	-.060	1.00								
5. Child Abuse	.217**	-.073	.109*	-.001	1.00							
6. Lack of Warmth	.086*	.002	.065	-.049	.529**	1.00						
7. Authoritarian	.037	-.089*	.110**	.098*	.095**	-.015	1.00					
8. Over-protectiveness	-.022	-.040	.087	-.210**	.193**	.424**	.184**	1.00				
9. Child IQ	-.015	.067	-.157**	.002	-.104*	-.074	-.201**	.011	1.00			
10. Emotionality	.093*	-.028	.094*	.023	.115**	.104*	.029	.013	-.001	1.00		
11. Activity	.040	.058	-.141**	.127**	.005	-.106*	.060	-.063	-.006	-.029	1.00	
12. Shyness	-.044	-.006	.044	-.055	-.042	.025	.072	-.001	-.094*	.143**	-.358**	1.00
13. Sociability	.064	.021	-.018	.010	.001	-.075	-.018	-.021	.027	.087*	.383**	-.374**

*p<.05, **p<.01

Table 13: Logistic regression of Conduct Disorder on anxiety trajectory by gender.

Conduct Disorder					
		B (Std. error)	Wald (df)	p-value	Odds-ratio
Gender (Main Effect)			2.67 (1)	.102	--
Anxiety (Main Effect)			9.08 (2)	.011	--
Gender x Anxiety*	Females - Medium	-1.26 (.5)	6.21 (1)	.013	.29
	Females - High	-1.59 (.56)	7.97 (1)	.005	.21
	Males – Medium	1.89 (.82)	5.34 (1)	.021	6.65
	Males - High	2.34 (.87)	7.22 (1)	.007	10.41

* Anxiety reference level=low.

2.3.4.2 Path Analysis

The MHPCD project has a strict protocol for maintaining data quality ensuring that erroneous values are caught and corrected. For this reason, outliers in the data cannot be arbitrarily removed. Data screening indicated 13 potentially influential outliers. A sensitivity analysis was performed removing these 13 values. The model did not differ substantially from the model with all participants included, both in fit indices and parameter estimates, therefore the outliers were retained.

For the theoretically specified model, there was a significant difference between the observed and modeled covariance matrices – i.e., the relations among the variables were not modeled (or explained) correctly (model #1, Table 14). However, five additional correlations were added to the model based on model diagnostics, including: child sociability with child activity, child shyness with child activity, child shyness with child sociability, parental overprotection with parental lack of warmth, and parental authoritarianism with parental overprotection. There was a significant improvement in model fit with these correlations added (model #2, Table 14). Pathways that had been specified in the theoretical model, but did not

significantly contribute to the model, were removed for parsimony. The final model met the criteria for good fit on all measures (model #3, Table 14).

Table 14: Model fit indices for models tested during model identification.

Model	χ^2 (df)	CFI	TLI	RMSEA	WRMR
1	403.89 (56)	.39	.04	.11	2.04
2	143.69 (51)	.94	.90	.04	.89
3	154.182 (62)	.95	.93	.03	.92

CFI=Comparative Fit Index (cut-off >.95), TLI= Tucker Lewis Index (cut-off >.90), RMSEA = Root Mean Square Error of Approximate (cut-off <.06), WRMR = Weighted Root Mean Square Residual (cut-off .90-1.0).

