PRENATAL DEPRESSIVE SYMPTOMS AND OFFSPRING INTERNALIZING SYMPTOMS AT 22 YEARS

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Prenatal depression has been linked to a number of adverse outcomes for the developing fetus. A few studies have explored the effects on offspring psychopathology in childhood and adolescence, but it is unclear whether these effects extend into adulthood. This study examined the effect of prenatal depressive symptoms on offspring internalizing score**s** at 22 years within the Maternal Health Practices and Child Development Study birth cohort. Mediation analysis was performed to examine potential mediators of this relationship. Latent growth curve modeling was utilized to perform a trajectory analysis to investigate whether changes in maternal depressive symptoms over time had an effect on offspring internalizing symptoms.

Prenatal depressive symptoms were common in our sample and were associated with higher internalizing symptoms in exposed offspring at 22 years. These associations remained significant while controlling for prenatal and current covariates of internalizing symptoms. This effect was not found to be mediated by birth weight. Latent growth curve modeling revealed that, on average, maternal depressive symptoms decreased slightly from the first trimester through 16 years. Within the trajectory analysis, higher first trimester maternal depressive symptoms were marginally associated with offspring internalizing scores at 22 years, however this effect was found to be mediated by offspring reports of childhood maltreatment. The change

in maternal depressive symptoms during the course of the study did not affect offspring internalizing scores.

While the association between prenatal depressive symptoms and offspring internalizing symptoms was shown to be mediated by childhood maltreatment, identifying women with elevated depressive symptoms during pregnancy nevertheless identifies a subgroup of children at increased risk of experiencing child abuse and neglect. The public health significance of our findings is that pregnancy may represent an ideal time for clinicians to screen and identify women whose offspring may benefit from targeted interventions to decrease childhood maltreatment.

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PREFACE

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1.0 INTRODUCTION

Depression during pregnancy is common and has been associated with adverse fetal and infant outcomes. Despite evidence suggesting that these effects may last into adolescence, there is a lack of longitudinal studies that investigate the effects beyond this time. Furthermore, it is unclear whether prenatal depression exerts a direct effect on offspring health, or if these associations are mediated by other exposures during the offspring's lifetime.

The primary goal of this dissertation was to address a gap in the literature by examining the relationship between prenatal depressive symptoms and adult offspring internalizing symptoms within the Maternal Health Practices and Child Development Study, a longitudinal birth cohort with data available from the first trimester through 22 years. To summarize, the aims of this research were as follows: (1) to determine whether prenatal depressive symptoms predicted offspring internalizing symptoms at 22 years while controlling for prenatal and 22-year covariates; (2) to examine whether birth weight or childhood maltreatment mediated the association between prenatal depressive symptoms and offspring internalizing symptoms at 22 years; and (3) to examine whether the change in maternal depressive symptoms during the offspring's life predicted their internalizing symptoms at 22 years. Understanding the mechanisms through which prenatal depression exerts its influence may help shape prevention efforts.

1.1 DEPRESSION

The Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV) recognizes four types of mood disorders, the most common of which is Major Depressive Disorder (MDD) (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, 1994). MDD is often referred to as unipolar depression and is characterized by low or depressed mood and anhedonia. For a diagnosis of MDD to be made, individuals must report experiencing at least five of the following nine symptoms, one of which must be either depressed mood or anhedonia, during the same two week period for most of the day, nearly every day: depressed mood, anhedonia, psychomotor agitation, significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation, fatigue, feelings of worthlessness or excessive guilt, inability to concentrate, and suicidal thoughts.

Major depressive disorder is a serious public health issue responsible for a significant proportion of disease-related disability within the United States and worldwide, ranking third among the top causes of worldwide sum of life years lost due to premature mortality and years lived with disability (WHO, 2008). Major depressive disorder is also one of the most common mental health disorders in the United States, with an estimated lifetime prevalence of 17% in the population aged 18 years and older (Kessler et al., 2005). Negative health behaviors often accompany depression, including substance use, engaging in unprotected sex, and poor dietary habits, to name a few (Kovacs & Goldston, 1991; Lynch & Clarke, 2006; Mahon & Yarcheski, 2001; Murray & Lopez, 1996; Walsh, Senn, & M.P., 2013). Additionally, individuals who experience a depressive episode are at an increased risk of experiencing depression in the future (Kessler, Zhao, Blazer, & Swartz, 1997).

A noticeable gender difference has been observed where rates of depression are twice as high among women as among men (Ness & Kuller, 1999). This trend is consistent across the globe beginning in adolescence and persisting throughout the rest of life. Epidemiologic studies suggest that anywhere from 8% to 20% of women will suffer from an episode of depression in their lifetime, with the peak prevalence of MDD occurring during the childbearing years (Moses-Kolko & Roth, 2004; Ness & Kuller, 1999; Orr, James, & Blackmore Prince, 2002). Consequently, many women who experience depression are mothers whose families and children may directly be affected by the depression. Depression during pregnancy poses a particularly unique public health challenge as both the mother and her offspring are at risk for the negative consequences associated with depression.

1.2 DEPRESSION DURING PREGNANCY

1.2.1 Epidemiology of Depression during Pregnancy

Research suggests that depression during pregnancy may be even more common than postpartum depression (Gaynes et al., 2005). Prevalence estimates of prenatal depression range from 5.6-44%, (Andersson, Sundstrom-Poromaa, Wulff, Astrom, & Bixo, 2006; Dayan et al., 2006; Deave, Heron, Evans, & Emond, 2008; Heron et al., 2004; Kim et al., 2008; Maki et al., 2003; Pawlby, Hay, Sharp, Waters, & O'Keane, 2008; Rahman, Iqbal, Bunn, Lovel, & Harrington, 2004; Thoppil, Riutcel, & Nalesnik, 2005). Although most estimates fell in the range of 10-15%, rates as high as 44% were reported for high risk populations within the United States (Li, Liu, & Odouli, 2008; Orr et al., 2002). Differences in prevalence estimates may partially be explained

by differing samples and study methodologies. Table 1 on the following page summarizes each of these studies by presenting prevalence estimates, timing of the assessments, and instruments used to identify depression. Additionally, the prevalence of depression was higher during pregnancy than it was in the postnatal period in a number of studies that followed and assessed the same women during that time (Table 2). Women who experience depression during the prenatal period are at increased risk of experiencing depression in the future, and one of the most significant predictors of postnatal depression is prenatal depression (Heron et al., 2004; Leigh & Milgrom, 2008). Within a birth cohort that followed mothers from the first trimester through the time when their offspring were 16 years old, 90% of the mothers who were depressed during pregnancy became depressed again (Pawlby et al., 2008).

Risk factors for depression during pregnancy are largely consistent with risk factors for depression at other times. Lancaster and colleagues conducted a systematic review of the literature published from 1980-2008 to evaluate risk factors for depressive symptoms during pregnancy (Lancaster et al., 2010). They identified 159 articles that met their inclusion criteria, but limited their meta-analysis to 57 high quality studies in the top 25th percentile of quality scores. Risk factors for prenatal depression in the bivariate analysis included maternal anxiety, life stress, history of depression, lack of social support, unintended pregnancy, Medicaid insurance, intimate partner violence, lower income, lower education, smoking, being single, and poor relationship quality. In the multivariate analysis, only life stress, lack of social support, and intimate partner violence continued to be significant predictors. Pooled results were inconsistent for unemployment, maternal age, maternal race/ethnicity, and alcohol and other illicit drug use, however this does not necessarily mean that they are not significant risk factors for prenatal depression. Lancaster and colleagues note that the inconsistent results may partially be

Table 1. Summary of prenatal depression prevalence studies

Study Author, Year	Sample Size (number of women)	Location	Prevalence (%)	Time of Measurement (weeks gestational age)	Depression Assessment
(Andersson et al., 2006)	1,555	Sweden	29.2	16-18	Clinical Diagnosis
(Dayan et al., 2006)	681	France	14.5	20-28	EPDS
(Heron et al., 2004)	8,323	England	11.4 and 13.1[a]	18 and 32[a]	EPDS
(Evans, Heron, Francomb, Oke, & Golding, 2001)	12,059	England	13.9 and 15.2[a]	18 and 32[a]	EPDS
(Faisal-Cury & Rossi Menezes, 2007)	432	Brazil	19.6	>21	BDI
(Field et al., 2008)	430	Florida, USA	20.0	22	Clinical Diagnosis
(Flynn, O'Mahen, Massey, & Marcus, 2006)	1,298	Michigan, USA	5.6	8.5-35[b]	Clinical Diagnosis
(Kim et al., 2008)	1,584	Illinois, USA	7.7	24-28	EPDS
(Leigh & Milgrom, 2008)	367	Australia	16.9	26-32	BDI
(Li et al., 2008)	791	California, USA	41.2	10	CES-D
(Maki et al., 2003)	11,804	Finland	14.4	24-28	Self-report[c]
(Orr, Blazer, James, & Reiter, 2007)	1,163	North Carolina, USA	44.0	First prenatal care visit[d]	CES-D
(Pawlby et al., 2008)	127	England	20 and 21[a]	14-20 and 36	Clinical Diagnosis
(Rahman et al., 2004)	632	Pakistan	25	27-42	Clinical Diagnosis
(Thoppil et al., 2005)	109	Texas, USA	9.8	32	EPDS

[a] Prenatal prevalence and time measurements respectively

[b] Average screening taken at 15 weeks gestational age

[c] Reported feeling depressed or very depressed when asked about their mood by an interviewing nurse

[d] Gestational age not reported

EPDS=Edinburgh Postnatal Depression Scale

CES-D=Center for Epidemiologic Studies Depression Scale

BDI=Beck Depression Inventory

Table 2. Summary of studies comparing the prevalence of prenatal depression to the prevalence of postnatal depression

Study Author, Year	Prenatal Prevalence %	Time of prenatal measurement (gestational age)	Postnatal Prevalence %	Time of postnatal measurement
(Andersson et al., 2006)	29.2	16-18 weeks	16.5	3-6 months
(Heron et al., 2004)	11.4 and 13.1[a]	18 weeks and 32 weeks[a]	8.9 and 7.9[b]	8 weeks and 8 months[b]
(Kim et al., 2008)	7.7	24-28 weeks	6.8	6 weeks
(Leigh & Milgrom, 2008)	16.9	26-32 weeks	11.2	10-12 weeks
(Pawlby et al., 2008)	33.1	14-36 weeks	31.0	1 year
[a] Antenatal prevalence and time measurements, respectively [b] Postnatal prevalence and time measurements, respectively				

explained by homogeneous study populations that lack the variability in these factors needed to detect an association.

While effective treatments for depression exist, choosing a treatment regimen during pregnancy is complicated by calculating the risks and benefits of each alternative with regards to both the mother and the fetus. The subject of antidepressant use is controversial amidst concerns about the adverse effects of antidepressant use on the fetus. Meta-analyses found that infants exposed to antidepressants had lower birth weights, lower Apgar scores, lower gestational ages, more prematurity, and an increased risk of poor neonatal adaptation syndrome, (Grigoriadis et al., 2013; Ross et al., 2013). In order to assist women in making an informed decision regarding antidepressant use during pregnancy, clinicians need to understand the risks that untreated depression poses to the fetus.