2.3.4.3 Final Model Results

Five pathways were proposed to explain the relationship between PPNA and the risk of CD. As hypothesized, the prediction of CD by PPNA was significantly moderated by gender (Figure 6). The inclusion of the two gender/anxiety interaction effects significantly contributed to the model ($\Delta\chi^2(2) = 7.44$, p=.02). Furthermore, the two gender/anxiety interaction parameters were significant for both the medium (compared to low) and high (compared to low) trajectories (p=.02 and p=.01, respectively). Thus, the association between anxiety trajectory and CD differed by gender in the medium and high anxiety trajectory groups compared to the low trajectory group. Males exposed to medium and high PPNA trajectories were at increased risk of CD, compared to low exposed males, and females exposed to medium and high PPNA were at reduced risk of CD compared to low PPNA-exposed girls. The direct pathway from PPNA to CD
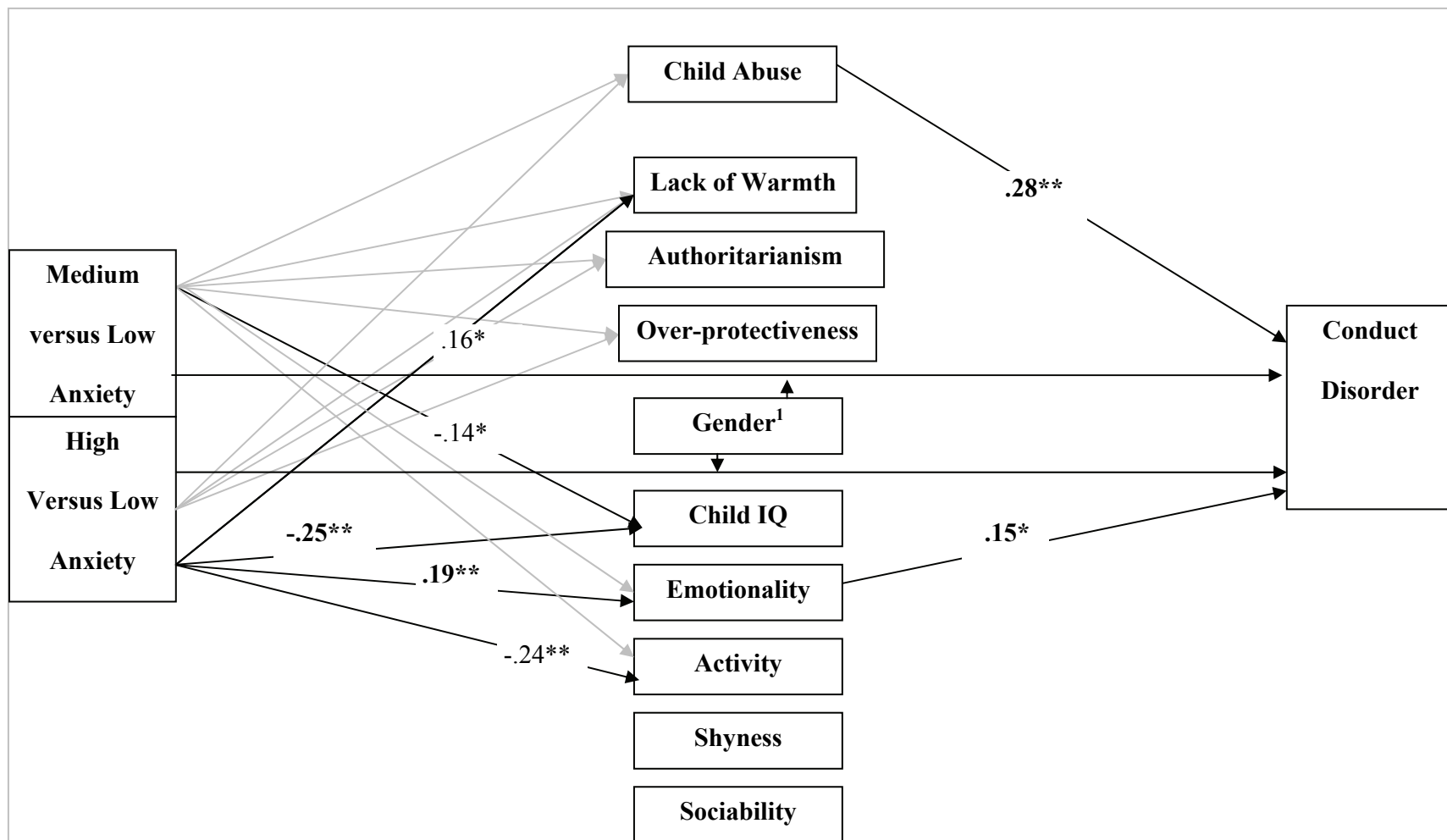
Figure 6: Standardized estimates of paths between exposure to pre- and postnatal anxiety trajectories and risk of conduct disorder.

[1]Gender moderation: $\Delta\chi^2$= 7.441, df=2, p=.02. Medium versus low anxiety trajectory by gender, p=0.02 and high versus low anxiety trajectory by gender, p<0.01. Model fit statistics: Satorra-Bentler scaled χ^2 = 47.385 (30), p=.023; CFI=.95, TLI=.93, RMSEA=.032, WRMR=.92. *p<.05, ** p<.01, non-significant pathways are shown in gray.

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remained significant even after controlling for child abuse, negative parenting styles, child IQ, and child temperament.

Medium and high PPNA exposure did not predict the risk of child abuse (β=.03, z=.38, p=.71 and β=.13, z=1.64, p=.10, respectively), although child abuse predicted higher CD risk (β=.28, z=5.4, p<.01). Thus, the hypothesis that PPNA would increase the risk of child abuse, thereby increasing the risk of CD, was not substantiated.

Children exposed to high PPNA were more likely to rate their primary caregiver as lacking in warmth compared to children exposed to low PPNA (β=.16, z=2.13, p=.03). There was no difference in parental warmth ratings between medium PPNA-exposed children and their low exposure peers (β=.07, z = 89, p=.37). PPNA exposure was not associated with authoritarian parenting or with over-protection. After controlling for the correlation between child abuse and negative parenting styles (lack of warmth, authoritarianism, and overprotection), parenting styles did not predict the risk of CD. The hypothesis that PPNA would increase the risk of CD through negative parenting styles, therefore, was not substantiated.

As hypothesized, PPNA exposure was associated with lower IQ scores in both the medium and high PPNA exposed groups compared to the low exposure group (β= -.14, z = -2.12 p=.04; β= -.25, z = -3.72, p<.01, respectively). However, IQ scores were not associated with an increased risk of CD when negative parenting styles were controlled.

Both child's emotionality and activity were associated with high PPNA exposure but only emotionality was associated with CD risk. High PPNA exposed children had higher emotionality scores compared to low PPNA-exposed children (β=.19, z = 2.76, p=.01). Higher emotionality was also associated with an increased risk of CD (β =.15, z = 2.18, p=.03). High PPNA exposure was related to lower activity levels compared to low PPNA exposure (β=-.24, z = -3.21). Activity

level was not associated with CD risk. Child's sociability and shyness were not associated with PPNA exposure or CD risk. Thus, the hypothesis that PPNA would affect child temperament was partially supported.

2.3.5   Discussion

2.3.5.1 PPNA and CD

The direct path between PPNA and CD risk was not completely mediated by the other four hypothesized pathways. The interaction between PPNA and child gender showed a higher risk of CD in medium and high PPNA-exposed males and a lower CD risk in medium and high PPNA-exposed females. These associations remained significant after controlling for abuse, negative parenting styles, child temperament, and child IQ. This suggests that either the pathway operates through a direct biological mechanism or through an unidentified alternative pathway. It is more likely that this represents a biological pathway, given the strong moderation of the direct path by gender. It is unlikely that changes in child development resulting from environmental characteristics altered by PPNA would show as strong a difference by gender, as this would require the mothers to react to their own anxiety differently for male or female children.

The other pathway from PPNA to CD that was confirmed was through the child's emotionality. Emotionality is a propensity for distress accompanied by intense automatic arousal [237]. Children exposed to high PPNA had higher emotionality scores compared to those exposed to low levels, which in turn were associated with higher risk of CD. Medium level PPNA exposure (compared to low) was not associated with child's emotionality. These findings of higher emotionality in high PPNA-exposed children are similar to findings of more distress to limitations and lower soothability found in some of the research into postnatal anxiety exposure

and temperament in infants [133, 135]. These new findings provide evidence of a persistent effect of PPNA into older ages.