1.2.2 Effects of Depression during Pregnancy on the Fetus

The most well established effects of prenatal depression exist for fetal growth and development. Offspring of depressed mothers have been shown to have higher rates of preterm birth (Dayan et

al., 2006; M. A. Diego et al., 2009), slower fetal growth rates (M. A. Diego et al., 2009), lower birth weights and were more likely to be small-for-gestational age (Dayan et al., 2006; Orr et al., 2002; Rahman et al., 2004; Steer, Scholl, Hediger, & Fischer, 1992).

Several studies have also found associations between prenatal depression and offspring behavior including increased fussiness and crying among neonates 5-13 days old (M. A. Diego et al., 2004), negative infant reactivity at 2 months old (Davis et al., 2007), and higher generalized anxiety scores among 1 year old infants (Gerardin et al., 2011). The Avon Longitudinal Study of Parents and Children found that prenatal depression was associated with both increases in externalizing problems and decreases in verbal IQ among children 7-8 years old (E. D. Barker, Jaffee, Uher, & Maughan, 2011) A path analysis revealed that the association between prenatal depression and child internalizing difficulties was mediated by maternal anxiety and depression at 21 months. Davis and Sandman also found that children exposed to elevated levels of prenatal stress, as measured by maternal cortisol, depression, perceived stress, and pregnancy specific anxiety, had an increased risk of developing anxiety problems at 6-9 years (Davis & Sandman, 2012). Again, offspring behaviors were based on maternal reports. However the effects remained significant after controlling for maternal psychological state at the time of reporting.

Few prospective studies have examined whether effects persist beyond childhood. Within the Mater University of Queensland Study of Pregnancy, researchers found an association between decreasing birth weight and increasing depressive symptoms at 21 years among the females in their sample, controlling for prenatal depression and prenatal alcohol and tobacco use (Alati et al., 2007). While prenatal depression was significantly associated with offspring depression at 21 years in the bivariate analysis and remained in the final model, the significance and effect size of prenatal depression in the final model were not reported. Pawlby

and colleagues (2009) found that for 16 year olds exposed to prenatal depression, the risk of depression was nearly 5 times greater than for offspring not exposed. This effect was mediated by subsequent episodes of maternal depression; however, researchers did not formally explore the mediation. Additionally, exposure to maternal depression during other periods in the child's life, in the absence of prenatal exposure, was not associated with offspring depression. In a trajectory analysis of pre- and postnatal depressive and anxiety (PPNDA) symptoms across five assessments from the first trimester through 18 months postpartum, Glasheen (2010) failed to find an association between PPNDA symptom trajectories and MDD diagnosis at 16 years. But pre- and postnatal trajectories of anxiety were associated with an increased risk for conduct disorder in boys and a lower risk for conduct disorder in girls.

1.2.2.1 Proposed Mechanisms

Collectively, the evidence suggests that prenatal depression may affect offspring development and psychopathology. However, the pathway through which this risk is conferred is unclear. Goodman and Gotlib (1999) proposed several mechanisms to explain the transmission of psychopathology from mother to offspring including genetics, innate dysfunctional neuroregulatory mechanisms, and exposure to mother's negative health behaviors. Each of these mechanisms will be discussed in further detail.

Genetics

Family studies suggest that MDD is strongly familial with genetic factors playing an important role in the development of the disease (Sullivan, Neale, & Kendler, 2000). Bottom-up genetic studies reveal that first degree relatives of child and adolescent probands with MDD have

a two-fold increased prevalence of MDD compared to controls with no psychopathology and controls with a history of non-mood disorders (Wickramaratne, Greenwald, & Weissman, 2000). In their review examining the familiality of depressive symptoms in children and adolescents, Rice, Harold, and Thapar (2002) found heritability estimates ranging from 30-80% for parent-rated depressive symptoms and 15-80% for self-reported depressive symptoms in twin studies of depression. Most studies of prenatal depression are unable to separate the effects of prenatal exposure to depression from genetic factors as genetically informed study designs are required to do so. However, heritability of depression remains an important mode of transmission from the mother to the offspring that should be kept in mind when interpreting the results of these studies.

Innate Dysfunctional Neuroregulatory Mechanisms

The fetal origins of disease hypothesis provides the model to support the mechanism of innate dysfunctional neuroregulatory processes that may predispose offspring to be susceptible to depression. This hypothesis was originally developed by Barker (1995) to explain the observed relationship between increasing rates of heart disease with lower birth weights, but it has since been applied to other diseases, including psychiatric disorders (Cannon, Jones, & Murray, 2002). Also commonly referred to as the fetal programming hypothesis, it proposes that adaptations made by the fetus to promote health and survival in utero may ultimately alter growth and development in a way that increases their susceptibility to certain diseases later in life.

Prenatal depression is one such exposure that may permanently impact fetal development. Depression during pregnancy has been associated with elevated maternal cortisol levels (M. A. Diego et al., 2009; M. A. Diego et al., 2006; Field, Diego, & Hernandez-Reif, 2006), which have been shown to be capable of crossing the placenta (Gitau, Fisk, Teixeira, Cameron, & Glover, 2001; Murphy, Clark, Donald, Pinsky, & Vedady, 1974) and stimulating the fetal hypothalamic-

pituitary-adrenocortical (HPA) axis (Gitau et al., 2001; Liu & Matthews, 1999). The HPA axis plays a critical role in regulating the body's stress response. Prolonged exposure to elevated maternal cortisol levels during development may alter the fetal HPA axis in a way that programs it to respond inappropriately to stressful stimuli and increases susceptibility to depression in the future.

Negative Maternal Health Behaviors

Maternal depression has been associated with a number of negative health behaviors that could be driving the observed associations between prenatal depression and offspring outcomes. One such behavior that may confound the association between prenatal depression and offspring mental health is substance use. Depressed women are more likely to use substances (Seto, Cornelius, Goldschmidt, Morimoto, & Day, 2005), and prenatal substance use has also been associated with offspring mental health.

High rates of MDD were found among adults with Fetal Alcohol Syndrome (FAS) or fetal alcohol effects (Famy, Streissguth, & Unis, 1998). Major depressive disorder was also common among a sample of children between the ages of 5 and 13 years, six of whom met criteria for FAS or partial FAS, with histories of heavy prenatal alcohol exposure (O'Connor et al., 2002). Likewise, among a sample of 5- to 6-year-olds without FAS, self-report depressive symptoms were associated with increased maternal report of average drinks per drinking occasion during pregnancy (O'Connor & Kasari, 2000). Most recently, prenatal alcohol exposure was shown to have an effect on offspring problem behaviors at 22 years (N. L. Day, Helsel, Sonon, & Goldschmidt, 2013).

Several studies have examined the effect of prenatal tobacco exposure on later psychiatric outcomes, but results have been conflicting. While some studies have found associations

between prenatal tobacco exposure (PTE) and internalizing symptoms among children and adolescents (Ashford, van Lier, Timmermans, Cuijpers, & Koot, 2008; Ekblad, Gissler, Lehtonen, & Korkeila, 2010; Gray, Day, Leech, & Richardson, 2005; Indredavik, Brubakk, Romundstad, & Vik, 2007), others have not (Fergusson, Woodward, & Horwood, 1998; Lavigne et al., 2011; Williams et al., 1998). Additionally, a study by Gray and colleagues reported effects for prenatal exposure to marijuana, with exposed offspring having higher depressive symptoms at 10 years compared to children who were not exposed (Gray et al., 2005).

Considering this, prenatal substance use represents an alternative pathway by which mothers may confer susceptibility to psychopathology in the offspring. Some of the mental health effects previously ascribed to prenatal depression may actually be attributable to substance use. Prenatal substance use represents an important confounder that future studies of prenatal depression and offspring health should take into account.

1.2.2.2 Limitations and Gaps in Knowledge

Depression during pregnancy is common and the weight of the evidence suggests that it may have lasting effects on offspring health and development. However, few longitudinal studies have examined the effects of prenatal depression beyond infancy, and those that have suffer from limitations. Although studies by Barker et al. (2011) and Davis and Sandman (2012) utilized validated instruments to assess child behavior, both relied on maternal reports which may be biased and influenced by maternal mood. For example, studies have associated maternal depressive symptoms with more rating errors in reporting child behavior (M.H. Boyle & Pickles, 1997). Davis and Sandman (2012) had a relatively small sample size (178 mother-child dyads) that was of a considerably higher socioeconomic status than the general population. On average,

the mothers were 38 years old at the 6-9 year assessment, 82% were married or cohabiting, and nearly 50% reported an annual household income over $100,000. While Barker et al. (2011) had a substantially larger sample size (3,298 mother-child dyads), it was representative of only 23% of the original ALSPAC birth cohort from which it came. Despite its size, the sample had a low rate of ethnic minorities and results may not be generalizable to more diverse populations.

In spite of having maternal depression assessments available prenatally and again at 1, 4, 11, and 16 years, Pawlby et al. (2009) performed a standard logistic regression analysis and did not fully take advantage of the longitudinal nature of their data. This was largely attributable to having a small sample size (127 mother-child dyads) with little variation in depression during the study. The effect of subsequent episodes of maternal depression was estimated by entering a variable into their model for the total number of maternal depressive episodes. Because this variable was significant in the model with prenatal depression, they concluded that subsequent depression mediated the association between prenatal and offspring depression. However, they did not perform any formal tests of mediation and prenatal depression remained significant in the model controlling for the number of subsequent depressive episodes. It is also unclear what confounders were considered, with the exception of family structure which was included in one of the models. Notably, researchers commented that they did not take prenatal substance use into account.

While these studies set the stage for further research investigating the effects of prenatal depression on offspring, room for improvement remains. First, it is unknown whether the effects of prenatal depression persist beyond adolescence and into adulthood. Additionally, the pathways and mechanisms through which prenatal depression exerts its influence are unclear. With the exception of the Barker et al. (2011) study, previous research has not formally

examined potential mediators in their analysis. Many events take place between a prenatal exposure and an outcome assessed in childhood or adolescence that may mediate or explain the observed associations.

Two possible mediators that previous studies have failed to consider but are worthy of further investigation are birth weight and childhood maltreatment. As was mentioned before, prenatal depression has been associated with fetal growth and development. Furthermore, a considerable body of research has emerged in response to the fetal origins of disease hypothesis investigating the association between birth weight and future psychopathology. Although this research has produced conflicting results, there is enough evidence available to warrant performing a formal mediation analysis. Similar evidence exists to suggest that childhood maltreatment may mediate the association as well. Childhood maltreatment is a well-accepted risk factor for depression (Fergusson, McLeod, & Horwood, 2013; Widom, DuMont, & Czaja, 2007), and studies have also linked depressive symptoms with abusive parenting attitudes in mothers (Lutenbacher, 2002). Future studies should explore the role of these potentially significant mediators.