2.3.5.2 PPNA and Other Intermediaries

Contrary to our hypotheses, neither medium nor high levels of PPNA were associated with an increased risk of child abuse after controlling for the correlation between child abuse and negative parenting styles. As previous research has demonstrated, the risk of CD was positively associated with reports of child abuse [221].

Only one of the negative parenting style variables was associated with PPNA. Children of high PPNA mothers were more likely to rate their primary caregivers as lacking in warmth, compared to their low exposure counterparts. Children exposed to medium levels of PPNA did not differ from the low exposure group with respect to perceptions of parental warmth. Authoritarian parenting and parental over-protectiveness were not associated with PPNA exposure after controlling for the correlations between the parenting styles and child abuse. Previous research has not specifically examined PPNA and these parenting outcomes, although the findings of lack of warmth are similar to the findings by Woodruff-Borden et al., who reported that clinically anxious mothers were more withdrawn and disengaged [227].

In addition to the relationship between PPNA and emotionality, one other child temperament variable was associated with PPNA exposure. Contrary to the findings of Coplan et al. [133], who found no association between trait anxiety and activity level and a positive association between state anxiety and activity level, high PPNA exposure (compared to low) was associated with higher activity in this study. Medium PPNA-exposed children did not significantly differ from low PPNA-exposed children in their activity levels. Neither shyness nor

sociability was associated with PPNA; however, other literature has not examined these outcomes in relation to PPNA so comparison is not possible.

Finally, child's IQ was negatively and significantly associated with medium and high PPNA exposure, compared to low PPNA-exposed children. There is very little research on the effects of pre- or postnatal anxiety exposure on child's IQ so these findings suggest that this is an important avenue for future research. Furthermore, lower IQ is associated with a number of other psychiatric illnesses including schizophrenia [241] and dementia [242], which would merit further research.

2.3.5.3 Strengths/Limitations

A limitation to this study is the unknown reliability of CD diagnosis using the DIS-IV. Only one study has been done to assess reliability of CD diagnosis by the DIS, and the authors reported only fair test-retest results [230]. The study used an older version of the DIS (III) and, unlike our sample, it was comprised of a sample of adults with substance use problems. It is probable that the reliability of the DIS-IV is better in this sample because our sample, being younger and experiencing symptoms for less time, would be less prone to recall bias for the age of onset and duration of symptoms.

Generalizability is a concern in this sample because mothers were recruited based on their prenatal drug use. While this may limit the generalizability of these findings, it should be noted that over one-quarter of the mothers in this sample used no alcohol or illicit drugs during the prenatal period. Furthermore, none of the studies examining PPNA trajectories in this sample have found a relation between alcohol or drug use and maternal anxiety, either in the pre- or postnatal period [202, 220]. This minimizes the concern of the applicability of these results to a more general population. Furthermore, this study over-samples women from under-represented

minority groups, which are often omitted from other studies, thereby increasing the relevance of this report to an important part of the population.

To our knowledge, this is the only study to examine potential pathways from PPNA exposure to CD risk and therefore the results need to be replicated. However, these findings provide a starting point for studies to investigate PPNA as a risk factor for CD and to identify points for intervention. This study clearly demonstrates that untreated PPNA is a risk factor, especially for male offspring.

Additionally, the intermediary points tested in the path analysis are important as independent outcomes. We have documented serious consequences involving lack of parental warmth, difficult child temperament, and lower child IQ. These findings can be used as a guide for future studies as they consider other potential effects of PPNA exposure, such as impairment in mother-child bonding, child cognitive and physical development, and other psychiatric illnesses.

3.0   SUMMARY DISCUSSION

3.1.1   Summary of Findings

The overarching goal of this research was to examine the relationship between pre-and postnatal depression and anxiety exposure and psychiatric illness in exposed offspring. The purpose of the first in this series of analyses was to identify if there were distinct, individual-level trajectories of maternal depression and anxiety symptoms across pregnancy through 18 months postpartum and, if so, what maternal factors were associated with membership in the trajectories. GMM analyses of PPND trajectory indicated two distinct pattern groups: one, a group of high symptom women who remained high across the entire time period; and two, a low symptom group who remained stable across the period. Over 80% of the women in this sample were classified as being in the high symptom trajectory, which is likely a result of the sample characteristics (low-socioeconomic, urban women) and the measure used (the CES-D tends to find higher rates of probable depression in pregnancy than other scales). Interestingly, symptoms were stable across the pre- and postnatal period and there was no group identified that experienced solely "postpartum depression". Instead, they tended to have stable levels of PPND. This finding is similar to the Fergusson and colleagues study that found that delivery was a time of decreasing probability for meeting depression criteria, contradicting the hypothesis that "postpartum depression" is the more common presentation of symptoms [28].

PPND trajectory group membership was associated with social support and cigarette smoking, but not with maternal age, race, marital status, monthly income, employment status, education, pre-pregnancy alcohol, marijuana, cocaine, and other drug use, stressful life events, or the occurrence of pregnancy, labor, or delivery complications. Social support and cigarette smoking are consistent correlates of PPND, as found in other studies in similar populations [162-165, 243]. In contrast to other research, women in the high PPND trajectory were not more likely to use alcohol or other illicit substances [244]. This may be because the study utilized a depression symptom measure instead of a clinical diagnosis, which includes symptoms as well as impairment and duration criteria or it may be due to a ceiling effect caused by the large proportion of women in the high symptom trajectory.

Analysis of the PPNA symptoms found three distinct trajectories, a high, medium, and low group. The distribution of women in these trajectories was 12%, 52%, and 32%, respectively. The anxiety symptom trajectories had stable symptom levels across pregnancy and the postpartum, similar to the PPND trajectories. Maternal factors that were associated with PPNA trajectory group membership included social support and maternal education. PPNA was not associated with maternal age, race, marital status, monthly income, employment status, education, cigarette smoking, pre-pregnancy alcohol, marijuana, cocaine, and other drug use, stressful life events, or the occurrence of pregnancy, labor, or delivery complications.

PPND and PPNA trajectories were highly correlated. Of the six possible combinations of PPND (low, high) and PPNA (low, medium, high), five were represented with any frequency: low PPND and low PPNA (7.8%), low PPND and medium PPNA (8.1%), low PPND and high PPNA (0.7%), high PPND and low PPNA (4.3%), high PPND and medium PPNA (43.7%), and high PPND and PPNA (35.5%). There were only four individuals in the low PPND and high

PPNA group. For the most part, women with high PPND had medium or high levels of PPNA. The only maternal factor significantly associated with combined trajectory group membership was social support. There were no variables that were uniquely predictive of combined, as opposed to individual, trajectory groups.

The purpose of the second part of these analyses was to examine if PPND and PPNA trajectory groups affected the risk of onset of psychiatric illness overall in exposed offspring and if they affected the risk of MDD and CD, specifically. The effect of combined trajectory group membership on the risk of these disorders was also evaluated. There was no evidence that PPND, PPNA, or combined group membership affected the risk of onset of overall psychiatric illness by age 16 in this sample, nor were they associated with risk for MDD specifically. PPND and the combined trajectory group exposure were also not associated with CD risk. There are several possible reasons why these relationships were not significant. First, there may be no increase in risk associated with PPND or PPNA exposure. Second, not all psychiatric diagnoses were assessed. While overall risk and MDD risk did not change as a result of exposure, there may be an association with another disorder not measured, or with a specific disorder that did not occur frequently in this sample. A related possibility is that age 16 is not old enough to detect differences in the occurrence of these disorders as the incidence of certain psychiatric illnesses increases rapidly from puberty into young adulthood [5]. Finally, the use of symptom assessments to measure exposure may not capture the necessary severity to translate into clinical outcomes. It may require the use of clinical diagnosis, which requires a certain level of impairment and duration be present to see any effect of exposure.