While prior studies have attempted to take into account the chronic nature of depression when exploring its effects during the prenatal period, they failed to consider the role that the actual developmental course of depressive symptoms may have. Research has uncovered considerable variation in the patterns of depressive symptoms experienced by individuals (Nandi, Beard, & Galea, 2009), with some studies suggesting that changes in depressive symptoms over time may in fact have unique effects on offspring mental health (Gunlicks & Weissman, 2008). Trajectory analyses represent a novel technique for exploring depressive symptoms during the life course that allow researchers to simultaneously take into account severity, chronicity, and

change. These methods can be applied to studies of prenatal depression to determine if changes in depressive symptoms following pregnancy influence psychopathology.

Lastly, previous studies have not addressed whether prenatal depression has differential effects by race. This gap in the literature may be attributable to a scarcity of large, racially diverse samples that possess the statistical power needed to investigate racial differences. There is some evidence to suggest that rates of prenatal depression and depression trajectories may differ by race (Gavin et al., 2011; Mora et al., 2009), and future studies should test for moderation by race in the prediction of offspring health outcomes.

1.3 AIMS

The goal of this dissertation is to address a gap in the literature by examining the effect of prenatal depressive symptoms on adult offspring internalizing symptoms and investigating the nature of the relationship. This will be achieved by addressing the following specific aims:

1) Determine whether prenatal depression predicts offspring internalizing symptoms in young adults while controlling for significant prenatal and current covariates of internalizing symptoms.
2) Examine whether birth weight mediates the association between prenatal depressive symptoms and offspring internalizing symptoms.
3) Evaluate whether the associations between prenatal depressive symptoms, birth weight, and offspring internalizing symptoms differ by gender and race.
4) Identify trajectories of maternal depressive symptoms from the first trimester through 16 years.

5) Examine whether first trimester maternal depressive symptoms and/or change in maternal depressive symptoms over time significantly affect offspring internalizing symptoms.
6) Explore whether childhood maltreatment mediates the association between trajectories of maternal depressive symptoms and offspring internalizing symptoms.

2.0 PAPERS

2.1 PAPER 1: THE ASSOCIATION BETWEEN PRENATAL DEPRESSIVE SYMPTOMS AND OFFSPRING INTERNALIZING SYMPTOMS AT 22 YEARS

2.1.1 Abstract

Background: Prenatal depression has been associated with adverse fetal and infant outcomes. Few studies have examined the long-term effects of exposure to prenatal depressive symptoms on offspring beyond childhood.

Methods: Data for this study came from the Maternal Health Practices and Child Development Study birth cohort. Prenatal depression was assessed at the first trimester visit with the Center for Epidemiologic Studies Depression Scale, and offspring internalizing symptoms were assessed at the 22-year follow-up with the Adult Self Report. Multiple imputation was used to estimate covariates with missing data and regression analyses were performed to examine the effect of prenatal depressive symptoms on offspring internalizing symptoms while controlling for significant prenatal predictors and 22-year covariates.

Results: Prenatal depressive symptoms were significantly associated with higher internalizing problem scores in exposed offspring at 22 years. These associations remained significant while controlling for prenatal and current covariates of internalizing problem scores. Other significant

covariates of internalizing problem scores included prenatal sexually transmitted infections, offspring age, sex, race, personal income, alcohol use, cigarette use, and other illicit drug use at 22 years.

Conclusions: Prenatal depression has significant long-term effects on offspring internalizing symptoms. Identifying prenatal predictors of adult health outcomes will help us uncover the mechanisms through which these exposures exert their influence.

2.1.2 Introduction

Maternal depression has long been recognized as a risk factor for depression in offspring (Beardslee, Versage, & Gladstone, 1998; Gelfand & Teti, 1990; Goodman et al., 2011; Klein, Lewinsohn, Seeley, & Rohde, 2001). Although researchers have traditionally been interested in studying the effects of depression in the postpartum period, a meta-analysis found similar estimates of Major Depressive Disorder (MDD) prevalence and incidence for both the prenatal and postpartum periods, suggesting that pregnancy and the postpartum are equally important times during which offspring may be vulnerable to the effects of maternal depression (Gaynes et al., 2005). Most studies of prenatal depression have focused on immediate pregnancy and neonatal physical outcomes (Davalos, Yadon, & Tregellas, 2012) and have consistently shown associations between prenatal depression and preterm birth (Dayan et al., 2006; Field et al., 2008; Steer et al., 1992), as well as prenatal depression and low birth weight (Field et al., 2008; Rahman et al., 2004; Steer et al., 1992).

Several studies have also found associations between prenatal depression and offspring behavior including increased fussiness and crying among neonates 5-13 days old (M. A. Diego et al., 2004), negative infant reactivity at 2 months old (Davis et al., 2007), and higher generalized

anxiety scores among 1 year old infants (Gerardin et al., 2011). The Avon Longitudinal Study of Parents and Children found that prenatal depression was directly associated with increases in externalizing problems and decreases in verbal IQ among children 7-8 years old (E. D. Barker et al., 2011). Additionally, a path analysis revealed that the association between prenatal depression and child internalizing difficulties was mediated by maternal anxiety and depression at 21 months.

The fetal origins of disease (FOD) hypothesis suggests that adult disease is the result of in utero exposures and experiences (D. J. Barker, Eriksson, Forsen, & Osmond, 2002). The FOD hypothesis was originally proposed by Barker to explain the association between increasing rates of heart disease and lower birth weights (D. J. Barker, 1995) and has since been applied to other diseases including psychiatric disorders (Cannon et al., 2002; Schlotz & Phillips, 2009). Goodman and Gotlib (1999) hypothesized that in utero exposure to maternal depression may result in dysfunctional neuroregulatory mechanisms in the offspring that contribute to future mental health problems. The effects of prenatal depression on offspring may remain latent until the age at which depression rates begin to increase. Considering this, the long-term effects of prenatal depression on offspring deserve attention.

Nonetheless, few prospective studies have examined the effects of prenatal depression on offspring outcomes beyond infancy and early childhood. Researchers found an association between decreasing birth weight and increasing depressive symptoms at 21 years among females, controlling for prenatal depression and prenatal alcohol and tobacco use in the Mater University of Queensland Study of Pregnancy (Alati et al., 2007). While prenatal depression was significantly associated with offspring depression at 21 years in the bivariate analysis and remained in the final model, the significance and effect size of prenatal depression in the final

model were not reported. Pawlby and colleagues (2009) found that for 16 year olds exposed to prenatal depression, the risk of depression was nearly 5 times greater than for offspring not exposed. Exposure to maternal depression during other periods in the child's life, in the absence of prenatal exposure, was not associated with offspring depression (2009). In a trajectory analysis of pre- and postnatal depressive and anxiety (PPNDA) symptoms across five assessments from the first trimester through 18 months postpartum, failed to find an association between PPNDA symptom trajectories and MDD diagnosis or depressive symptoms at 16 years (Glasheen et al., In press).

Longitudinal studies examining the long-term effects of prenatal depression on offspring are lacking in the current literature, and the few existing studies suffer from limitations. The Alati et al. (2007) study experienced high loss to follow-up (47%) and the Pawlby et al. (2009) study had a small sample size (n=127). Both studies were racially homogeneous (93% and 78% white, respectively) and completed in Brisbane, Australia and South London, respectively. Their results may not be generalizable to other races or to women in the U.S. The Pawlby et al. (2009) study also failed to consider potentially important prenatal covariates, including substance use, in their analyses. Glasheen's (In press) trajectory study addressed some of these weaknesses by including equal numbers of African American and Caucasian women in a cohort with a high follow-up rate (76%). It is possible the effects of prenatal depression may remain latent until adulthood when rates of depression continue to increase.

Considered together, the evidence suggests that there is an association between prenatal exposure to depression, behavior in childhood, and depressive symptoms in adolescents. The effects of prenatal depression on adult offspring are not well studied and deserve further investigation. The aim of this analysis was to examine the association between prenatal

depression and offspring internalizing symptoms at 22 years, while controlling for other prenatal and current risk factors for depression. We hypothesized that prenatal maternal depressive symptoms would lead to increased internalizing symptoms among the adult offspring.

2.1.3 Methods

2.1.3.1 Sample Selection and Study Design

Data for these analyses come from two cohorts within the Maternal Health Practices and Child Development (MHPCD) project, which was designed to examine the long-term effects of prenatal substance use on offspring. Between 1982 and 1985, a sequential sample of adult, English-speaking women in their fourth or fifth prenatal month was recruited from a prenatal clinic. Fifteen percent of the women approached refused participation, resulting in an initial sample of 1,360 women. Two groups were selected from this sample. The first cohort was selected based on first trimester alcohol use and included all women who drank at least 3 alcoholic drinks per week in the first trimester and a random sample of 1/3 of those who drank less or abstained. The second cohort was selected based on first trimester marijuana use and included all women who smoked two or more joints per month in the first trimester and a random sample of 1/3 of those who smoked less or abstained. Sampling was done with replacement, so a woman could be selected for either or both cohorts. Because these studies were conducted simultaneously, had considerable overlap, and used the same protocol, instruments, and personnel, the two cohorts can be combined for this analysis. The combined birth cohort consisted of 763 women with live singleton infants.

The cohorts have completed 11 assessments to date. Women were assessed at their fourth or fifth prenatal month (first trimester), seventh prenatal month (second trimester), and

with their offspring at delivery, 8 and 18 months postpartum, and at offspring ages 3, 6, 10, 14, 16, and 22 years. These analyses used data from the first and second prenatal assessments, the delivery assessment, and the 22-year assessment. Mothers were interviewed about demographic factors, substance use, psychological status, medical history, and current home environment at the initial visit and each follow-up, while offspring growth, cognitive and physical development, mental health, and behaviors were measured at each of the follow-up times. Mothers and offspring were interviewed separately at the 22-year assessment.

At the 22-year phase, 80% (n=608) of the birth cohort was interviewed. Missing were 30 offspring who refused to participate, 3 were adopted, 18 were institutionalized (jail or rehabilitation center), 56 were lost to follow-up, 29 moved out of the Pittsburgh area, 11 died, and 8 were unable to participate due to low cognitive functioning. One offspring did not complete the behavioral assessment, resulting in a sample of 607 offspring for this analysis. There were no significant differences between those included in the 22-year analyses and those who were not when baseline, defined as the first assessment, maternal education, race, depression, and alcohol, marijuana, or cigarette exposure were considered (Table 3). Missing offspring were more likely to be male, but the effect size was negligible suggesting that results should be generalizable to the original birth cohort.

2.1.3.2 Measures

Outcome. Offspring completed the Adult Self Report (ASR) at the 22-year interview (Achenbach & Rescorla, 2003). This instrument is an adult continuation of the Child Behavior Checklist (Achenbach, 1991) and has subjects self-report on their behavioral, emotional, and social problems. It consists of 126 items that assess eight syndromes and has been shown to be reliable and valid (Achenbach & Rescorla, 2003). These eight syndromes can be grouped and

Table 3. Comparison of the analyzed sample to those who were missing at 22 years

Baseline Demographics	Analyzed Sample (n=607)	Missing (n=156)	p-value[a]	Effect Size[b]
Race (% Caucasian)	48.1	50.0	.67	.02
Age (years)	23.0	23.1	.89	.01
Education (years)	11.8	11.9	.69	.07
Household income ($/month)	300-399	300-399	.73	.02
CES-D score	21.0	20.2	.29	.10
Average daily volume of alcohol	.58	.74	.32	.11
Any alcohol use (%)	64.4	66.7	.60	.02
Average daily joints of marijuana	.38	.43	.93	.05
Any marijuana use (%)	41.0	38.5	.56	.02
Average daily cigarettes	8.2	8.7	.45	.04
Any cigarette use (%)	53.4	57.7	.34	.03
Any other illicit drug use (%)	10.5	12.8	.42	.03
Gender (% male)	47.4	60.9	<.01	.14

[a] t-test for continuous variables and chi-square test for dichotomous, non-parametric used for skewed continuous variables
[b]Cohen's D for continuous variables and Cramer's V for dichotomous (absolute values)

summed to produce internalizing and externalizing scores. The internalizing grouping consists of problems that are mainly within the self and includes all items from the Anxious/Depressed, Withdrawn, and Somatic Complaints syndrome scales. The internalizing problem score was computed by summing the scores of the three internalizing syndrome scales. This score was then standardized based on a normative sample. The T-scores indicate how elevated the individual's internalizing score is in relation to the normative sample, with higher scores indicating more internalizing symptoms. The clinical cut-point for internalizing scores is a T-score>63, with T-scores in the 60-63 range considered borderline. A Cronbach's alpha of 0.93 was found for the internalizing items on the ASR (Achenbach & Rescorla, 2003).

Exposure. Maternal depressive symptoms were assessed at each visit with the Center for Epidemiologic Studies-Depression (CES-D) Scale (Radloff, 1977). The CES-D is a widely used 20-item instrument with a 4-point Likert response scale that measures the frequency of

depressive symptoms. Scores range from 0-60 with higher scores indicating greater depressive symptoms. The scale has been shown to be both reliable and valid (Radloff, 1977) and has frequently been used in studies of pregnant women (Gaynes et al., 2005). Within our cohort, the Cronbach's alpha for the CES-D was 0.89 at the 18-month assessment (Seto et al., 2005). For this analysis, continuous CES-D scores from the first assessment will be utilized (mean gestational age at assessment: 18 weeks).

Prenatal Covariates. Mothers reported their age, marital status, education, household income, and employment status at all phases. Data from the baseline assessment were used for this analysis. Maternal substance use during the first trimester was assessed at the baseline prenatal visit. Substance use measures were designed specifically for this study and have been shown to be both reliable and valid (N. L. Day & Robles, 1989; Robles & Day, 1990). For alcohol, women reported their usual, minimum, and maximum quantity and frequency of beer, wine, liquor, and beer and wine coolers. From this, the average daily volume of alcohol (ADV) was calculated. Marijuana use was similarly assessed and converted into average daily joints (ADJ). Tobacco use was considered as the average number of cigarettes smoked per day. Other illicit drug use (cocaine, barbiturates, prescription drug abuse, etc.) in the first trimester was combined and dichotomized as any versus none.

A study nurse abstracted data on illnesses including sexually transmitted infections (STIs) and maternal antidepressant use during pregnancy from obstetric and medical records at the delivery assessment. Prenatal antidepressant use was dichotomized as "no antidepressants" or "any antidepressants". While antidepressant use was relatively rare during the early phases of this study (n=5 during pregnancy), the final model was run excluding these offspring to see if the results changed. The PERI Life Events Scale was adapted to measure the number of stressful

life events (Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978). Thirty-four events from the past year were assessed at the delivery interview and summed to create a total score. The social support measure was adapted from the Alameda County Health Study (Berkman & Syme, 1979) and was used at the baseline visit. Social support scores range from .25-4 with higher scores indicating more social support.

22-Year Covariates. Offspring race, education, personal income, marital status, employment, number of children, and living situation were assessed at the 22-year interview. Offspring substance use at 22 years was assessed using the same instrument that was used for the mothers. Offspring alcohol, marijuana, tobacco, and other illicit drug use were considered in this analysis. Ninety-two percent (n=559) of the offspring had maternal interviews available at the 22-year assessment. Fifty of these interviews (9%) were completed by a caretaker who was not the biological mother. Maternal/caretaker depressive symptoms were assessed using the CES-D.

2.1.3.3 Analysis

The analysis was limited to those who completed the ASR internalizing problem score at 22 years. Potential covariates of the offspring's internalizing problem scores were identified based on a review of the literature and prior analyses and experience with this sample. Covariates with missing data (maternal baseline household income, prenatal depressive symptoms, maternal baseline binge drinking, offspring personal income, maternal/caregiver depression at 22 years; range: 1-8% missing) were imputed using multiple imputation (Azur et al., 2011; Royston, 2005). Per Rubin's method, five imputed datasets were created to yield a relative efficiency of .95 for our sample as the rate of missing information was low (Rubin, 1987). Summary statistics (means, standard deviations, minimum and maximum values, ranges) for the imputed covariates

were compared to those in the original dataset to identify any problems with the imputation procedure, of which there were none. The regression results presented are the pooled estimates from the imputed datasets. Bivariate analyses, including the Student's T-test, ANOVA, and correlations, were performed to identify variables that were significantly ($p<.10$) associated with the outcome of offspring internalizing problem scores.

Regression analyses were performed in three steps. First, in Model 1, the prenatal model, all significant prenatal covariates from the bivariate analyses were entered into a single regression model as predictors of offspring internalizing problem scores. Backward stepwise regression was performed removing variables with the largest p-value until all remaining variables had a $p<.10$ to arrive at a model of prenatal predictors. Second, in Model 2, the 22-year model, all significant 22-year covariates from the bivariate analysis were entered into a single regression model predicting the internalizing score. Lastly, in Model 3, the final model, the significant variables from Models 1 and 2 were entered into a single regression model to examine the associations between prenatal and current covariates and offspring internalizing problem scores at 22 years. Backwards stepwise regression was used to arrive at a final model. All variables with a $p\leq.05$ were retained in the final model.

Regression diagnostics were performed on the final model to verify that the assumptions of regression had not been violated (tests for normality of the residuals, homoscedasticity, and multicollinearity). Bootstrapping analysis was also performed to examine the sensitivity of the results to potential outliers or influential points. Because bootstrapping produced similar results, only the original results will be presented and discussed.

2.1.4 Results

At the first prenatal assessment, the mean maternal age was 23 years (Table 4). Forty-eight percent of the women were white, 25% worked or attended school, and 32% were married. They had, on average, 11.8 years of education and a median monthly household income of $300-399 in 1982-1985 currency, 2 life events during the year prior to delivery (range: 0-9), and reported a social support quality of 3.3 on a scale of 0-4. Sixty-four percent reported alcohol use with an ADV of 0.9 among users, 41% reported marijuana use with an ADJ of 0.9 among users, 11% reported other illicit drug use, and 53% reported cigarette use with an average of 15.4 cigarettes daily among users.

At birth, the offspring had an average weight of 3.2 kg (7 lbs.) with a gestational age of roughly 40 weeks and 48% were male. Nine percent were born preterm, 10% were low birth weight (≤2.5 kg), and 11% were small for gestational age (birth weight ≤10^{th} percentile for gestational age).

At the 22-year assessment, 6% of the offspring were married, 37% had at least one child, and 60% worked or attended school. On average, they were 22.8 years old, had 12.8 years of education and earned a median personal monthly income of $800 in 2004-2007 currency. Ninety-two percent reported alcohol use with an ADV of 2.1 among users, 50% reported any marijuana use with 1.6 ADJ among users, 44% reported cigarette use with 9.9 average daily cigarettes among users, and 17% reported other illicit drug use. They had an average internalizing problems score of 51.4, with 15% scoring above the clinical cut-point (>63).

Depressive symptoms were prevalent among the mothers in this sample, with an average CES-D score of 21 at the first trimester assessment. Higher prenatal depressive symptoms were

Table 4. Sample characteristics

Maternal at baseline	**Mean (range)**
Age (years)	23 (18-42)
Race (% Caucasian)	48.1
Education (years)	11.8 (7-18)
Household income (median $/month)	300-399 (0-1,000+)
Marital status (% married)	31.8
Work/school status (% working/in school)	25.2
Pregnancy STI's (%)	12.4
Life events (#)	1.7 (0-9)
Social support quality	3.3 (.25-4)
CES-D score	21.0 (1-51)
Any alcohol use (%)	64.4
Alcohol use among users (avg. daily drinks)	.9 (<.1-19.6)
Binge drinking (%)	34.3
Any marijuana use (%)	41.0
Marijuana use among users (avg. daily joints)	.9 (<.1-7.4)
Any cigarette use (%)	53.4
Cigarette use among users (avg. daily cigs)	15.4 (.5-50)
Any other illicit drug use (%)	10.5
Offspring at 22 years	
Sex (% male)	47.5
Age (years)	22.8 (21-26)
Education (years)	12.8 (8-18)
Marital status (% married)	5.8
Has any children (%)	37.2
Personal income (median $/month)	800 (0-5,000)
Work/school status (% working/in school)	60.3
Any alcohol use (%)	92.4
Alcohol use among users (avg. daily drinks)	1.9 (<.1-25.8)
Binge drinking (%)	61.3
Any marijuana use (%)	49.8
Marijuana use among users (avg. daily joints)	1.6 (<.1-18)
Any cigarette use (%)	43.7
Cigarette use among users (avg. daily cigs)	9.9 (.5-50)
Other illicit drug use (% any)	16.5
ASR internalizing score	51.4 (30-88)

associated with lower household incomes, greater alcohol use, more life events, and less social support at baseline (Table 5).

Model 1 consisted of the significant prenatal covariates of offspring internalizing scores. Prenatal covariates of the internalizing score that were significant in the bivariate analysis included prenatal depression, maternal education, maternal work/school status, alcohol use, cigarettes, pregnancy STIs, and number of life events (Table 5). Cigarettes and life events were not significant in the multivariate model when all covariates within this group were considered. Model 1 is presented in Table 6. Substance use covariates were log-transformed to reduce skewness and the coefficients presented are based on these transformations. Model 1 explained 4.2% of the variance in offspring internalizing problem scores and was significant with an $F(6,600)=5.29$, $p<.001$.