By contrast to the PPND trajectories, PPNA exposure was significantly associated with an increased risk for CD in boys, but appeared to decrease the risk for CD in girls. Evidence in

the literature suggests that this gender difference may be due to hormonal conditions during pregnancy that differentially affect male and female fetal development. Studies have shown that the primary HPA-axis stress hormone, cortisol, readily crosses the placental barrier and is associated with increased levels of testosterone in the fetus [75, 98, 245]. In males, this may directly "prime" the fetus for a more "fight" oriented response of the fight or flight mechanism making CD more likely. In female fetuses, the testosterone suppresses natural estrogen function and may prime the fetus for a more "flight" oriented response, making CD less likely.

The final analysis in this series focused on the mechanisms by which PPNA exposure might increase the risk of CD in exposed children. Several potential mechanisms were hypothesized following the findings of Burke et al. [221]: 1) a direct mechanism from PPNA exposure to CD risk, moderated by gender, 2) a pathway by which PPNA increases the risk of parental child abuse, which then increases the risk of CD, 3) a mechanism whereby PPNA increases the likelihood of certain negative parenting qualities (lack of warmth, authoritarianism, and overprotection), which increases CD risk, 4) a pathway by which PPNA lowers IQ, which increases the risk for CD, and 5) a pathway where PPNA affects infant temperament (emotionality, activity, sociability, and shyness) and thereby increases risk of CD. Two of these pathways were supported. The direct pathway of PPNA predicting higher risk of CD in boys and lower risk in girls remained significant even after controlling for the other potential mechanisms. While this direct pathway could encompass any number of unmeasured mechanisms, it is most probable that it is a biological pathway. The MHPCD study does not have data on biological mechanisms to test this; however, the gender differences in the effect of PPNA exposure support a biological hypothesis. It is unlikely that maternal anxiety would affect an environmental or social factor differently in boys and girls to the degree that it increases the risk of CD in boys and

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decreases it in girls. This is consistent with the HPA-axis research into fetal cortisol exposure [75, 98, 245]. The second supported pathway was between PPNA exposure and higher child emotionality, which predicted a higher likelihood of CD diagnosis. Previous research has not examined the relationship between PPNA and the EAS specifically. However, there are studies suggesting alterations in temperament (as measured by a number of other scales) may be associated with PPNA exposure, although this research has mixed results [54, 133, 135, 229].

Additionally, while the SEM analysis did not support an effect of PPNA on CD through child IQ, parenting, or child abuse, several of the partial paths were supported. PPNA exposure predicted children rating their primary caregivers as lacking in warmth, similar to the findings of Woodruff-Borden et al. [227] who found clinically anxious mothers were more withdrawn and disengaged during mother-child interactions. PPNA also predicted lower IQ similar to the findings of two other studies examining cognitive outcomes [9, 228], and higher levels of child activity, which was consistent with Coplan et al. [133].

3.1.2 Strengths and Limitations

There are a few issues to consider when interpreting these findings. One potential concern of this study is the use of a sample selected based upon substance use. This would limit the generalizability of this study to other substance-using pregnant women. However, over a quarter of this sample abstained from alcohol and illicit substance use during the first trimester and those who did not use substances during the first trimester were unlikely to start in later trimesters. Furthermore, neither pre-pregnancy substance use nor average prenatal alcohol and illicit substance use were associated with trajectory membership, mitigating this concern. A more likely concern for generalizability is the use of a low-socioeconomic sample with a large

percentage of African-American participants. Women in this demographic group tend to have higher rates of depression and anxiety overall and therefore our results may not be generalizable to all women [167, 168]. These results need to be verified among higher socioeconomic groups. Still, the lack of generalizability does not trivialize the importance of these findings. There are higher rates of CD in low-socioeconomic status communities and the need for primary prevention is significant [246]. Identifying and treating women with medium and high PPNA may be a novel way to prevent CD.