Model 2 included the significant 22-year covariates of the offspring internalizing scores. Offspring age, sex, race, education, personal income, work/school status, alcohol, cigarette, other illicit drugs, and maternal/caregiver depression were significant covariates of the internalizing score at 22 -years in the bivariate analyses (Table 7). Education, and work/school status were no longer significant in the multivariate model of the combined 22-year covariates. Model 2 explained 9.3% of the variance in internalizing problems scores and was statistically significant with an $F(8, 598)=7.65$, $p<.001$ (Table 6). Higher personal income, offspring age, and being male were associated with lower internalizing symptoms, while being Caucasian, reporting other illicit drug use, higher alcohol and cigarette use, and higher maternal/caregiver depression at 22 years were associated with higher offspring internalizing scores.

Model 3, the final model, included the significant prenatal and 22-year covariates from Models 1 and 2. After combining the significant prenatal and 22-year covariates of internalizing

Table 5. Correlations between prenatal depressive symptoms, prenatal covariates, and offspring internalizing symptoms at 22 years

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)
1. Internalizing symptoms	1.00															
2. First trimester CES-D	.11**	1.00														
3. Age	-.09**	<.01	1.00													
4. Sex	-.08*	-.05	.11**	1.00												
5. Race	.11**	-.02	.11**	.04	1.00											
6. Education	-.09**	-.07*	<.01	-.06	.10**	1.00										
7. Personal income	-.11**	-.03	.14**	.15**	.17**	.18**	1.00									
8. Marital status	-.03	.02	.10**	<.01	.11**	.02	.15**	1.00								
9. Work/school status	-.07*	-.06	-.05	.05	.08**	.21**	.60**	.06	1.00							
10. Alcohol	.10**	-.02	.05	.17**	.04	-.05	<.01	.07*	-.07*	1.00						
11. Marijuana	.05	.14**	-.06	.14**	-.11**	-.11**	-.07*	-.04	-.10**	.21**	1.00					
12. Cigarettes	.16**	.06	<.01	.08*	.21**	-.31**	-.06	-.02	-.13**	.30**	.21**	1.00				
13. Other illicit drug use	.19**	.04	<-.01	.17**	.19**	-.14**	<-.01	<.01	-.08*	.30**	.17**	.30**	1.00			
14. Has children	-.03	.02	<.01	-.17**	-.26**	-.30**	-.13**	.07*	-.20**	.02	.05	.03	-.01	1.00		
15. Lives with mom	-.01	-.04	-.05	.07	<.01	.02	-.15**	-.12**	-.06	-.03	-.02	.02	.02	-.15**	1.00	
16. Maternal CES-D at 22 years	.10**	.35**	-.01	<-.01	.04	-.12**	-.09**	.01	-.05	.04	-.01	.04	.04	.05	-.04	1.00

*p<.10
**p<.05

Table 6. Predicting offspring internalizing symptoms

Variable	Model 1 (R^2=.042)			Model 2 (R^2=.093)			Model 3 (R^2=.103)			
	b*	β	**p**	**b**	β	**p**	**b**	β	**p**	**sr^2**
Baseline maternal CES-D score	.12	.09	.028				.12	.09	.020	.008
Baseline maternal education	-.67	-.08	.053							
Baseline maternal alcohol	1.95	.08	.059							
Baseline maternal cigarettes	.66	.08	.053							
Pregnancy STI's	2.37	.074	.088				3.07	.09	.026	.007
Offspring age (years)				-1.34	-.08	.036	-1.26	-.08	.048	.006
Offspring sex[a]				-2.42	-.11	.009	-2.23	-.10	.016	.009
Offspring race[b]				2.00	.09	.032	2.54	.11	.008	.011
Offspring personal income				<-.01	-.08	.059	<-.01	-.09	.028	.007
Offspring alcohol use				1.20	.07	.082	1.38	.09	.045	.006
Offspring cigarette use				.84	.09	.041	.83	.09	.044	.006
Offspring other illicit drug use				4.21	.14	.002	3.94	.13	.003	.013
Maternal depression at 22 years				.09	.08	.035				
Model F-test	F(6, 600)=5.29 , p<.001			F(8, 598)=7.65, p<.001			F(10, 596)=7.61, p<.001			

Model 1: Significant prenatal variables
Model 2: Significant offspring 22-year variables
Model 3: Combined prenatal and offspring 22-year variables
* b=unstandardized regression coefficient, β=standardized regression coefficient
[a] 0=female, 1=male
[b] 0=black, 1=white

Table 7. Correlations between prenatal depressive symptoms, offspring 22 year covariates, and offspring internalizing symptoms at 22 years

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)
1. Internalizing symptoms	1.00															
2. First trimester CES-D	.11**	1.00														
3. Age	-.09**	<.01	1.00													
4. Sex	-.08*	-.05	.11**	1.00												
5. Race	.11**	-.02	.11**	.04	1.00											
6. Education	-.09**	-.07*	<.01	-.06	.10**	1.00										
7. Personal income	-.11**	-.03	.14**	.15**	.17**	.18**	1.00									
8. Marital status	-.03	.02	.10**	<.01	.11**	.02	.15**	1.00								
9. Work/school status	-.07*	-.06	-.05	.05	.08**	.21**	.60**	.06	1.00							
10. Alcohol	.10**	-.02	.05	.17**	.04	-.05	<.01	.07*	-.07*	1.00						
11. Marijuana	.05	.14**	-.06	.14**	-.11**	-.11**	-.07*	-.04	-.10**	.21**	1.00					
12. Cigarettes	.16**	.06	<.01	.08*	.21**	-.31**	-.06	-.02	-.13**	.30**	.21**	1.00				
13. Other illicit drug use	.19**	.04	<-.01	.17**	.19**	-.14**	<-.01	<.01	-.08*	.30**	.17**	.30**	1.00			
14. Has children	-.03	.02	<.01	-.17**	-.26**	-.30**	-.13**	.07*	-.20**	.02	.05	.03	-.01	1.00		
15. Lives with mom	-.01	-.04	-.05	.07	<.01	.02	-.15**	-.12**	-.06	-.03	-.02	.02	.02	-.15**	1.00	
16. Maternal CES-D at 22 years	.10**	.35**	-.01	<-.01	.04	-.12**	-.09**	.01	-.05	.04	-.01	.04	.04	.05	-.04	1.00
*p<.10, **p<.05																

problem scores, prenatal depression and pregnancy STIs were the only prenatal covariates to remain significant in Model 3. Maternal/caretaker depression was the single 22-year covariate that failed to be significant and was removed from the model. Model 3 was statistically significant with an $F(10, 596)=7.61$, $p<.001$ (Table 6). While holding the other covariates constant, higher prenatal depressive symptoms were associated with greater offspring internalizing symptoms. The total variance in internalizing problem scores explained by the final model was 10.3%: 0.7% of the variance was uniquely explained by prenatal depression. While these semi-partial correlations are small, prenatal depression had a semi-partial correlation value that was comparable to the other predictors of 22 year depressive symptoms (semi-partial correlation=0.6-1.3%). Similar regression results were found after excluding the women with prenatal antidepressant use, so the presented results include these women. The association was not moderated by offspring race or sex.

Additionally, we tested for a possible moderation between prenatal depression and maternal depression at 22 years in the prediction of internalizing symptoms, however the effect was not significant. Because the cohort was selected based on substance use and prenatal substance use is also risk factor for psychopathology in the offspring, we tested for moderation by prenatal substance use. There was no moderation by first trimester alcohol use ($p=.420$), marijuana use ($p=.243$), cigarette use ($p=.901$), or any other illicit drug use ($p=.333$).

2.1.5 Discussion

Prenatal depressive symptoms were significantly associated with higher internalizing problem scores in exposed offspring at 22 years. While prior studies have identified an association between prenatal depression and offspring anxiety and depression in childhood and

adolescence (Davis & Sandman, 2012; Pawlby et al., 2009), our study extends the exploration of these effects into adulthood. These associations remained significant while controlling for prenatal and current covariates of internalizing problem scores. By contrast, Pawlby et al. (2009) reported that the association between prenatal depression and offspring depression diagnoses at 16 years was mediated by subsequent exposure to maternal depressive disorders. However, they did not formally test for mediation and nearly all of the women who experienced subsequent depression were depressed during pregnancy. While their cohort was socio-economically similar to ours, the mothers were racially homogeneous and had a very high prevalence of MDD (65% had at least one depressive episode from pregnancy through their child's 16th birthday vs. 34% of our mothers with a lifetime diagnosis of a depressive episode when their child was 16). Future analyses will examine the role that the pattern of subsequent maternal depression has in the relationship between prenatal depression and adult offspring mental health.

To our knowledge, this is the first cohort study to suggest an association between pregnancy STIs and adult internalizing symptoms. Animal studies have found increased anxiety- and depression-like behaviors in offspring exposed to prenatal infection (Enayati et al., 2012; Lucchina, Carola, Pitossi, & Depino, 2010). These findings are biologically plausible: inflammation resulting from infection may alter brain development and affect the future risk of psychopathology (Hagberg, Gressens, & Mallard, 2012). One human study found an association between exposure to maternal genital and reproductive infections during the periconception period (from 30 days before through 30 days after the last menstrual period) and adult schizophrenia (Babulas, Factor-Litvak, Goetz, Schaefer, & Brown, 2006). Alternatively, having an STI may represent other health characteristics of the mother, such as increased substance use,

which may be associated with internalizing scores. However, we attempted to take this into account by controlling for prenatal covariates, including substance use.

This study has several limitations. First, this cohort is relatively homogeneous with regards to education and income and these results may not be generalizable to those of a higher socioeconomic status. Second, we did not have maternal diagnoses of MDD during pregnancy and these results may not be applicable to women with a clinical diagnosis. Third, we only considered depressive symptoms experienced in the first trimester of pregnancy as our exposure. Depressive symptoms were relatively stable across pregnancy and the second and third trimester CES-D scores (CES-D=21.4 and CES-D=20.5, respectively) were highly correlated with first trimester depressive symptoms (r=.69 and r=.60, respectively). While we also took maternal depressive symptoms at 22 years into account, CES-D scores at this time were moderately correlated with first trimester CES-D scores (r=.36). We chose to keep the first trimester depressive symptoms in our model over the 22-year measure because our original research question was to examine the long-term effects of prenatal exposure. Lastly, it is difficult to disentangle the effect that genetics may have apart from the prenatal exposure to depression. Future studies that examine specific pathways through which prenatal depression may exert its influence can help us start to tease out the environmental effects from the genetic ones.

These limitations are offset by the strengths of the study. This was a longitudinal study with exposure data available from the first trimester of pregnancy to the outcome 22 years later. The prospective nature of the study helps to minimize issues with memory and recall bias. The sample is large, has equal proportions of African Americans and Caucasians, and was not recruited based on mental health or from a psychiatric facility. Furthermore, the study has excellent follow-up rates and remains representative of the original cohort at 22 years. Subject

loss was independent of baseline maternal depressive symptoms. This study also had reliable data on and took into account prenatal confounders that prior studies have failed to consider.

In summary, prenatal depression has significant long-term effects on offspring internalizing symptoms. Studies have consistently shown high levels of depressive symptoms, including those at subclinical levels, are associated with difficulties in cognitive and psychosocial functioning (Gotlib, 1992; Vredenburg, Flett, & Krames, 1993) and with an increased risk of a subsequent diagnosis of depression (Fergusson, Horwood, Ridder, & Beautrais, 2005). Thus, subclinical levels of depression or anxiety symptoms in pregnant women are not harmless and these women may represent a group who could benefit from early intervention.

Identifying prenatal predictors of adult health outcomes may help us uncover the mechanisms through which these exposures exert their influence and ultimately lead to effective prevention and treatment for these diseases. Additionally, pregnancy is a unique period in a woman's life when she is likely to have frequent contact with health care professionals. These interactions afford clinicians the valuable opportunity to identify those women suffering from depression so they can be targeted for prevention and intervention efforts.

2.2 PAPER 2: EXAMINING BIRTH WEIGHT AS A MEDIATOR OF THE RELATIONSHIP BETWEEN PRENATAL DEPRESSIVE SYMPTOMS AND OFFSPRING INTERNALIZING SYMPTOMS AT 22 YEARS

2.2.1 Abstract

Background: Depression during pregnancy is common and has independently been associated with lower birth weights and offspring mental health. Birth weight has also been associated with future psychological distress. We examined whether birth weight mediated the association between prenatal depressive symptoms and offspring internalizing symptoms at 22 years in the Maternal Health Practices and Child Development prospective cohort study.

Methods: Mediation was explored through three linear regression models in accordance with Baron and Kenny's causal steps approach to determine if the following four mediation criteria were met: (1) the independent variable is associated with the dependent variable, (2) the independent variable is associated with the proposed mediator, (3) the mediator is associated with the dependent variable, and (4) the effect of the independent variable on the dependent variable should be diminished when controlling for the mediator. Mediation was formally tested with Sobel's z-test.

Results: Controlling for prenatal demographics and maternal substance use, prenatal depressive symptoms predicted internalizing symptoms (β=.09, p=.022), but were not associated with birth weight (β=-.05, p=.229), resulting in a non-significant Sobel test-statistic (z=.93, p=.351). Results were similar when stratified by sex (47% male) and race (52% African American, 48% Caucasian).

Conclusions: While higher prenatal depressive symptoms predicted higher internalizing symptoms, this association was not mediated by birth weight, suggesting that prenatal depressive symptoms might have a direct effect on internalizing symptoms. Offspring sex and race did not moderate any of the associations.

2.2.2 Introduction

Depressive symptoms during pregnancy are common (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; Gaynes et al., 2005) and have been associated with offspring temperament and psychopathology (E. D. Barker et al., 2011; Davis et al., 2007; M. Diego, Field, & Hernandez-Reif, 2005; Gerardin et al., 2011; Pawlby et al., 2009). Although most of these studies focused on infant outcomes (Davis et al., 2007; M. Diego et al., 2005; Gerardin et al., 2011), the effects of prenatal depression have been shown to persist through childhood and adolescence. In the Avon Longitudinal Study of Parents and Children, prenatal depression as measured by the Edinburgh Postnatal Depression Scale (Cox, Holden, & Sagovsky, 1987), was associated with an increase in parent and teacher reports of child externalizing and internalizing difficulties at ages 7-8 years (E. D. Barker et al., 2011). Researchers found the effect on internalizing problems were mediated by maternal depression and anxiety at 21 months. Further, adolescents within a South London birth cohort whose mothers had an ICD-9 diagnosis of depression during pregnancy had a 5-fold greater odds of having a DSM-IV depressive disorder at 16 years compared to adolescents who were not exposed (Pawlby et al., 2009). In a recent analysis within the MHPCD study, we found that prenatal depressive symptoms were significantly associated with higher internalizing problem scores in exposed offspring at 22 years while controlling for significant prenatal and 22-year covariates.

While these studies suggest that prenatal depressive symptoms may have lasting effects on offspring mental health, the nature of this relationship deserves further investigation. Subsequent exposures may explain or mediate the associations between prenatal depression and offspring psychopathology. One such exposure that is worth exploring is birth weight, as a review of the literature reveals that it may be a potential mediator. A mediator is defined as "a variable that occurs in a causal pathway between an independent variable to a dependent variable" and is "statistically associated with both the independent and dependent variables (Last, 2001)." Baron and Kenny (1986) expanded upon this definition by proposing that a variable must meet the following conditions to be considered a mediator between an independent and dependent variable: (a) the independent variable accounts for variations in the mediator, (b) the mediator accounts for variations in the dependent variable, and (c) the effect of the independent variable on the dependent variable is diminished when controlling for the mediator. Birth weight has been shown to be influenced by prenatal depression in addition to being associated with future psychopathology and may meet the criteria for a mediator between prenatal depression and offspring psychopathology.

2.2.2.1 Prenatal Depression and Fetal Growth

In a study comparing fetal growth between pregnant women with a diagnosis of MDD and non-depressed pregnant women, the infants of depressed mothers weighed less at birth, both corrected and uncorrected for gestational age (M. A. Diego et al., 2009). While there was not a significant difference in gestational age at birth between the groups, the depressed women had a 15% greater incidence of a low birth weight infant and 13% greater incidence of premature delivery than their non-depressed counterparts (M. A. Diego et al., 2009). This study is also worth noting because it provided support for a biological mechanism through which prenatal

depression may exert its influence. Maternal cortisol levels during pregnancy have been linked to higher depressive symptoms and lower fetal weights (M. A. Diego et al., 2006; Field et al., 2006).

Other studies have confirmed these findings by showing associations between prenatal depressive symptoms and preterm birth, low birth weight, and small-for-gestational-age infants (Dayan et al., 2006; Orr et al., 2002; Steer et al., 1992), prenatal psychological distress as measured by the General Health Questionnaire and preterm birth (Hedegaard, Henriksen, Sabroe, & Secher, 1993), and diagnoses of Dysthymia or Major Depression with infants of lower gestational age and lower birth weights (Field et al., 2008).

2.2.2.2 Fetal Growth and Future Psychopathology

Since the introduction of the fetal origins of disease hypothesis by Barker (1995), considerable research has explored the effects of fetal growth on adult disease. Barker originally proposed the hypothesis to explain the observed association between lower birth weights and higher rates of heart disease, but increasing evidence has accumulated to suggest that birth weight likewise plays an important role in the development of other chronic diseases including type 2 diabetes (Forsen et al., 2000), breast cancer (Hilakivi-Clarke & de Assis, 2006), and potentially even psychiatric disorders (Betts, Williams, Najman, Scott, & Alati, 2012; Cannon et al., 2002; Schlotz & Phillips, 2009).

However, studies examining the effect of birth weight on future psychopathology have produced conflicting results. Some studies have shown an association between birth weight and future depression (M. H. Boyle et al., 2011; Burnett et al., 2011; Costello, Worthman, Erkanli, & Angold, 2007; Nomura et al., 2007; Patton, Coffey, Carlin, Olsson, & Morley, 2004; Thompson, Syddall, Rodin, Osmond, & Barker, 2001; Van Lieshout & Boylan, 2010), whereas other studies

have not (Elgen, Sommerfelt, & Markestad, 2002; Gale & Martyn, 2004; Indredavik et al., 2004; Osler, Nordentoft, & Andersen, 2005; Vasiliadis, Gilman, & Buka, 2008). Disparities also exist as to whether birth weight has different effects on depression by sex. Studies have reported everything from no sex by birth weight interaction (M. H. Boyle et al., 2011), to an effect only among men of low birth weight (Thompson et al., 2001), and most commonly, an effect of low birth weight only among females (Alati et al., 2007; Costello et al., 2007; Patton et al., 2004; Van Lieshout & Boylan, 2010). A single study reported an association between higher birth weights and higher depressive symptoms, but only among the females in the sample (Herva et al., 2008).

These discordant findings may partially be explained by differences in study design and methodologies, as definitions and measurements of birth weight varied greatly between the studies. While most utilized birth weight measures from medical records (Alati et al., 2007; Alati et al., 2009; Gale & Martyn, 2004; Indredavik et al., 2004; Osler et al., 2005), some studies used maternal reports of birth weight (Costello et al., 2007; Nomura et al., 2007; Van Lieshout & Boylan, 2010), with a single study using self-reported birth weights when data from the medical record were unavailable (27% self-reported) (Inskip et al., 2008). Moreover, there was variation in the consideration of birth weight as an exposure. Several studies examined categories of birth weight (Alati et al., 2007; Gale & Martyn, 2004; Herva et al., 2008; Vasiliadis et al., 2008), although categorization was inconsistent and ranged from three (Vasiliadis et al., 2008) to eight categories (Herva et al., 2008). Other studies used the traditional dichotomous categorization of low birth weight, defined as ≤2.50 kg (5.50 lb) (Costello et al., 2007; Van Lieshout & Boylan, 2010), or considered birth weight as a continuous variable (Alati et al., 2007; Alati et al., 2009;

Inskip et al., 2008). And while most studies adjusted birth weight for gestational age, some did not (Osler et al., 2005; Thompson et al., 2001)

There was substantial variation in the assessment of outcomes as well. Age at the time of depression assessment ranged from four to 68 years, with outcomes including everything from depression diagnoses (Costello et al., 2007; Herva et al., 2008; Indredavik et al., 2004; Osler et al., 2005), to depressive symptoms (Alati et al., 2007; Herva et al., 2008; Inskip et al., 2008; Thompson et al., 2001; Van Lieshout & Boylan, 2010), to anxiety and depressive symptoms (Alati et al., 2009), to psychological distress (Gale & Martyn, 2004).

Despite the literature providing support for the role of birth weight as a mediator between prenatal depression and offspring psychopathology, to our knowledge, no studies have statistically tested for birth weight as a mediator. As such, the aim of this analysis was to determine whether birth weight mediates the association between prenatal depressive symptoms and offspring internalizing scores at 22 years while controlling for significant prenatal covariates associated with internalizing scores. Additionally, considering the evidence suggesting that birth weight may have differential effects by sex, we will examine whether sex is a significant moderator in our analysis. Lastly, we will also explore race as a potential moderator. While there is a difference in birth weights between African American and Caucasians in the United States (Zhang & Bowes, 1995), few of the previous studies had diverse enough samples to explore race as a moderator. Within a study that explored the effects of prenatal depressive symptoms on pregnancy outcomes, researchers found an association between depressive symptoms and preterm birth, but only among the African American women in their sample (Orr & Miller, 1995). Given the racial diversity of our sample (52% African American, 48% Caucasian), we will examine whether birth weight has a differential effect by race.