Additionally, this study could have been strengthened by the addition of paternal information. It is possible that women who suffer from high depression or anxiety symptoms choose partners who are different than the general population, which might contribute to some of these research findings. For instance, if women with high anxiety are more likely to be with men who have a history of antisocial behavior or other externalizing problems, the father's psychopathology may contribute to the child's risk of CD. Unfortunately, these data are not available in this study to corroborate or dispute this possibility.

Another limitation of this research is the use of the CES-D, which may have over-estimated the levels of depression symptoms in this population. Over 80% of this sample was classified as having high depression symptoms. While this may be accurate in this low socioeconomic, large minority population, it may also be inflated due to the use of the CES-D in pregnancy. The CES-D consistently finds higher rates of probable depression among pregnant women and minority populations than other depression measures and may be capturing some of the physiological symptoms of pregnancy in its measure of somatic symptoms [156-159]. Despite this concern, a recent study suggests that the somatic component of the CES-D does not

bias assessment during pregnancy [247]. Replication of these analyses using other scales of depression symptoms during this time period would be prudent.

While not a limitation per se, it is important to keep in mind that the assessment of PPND and PPNA exposure consisted of symptom scales. These results may not be applicable to women with clinical level disorders, which are more restrictive in that there are duration and severity criteria that must be met for a positive diagnosis. Therefore, it needs to be kept in mind that while exposure to PPND symptoms was not associated with MDD or CD risk in children, diagnosed maternal major depression during this time may be. These analyses are not able to examine that question, which must be left for future research. On the other hand, the association between PPNA and CD is particularly compelling because a measure of "high anxiety" is less stringent than an anxiety diagnosis and an association was still detected. Furthermore, the risk of CD diagnosis was lower for those exposed to medium PPNA than for the high exposure group, which supports the idea of a dose-response relationship. This is one of the benefits of using an ordinal scoring method as opposed to a yes/no diagnosis.

This research contributes several new dimensions to the current literature on perinatal maternal mood and childhood outcomes. It is the first study to use individual-level trajectory patterns to look at depression and anxiety symptoms during both the pre- and postnatal periods. As the trajectories identified in this research suggest a stable level of symptoms across the pre- and postnatal periods, the use of combined exposures may be more representative than the traditional approach of examining one time period or the other.

Modeling the effects of PPND, PPNA, and their co-occurring patterns enabled the examination of potential combined effects on the risk for psychiatric illness in adolescents. It

also enabled the identification of the unique contribution of PPNA on CD risk, which identified a new risk factor for future research and a possible prevention target.

The use of data from a prospective cohort study with multiple assessments allowed for the assurance of temporality, as well as minimizing recall bias in data collection. Furthermore, the recruitment of a large proportion of African-Americans, as well as women from a low-socioeconomic status, contributes to research in traditionally understudied populations.

3.1.3   Public Health Implications

There are several important public health implications as a result of these findings. The first point of importance is that screening for depression and anxiety symptoms should begin early in pregnancy. Women reporting high levels of depression and anxiety symptoms in their first trimester are likely to continue experiencing these elevated levels through pregnancy and the postnatal period. Furthermore, women experiencing high levels of PPND symptoms are also likely to be suffering high PPNA levels, which should not be ignored given their association with CD. Currently, there is a large focus on maternal depression during pregnancy and the postpartum but much less focus on anxiety [64, 199]. The results of this study suggest that the consequences of PPNA exposure are as important as those of PPND. Moreover, the long-term effects differ by the type of exposure, suggesting that both need to be evaluated.