2.2.3 Methods

2.2.3.1 Sample Selection and Study Design

Data for these analyses come from two cohorts within the Maternal Health Practices and Child Development (MHPCD) project, which was designed to examine the long-term effects of prenatal substance use on offspring. Between 1982 and 1985, a sequential sample of adult, English-speaking women in their fourth or fifth prenatal month was recruited from a prenatal clinic. Fifteen percent of the women approached refused participation, resulting in an initial sample of 1,360 women. Two groups were selected from this sample. The first cohort was selected based on first trimester alcohol use and included all women who drank at least 3 alcoholic drinks per week in the first trimester and a random sample of 1/3 of those who drank less or abstained. The second cohort was selected based on first trimester marijuana use and included all women who smoked two or more joints per month in the first trimester and a random sample of 1/3 of those who smoked less or abstained. Sampling was done with replacement, so a woman could be selected for either or both cohorts. Because these studies were conducted simultaneously, had considerable overlap, and used the same protocol, instruments, and personnel, the two cohorts can be combined for this analysis. The combined birth cohort consisted of 763 women with live singleton infants.

The cohorts have completed 11 assessments to date. Women were assessed at their fourth or fifth prenatal month (first trimester), seventh prenatal month (second trimester), and with their offspring at delivery, 8 and 18 months postpartum, and at offspring ages 3, 6, 10, 14, 16, and 22 years. These analyses used data from the first and second prenatal assessments, the delivery assessment, and the 22-year assessment. Mothers were interviewed about demographic factors, substance use, psychological status, medical history, and current home environment at

the initial visit and each follow-up, while offspring growth, cognitive and physical development, mental health, and behaviors were measured at each of the follow-up times. Mothers and offspring were interviewed separately at the 22-year assessment.

At the 22-year phase, 80% (n=608) of the birth cohort was interviewed. Missing were 30 offspring who refused to participate, 3 were adopted, 18 were institutionalized (jail or rehabilitation center), 56 were lost to follow-up, 29 who moved out of the Pittsburgh area, 11 died, and 8 were unable to participate due to low cognitive functioning. One offspring did not complete the behavioral assessment and six mothers did not complete the depression assessment at the first antenatal visit, resulting in a sample of 601 offspring for this analysis. There were no significant differences between those included in the 22-year analyses and those who were not when baseline, defined as the first trimester assessment, maternal education, household monthly income, race, depression, and alcohol, marijuana, or cigarette use were considered (Table 8). While there were no significant differences when offspring birth weight and gestational age at delivery were considered, missing offspring were significantly more likely to be male. However, the effect size was negligible (Cramer's V=.12), and the results should be generalizable to the original birth cohort.

2.2.3.2 Measures

Outcome. Offspring completed the Adult Self Report (ASR) at the 22-year interview (Achenbach & Rescorla, 2003). This instrument is an adult continuation of the Child Behavior Checklist (Achenbach, 1991) and has subjects self-report on their behavioral, emotional, and social problems. It consists of 126 items that assess eight syndromes and has been shown to be reliable and valid (Achenbach & Rescorla, 2003). These eight syndromes can be grouped and summed to produce internalizing and externalizing scores. The internalizing grouping consists

Table 8. Comparison of analyzed sample to those who were missing for Paper 2

Baseline Maternal Demographics	Analyzed Sample (n=601)	Missing (n=162)	p[a]	Effect Size[b]
Race (% Caucasian)	48.1	50.0	.665	.02
Age (years)	23.0	23.1	.796	.01
Education (years)	11.8	11.9	.598	.02
Household income ($/month)	300-399	300-399	.735	.02
CES-D score	21.0	20.2	.273	.05
Average daily volume of alcohol	0.6	0.7	.207	.05
Average daily joints of marijuana	0.4	0.4	.677	.02
Average daily cigarettes	8.3	8.6	.727	.02
Any other illicit drug use (%)	8.7	9.9	.627	.02
Offspring at Delivery				
Gender (% male)	47.1	61.7	.001	.12
Birth weight (kg)	3.2	3.2	.692	.02
Gestational age (weeks)	39.8	39.6	.306	.05

[a] t-test for continuous variables and chi-square test for dichotomous, non-parametric used for skewed continuous variables
[b]Cohen's D for continuous variables and Cramer's V for dichotomous variables

of problems that are mainly within the self and includes all items from the Anxious/Depressed, Withdrawn, and Somatic Complaints syndrome scales. The internalizing problem score was computed by summing the scores of the three internalizing syndrome scales. This score was then standardized based on a normative sample. The T-scores indicate how elevated the individual's internalizing score is in relation to the normative sample, with higher scores indicating more internalizing symptoms. The clinical cut-point for internalizing scores is a T-score>63, with T-scores in the 60-63 range considered borderline. A Cronbach's alpha of 0.93 was found for the internalizing items on the ASR (Achenbach & Rescorla, 2003).

Exposure. Maternal depressive symptoms were assessed at each visit with the CES-D (Radloff, 1977). The CES-D is a widely used 20-item instrument with a 4-point Likert response scale that measures the frequency of depressive symptoms. Scores range from 0-60 with higher

scores indicating greater depressive symptoms. The scale has been shown to be both reliable and valid (Radloff, 1977) and has frequently been used in studies of pregnant women (Gaynes et al., 2005). Within our cohort, the Cronbach's alpha for the CES-D was 0.89 at the 18-month assessment (Seto et al., 2005). Studies have shown that stress exposure mid-gestation is associated with the greatest risk for LBW (Class, Lichtenstein, Langstrom, & D'Onofrio, 2011). Considering this, continuous CES-D scores from the first assessment will be utilized (mean gestational age at assessment: 18 weeks).

Mediator. Birth weight was transcribed by study nurses from the medical record at the delivery assessment. Gestational age was assessed by a study nurse at the delivery assessment using the Ballard modification of the Dubowitz assessment (Ballard, Novak, & Driver, 1979). The Ballard method estimates gestational age based on an examination of the physical and neurological characteristics of the neonate. We calculated birth weight z-scores using a population-based Canadian reference for sex and gestational age-specific population means and standard deviations of birth weight (Kramer et al., 2001). While the sample is Canadian, it is one of few modern (1994-1996) population-based references with a large sample (n=676,605) and published means and standard deviations. Continuous birth weight z-scores were calculated by subtracting the population-reference mean birth weight for the same sex and same gestational age as the participant from the participant's own birth weight and dividing by the population-reference sex and gestational age-specific standard deviation. While we had other measures of neonate growth and size available (low birth weight: $\leq$2.5kg, preterm birth: <37 weeks gestation, small for gestational age: birth weight $\leq 10^{th}$ percentile for gestational age), we choose to use the birth weight z-scores because they take into account gestational age and are a continuous

measure. To provide a better picture of offspring growth and size at birth in our sample, we will present descriptive statistics for the additional measures of size and growth noted above.

Prenatal Covariates. Mothers reported their age, marital status, education, household income, and employment status at all phases and data from the initial assessment were used for this analysis. Maternal substance use during the first trimester was assessed at the initial prenatal visit. Substance use measures were designed specifically for this study and have been shown to be both reliable and valid (N. L. Day & Robles, 1989; Robles & Day, 1990). For alcohol, women reported their usual, minimum, and maximum quantity and frequency of beer, wine, liquor, and beer and wine coolers. From this, the average daily volume of alcohol (ADV) was calculated. Marijuana use was similarly assessed and converted into average daily joints (ADJ). Tobacco use was considered as the average number of cigarettes smoked per day. Other illicit drug use in the first trimester (cocaine, barbiturates, prescription drug abuse, etc.) was combined and dichotomized as any versus none. First trimester binge drinking was defined as consuming ≥4 drinks in a single occasion. A study nurse also abstracted data on maternal antidepressant use during pregnancy from obstetric and medical records at the delivery assessment. Considering that only four women in the sample reported prenatal antidepressant use and that the results did not differ when excluding them, the presented results will include these women. It should be noted that five women in the previous analysis (Paper 1) had reported antidepressant use during pregnancy, however one of these women did not have a CES-D score available for the first trimester assessment and was not included in this analysis.

2.2.3.3 Analysis

Descriptive analyses were performed to summarize sample characteristics and we examined the distributions of variables to identify potential violations of normality assumptions. The

distributions of maternal substance use (alcohol, marijuana) were positively skewed and were log-transformed to reduce skewness. Pearson correlation coefficients were calculated to examine the bivariate associations between variables.

Mediation was explored using three linear regression models in accordance with Baron and Kenny's causal steps approach (Baron & Kenny, 1986). Baron and Kenny proposed four criteria that must be met for a variable to be considered a mediator: (1) the independent variable is associated with the dependent variable, (2) the independent variable is associated with the proposed mediator, (3) the mediator is associated with the dependent variable, and (4) the effect of the independent variable on the dependent variable should be diminished when controlling for the mediator (Baron & Kenny, 1986). Steps 3 and 4 are tested within the same equation, so only three regression models are required to explore the mediation effect. For this analysis, the independent variable is prenatal depressive symptoms, the dependent variable is the offspring internalizing score, and the mediator under investigation is the birth weight z-score.

Sobel's z-test was used to formally test the significance of the indirect effect, which is a measure of the amount of mediation (Sobel, 1982). Additionally, we used the bootstrapping method to assess the bias-corrected 95% confidence interval for the indirect effect based on 1,000 bootstrap samples. Bias-corrected confidence intervals correct for bias in the central tendency of the indirect effect estimate (Mackinnon, Lockwood, & Williams, 2004). We controlled for prenatal covariates that were significantly associated with internalizing scores with a $p<.10$ in all steps. To explore potential racial and sex differences, we reran the analysis first stratified by race, and then stratified by sex. Results were compared between the groups to determine if any of the associations were moderated by race or sex.

2.2.4 Results

2.2.4.1 Descriptive Statistics

Demographic characteristics of the mothers at baseline and the offspring at 22 years can be found in Table 4 of Paper 1. Since there were only seven participants excluded from this analysis that were included in the analysis for Paper 1, there were no significant differences in demographics between the groups. The sample included in the analysis was equally split by race (48% Caucasian, 52% African American) and offspring gender (47% male). The mothers in our sample were young at baseline (23 years), with 11.8 years of education and low incomes (median household income of $300-399/month in 1982-1985 currency). Only 32% of the sample was married and 25% were employed or in school at baseline. Prenatal substance use was common and reflected the selection criteria for the study, with 64% of mothers reporting alcohol use, 41% reporting marijuana use, and 54% reporting cigarette use at the first assessment. At the 22-year assessment, the offspring were 22.8 years old, had an average education of 12.8 years, a median personal monthly income of $800 in 2004-2007 currency, few were married (6%), and 60% were employed or attending school.