Social support was an important maternal factor associated with both PPND and PPNA group membership. Women in the high PPND and PPNA trajectories tended to have lower social support scores than women in the low trajectories. This may be an important avenue for intervention among these women [248, 249]. Additionally, cigarette smoking was more likely among women in the high depression trajectory. Tobacco exposure in utero is known to have a

number of adverse effects on offspring [250], and women smoking in the first trimester are likely to continue throughout pregnancy [251, 252]. The co-occurrence of depression symptoms and cigarette smoking may make smoking cessation more difficult and should be considered when counseling cessation.

This research has identified PPNA exposure as being a significant risk factor for several adverse childhood outcomes including CD, higher emotionality and activity levels for child temperament, lower child IQ, and more reporting of "lack of warmth" by children whose mothers were in the high PPNA trajectory. Each of these outcomes has negative consequences for child development and shows the importance of future research on the effects of PPNA exposure. Because of the novel use of symptom trajectories as the exposure in these analyses, the results can only be considered preliminary pending further replication. However, this research provides a solid foundation for future avenues of research as well as providing further support for the growing research interest in PPNA.

APPENDIX: MODEL FITTING FOR PATH ANALYSIS

Table 15: Model fit indices for models tested during model identification.

Model	χ^2 (df)	CFI	TLI	RMSEA	WRMR	$\Delta \chi^2$ (df)	p-value
1	403.890 (56)	.387	.037	.114	2.044	--	--
2	143.688 (51)	.944	.901	.037	.890	not nested	--
3	143.985 (53)	.947	.910	.035	.890	.297 (2)	.862
4	147.435 (55)	.948	.912	.034	.901	3.45 (2)	.178
5	147.707 (56)	.948	.915	.034	.901	.272 (1)	.602
6	147.845 (57)	.949	.917	.033	.901	.138 (1)	.710
7	149.580 (58)	.949	.920	.033	.901	1.735 (1)	.188
8	149.609 (59)	.951	.922	.032	.902	.029 (1)	.865
9	149.651 (60)	.951	.925	.032	.903	.042 (1)	.838
10	152.832 (61)	.950	.927	.031	.907	3.181 (1)	.074
11	154.182 (62)	.949	.926	.032	.921	1.35 (1)	.245

CFI=Comparative Fit Index, TLI= Tucker Lewis Index, RMSEA= Root Mean Square Error of Approximate, WRMR=Weighted Root Mean Square Residual.

Table 15 provides model fit indices for the path analysis model at each iteration.

Model 1 is the base model. The following pathways were specified (anxiety is always two variables: medium versus low and high versus low):

-CD on anxiety trajectories
-CD on child gender
-CD on anxiety trajectory by gender interaction
-CD on child abuse
-CD on lack of warmth
-CD on overprotection
-CD on authoritarianism
-CD on child IQ
-CD on child emotionality
-CD on child activity
-CD on child sociability

-CD on child shyness
-Child abuse on anxiety
-Lack of warmth on anxiety
-Overprotection on anxiety
-Authoritarianism on anxiety
-Child IQ on anxiety
-Child emotionality on anxiety
-Child activity on anxiety
-Child sociability on anxiety
-Child shyness on anxiety
-Child IQ on child abuse
-Child IQ on lack of warmth
-Child IQ on overprotectiveness
-Child IQ on authoritarianism
-Child abuse with lack of warmth
-Child abuse with overprotectiveness
-Child abuse with authoritarianism

Model 2 adds the following correlations to Model 1: child sociability with child activity, child shyness with child activity, child shyness with child sociability, parental overprotection with parental warmth, and parental authoritarianism with parental overprotection.

Model 3 fixes anxiety to child sociability

Model 4 fixes anxiety to child shyness

Model 5 fixes IQ to CD

Model 6 fixes parental warmth to CD

Model 7 fixes child activity to CD

Model 8 fixes child shyness to CD

Model 9 fixes parental authoritarianism to CD

Model 10 fixes parental overprotection to CD

Model 11 fixes child sociability to CD

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