Offspring birth characteristics are presented in Table 9. On average, offspring had a birth weight of 3.2 kg (7 lbs.) with a gestational age of roughly 40 weeks and a gestational age-standardized birth weight z-score of -0.60. Because there were some extreme values for birth weight z-scores, we reran the analyses excluding those with a z-score outside of the 95th percentile ($z<-1.96$ or $z>1.96$). Because the results did not change when excluding these offspring (n=48), we chose to keep them in the analysis and only present the results that include these observations. Nine percent were born preterm, 10% were low birth weight (<2.5 kg) and 11% were small for gestational age (birth weight $\leq 10^{th}$ percentile for gestational age). The

Table 9. Offspring characteristics at birth

Characteristic	Mean (range)
Birth weight (kg)	3.19 (1.04-4.99)
Gestational age (weeks)	39.8 (28-44)
Gestational age-standardized birth weight z-score	-.60 (-4.13-2.71)
Low birth weight (<2.5kg)	10.0%
Small for gestational age (birth weight $\leq 10^{th}$ percentile)	10.8%
Preterm (<37 weeks)	8.5%

average maternal CES-D score at the first prenatal assessment was 21 (range: 1-51), and offspring had an average internalizing score of 51.4 (range: 30-88) at 22 years (Table 4).

Pearson correlations between the dependent variable, independent variable, mediator, and prenatal covariates are presented in Table 10. Higher prenatal depressive symptoms were significantly associated with higher internalizing scores, while higher birth weights were associated with lower internalizing scores. Higher prenatal depressive symptoms were also associated with lower birth weights, and lower gestational ages, however their association with birth weight z-scores did not reach statistical significance (p-value=.13). Prenatal maternal demographics associated with higher birth weights include being Caucasian, having more years of education, and being married, while alcohol, marijuana, and cigarette use were associated with lower birth weights. Significant prenatal covariates of birth weight and offspring internalizing scores that we subsequently controlled for in the mediation analysis included maternal education, and alcohol and cigarette use.

2.2.4.2 Mediation Analysis

Results of the mediation analysis are presented in Table 11 with Figure 1 providing a visual representation of the mediation model being tested. Higher prenatal depressive symptoms significantly predicted higher offspring internalizing scores (path c), however they did not

Table 10. Correlations among variables for Paper 2

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)
Outcome																
1. ASR internalizing	1.00															
Exposure																
2. CES-D score	.11**	1.00														
Mediator																
3. Birth weight	-.10**	-.11**	1.00													
4. Gestational age	-.04	-.07*	.66**	1.00												
5. Birth weight z-score	-.09**	-.06	.74**	.03	1.00											
Prenatal Covariates																
6. Age	-.03	.02	-.03	-.05	<.01	1.00										
7. Race	.09**	-.01	.18**	.05	.19**	.04	1.00									
8. Education	-.10**	-.07	.06	<-.01	.08**	.19**	-.11**	1.00								
9. Household income	-.05	-.08**	.09**	.07	.07	.21**	.22**	.17**	1.00							
10. Marital status	.03	-.05	.12**	.01	.13**	.11**	.36**	.07*	.36**	1.00						
11. Employment status	-.08*	-.01	.05	.06	.04	.01	-.09*	.20*	.14*	-.10*	1.00					
12. Alcohol	.13**	.07**	-.06	.01	-.09*	.04	.01	.01	-.03	-.10*	-.02	1.00				
13. Marijuana	.04	.03	-.05	.02	-.08*	-.01	-.18**	-.06	-.08**	-.12**	-.10**	.09**	1.00			
14. Cigarettes	.10**	.04	-.11**	.06	-.17*	.06	.33	-.21*	.06	.09*	-.09*	.16*	.04	1.00		
15. Other illicit drug use	-.01	.06	-.04	.02	<.01	.02	.14*	-.07*	<.01	.06	-.01	.10**	.11**	.16**	1.00	
16. Offspring gender	-.08**	-.05	.10**	<.01	.03	.05	.03	.13**	.04	.04	.03	-.01	-.02	-.02	-.05	1.00

* p<.10
** p<.05

Table 11. Birth weight mediation analysis

Baron & Kenny Mediation Steps	Outcome	Predictor	b	β	*p*	R^2	Sobel test
1. IV predicts DV	Internalizing symptoms	Prenatal depression	.12	.09	.022	.034	z-statistic =.94 *p*=.348 Proportion of effect mediated=3.22%
2. IV predicts mediator	Birth weight z-score	Prenatal depression	<-.01	-.05	.229	.036	
3&4. IV, mediator predict DV	Internalizing symptoms	Prenatal depression	.12	.09	.027	.038	
		Birth weight z-score	-.74	-.06	.135		
*Controlling for maternal education, and alcohol and cigarette use at the first antenatal assessment b=unstandardized coefficient, β=standardized coefficient Results of bootstrapping analysis: Indirect effect coefficient (.004, p=.424), 95% CI (-.002- .021)							

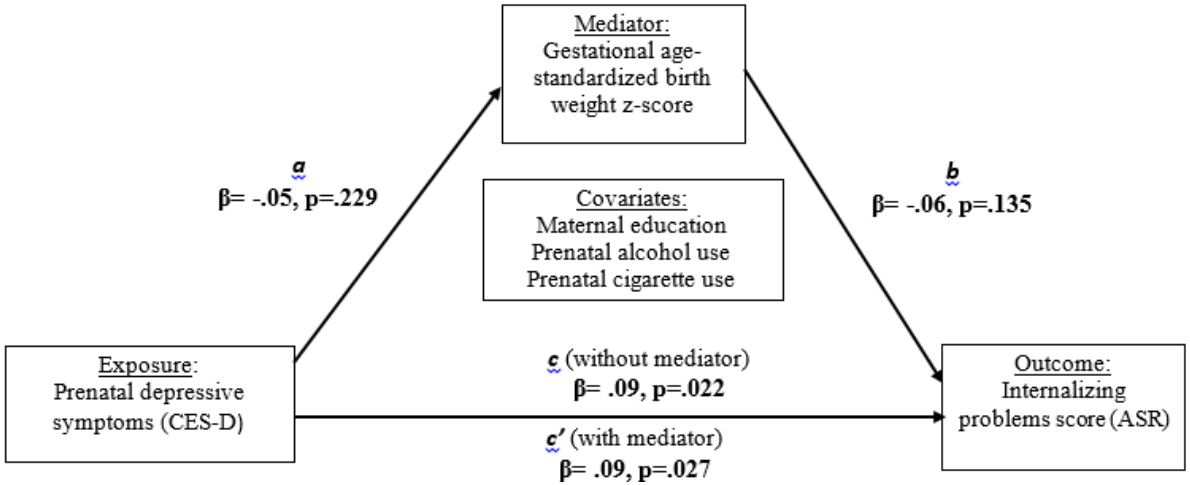

Figure 1. Birth weight mediation model with results

predict birth weight (path a). Higher birth weights were marginally predictive of lower internalizing scores (path b), but their addition to the model did not significantly diminish the effect of prenatal depressive symptoms on internalizing scores (path c'). In addition to failing to meet the Baron and Kenny mediation criteria for steps 3 through 4, the Sobel test of the indirect effect was non-significant as well (p=.349). The bootstrapping analysis produced similar results with an estimated indirect effect of 0.004 (p=.420, 95% CI: -.006-.015). Table 12 presents the results of the stratified mediation analysis. Birth weight failed to emerge as a mediator when stratified by race and sex.

As a sensitivity analysis, we reran the models replacing the birth weight z-scores with the raw offspring birth weights unadjusted for gestational age. While the raw birth weight met the Baron and Kenny mediation criteria for steps 1 and 2, birth weight did not significantly predict internalizing symptoms while controlling for prenatal depressive symptoms (p=.054) and failed to diminish the effect of prenatal depressive symptoms on internalizing scores (Sobel p-value=.121).

2.2.5 Discussion

In this analysis, birth weight did not mediate the association between prenatal depressive symptoms and offspring internalizing scores. In contrast to previous studies, prenatal depressive symptoms were not significantly associated with birth weight. Hoffman and Hatch (2000) found an association between elevated CES-D scores (≥16) and lower gestational age-standardized birth weights, but only among women with a low household occupational status. This association was significant for elevated second-trimester (28 weeks gestation) CES-D scores, but not for elevated first- (13 weeks) or third-trimester (36 weeks) scores. While our study utilized

Table 12. Birth weight mediation analysis stratified by race and sex

Baron & Kenny Mediation Step	Outcome	Predictor	b	β	*p*	R^2	Sobel test
African Americans (n=312)							
1	Internalizing symptoms	Prenatal depression	.10	.09	.128	.037	z-statistic =.04 *p*=.970 Proportion of effect mediated=.26%
2	Birth weight z-score	Prenatal depression	<-.01	-.002	.970	.043	
3&4	Internalizing symptoms	Prenatal depression	.10	.09	.121	.049	
		Birth weight z-score	-1.34	-.11	.057		
Bootstrapped	Indirect effect coefficient: <.001	p-value: .974		Bias-corrected 95% CI: (-.02 - .02)			
Caucasians (n=289)							
1	Internalizing symptoms	Prenatal depression	.16	.11	.068	.031	z-statistic =.79 *p*=.429 Proportion of effect mediated=4.81%
2	Birth weight z-score	Prenatal depression	-.01	-.09	.104	.105	
3&4	Internalizing symptoms	Prenatal depression	.15	.10	.084	.034	
		Birth weight z-score	-.69	-.06	.364		
Bootstrapped	Indirect effect coefficient: .008	p-value: .501		Bias-corrected 95% CI: (<-.01 - .04)			
Females (n=318)							
1	Internalizing symptoms	Prenatal depression	.11	.09	.117	.048	z-statistic =.60 *p*=.547 Proportion of effect mediated=4.06%
2	Birth weight z-score	Prenatal depression	<-.01	-.04	.523	.025	
3&4	Internalizing symptoms	Prenatal depression	.11	.08	.132	.058	
		Birth weight z-score	-1.17	-.10	.077		
Bootstrapped	Indirect effect coefficient: .005	p-value: .566		Bias-corrected 95% CI: (<-.01 - .03)			
Males (n=283)							
1	Internalizing symptoms	Prenatal depression	.13	.10	.104	.019	z-statistic =.124 *p*=.902 Proportion of effect mediated=.49%
2	Birth weight z-score	Prenatal depression	<-.01	-.06	.287	.055	
3&4	Internalizing symptoms	Prenatal depression	.13	.10	.107	.019	
		Birth weight z-score	-.10	-.01	.901		
Bootstrapped	Indirect effect coefficient: .008	p-value: .501		Bias-corrected 95% CI: (<-.01 - .04)			

*Controlling for maternal education, and alcohol and cigarette use at the first antenatal assessment
b=unstandardized coefficient, β=standardized coefficient

continuous CES-D scores assessed at 18 weeks gestation, we did have CES-D scores available for the second-trimester assessed at an average of 28 weeks and could also categorize women as having elevated symptoms using the same cut-off employed in the Hoffman and Hatch study. Pearson correlation analyses within our sample revealed that neither second-trimester nor first-trimester CES-D scores considered as dichotomous variables were associated with birth weight.

Differences between our sample and Hoffman and Hatch's sample may partly explain the discrepant results. Their sample was recruited from a private obstetric practice and even the women classified as having a low household occupational status were likely of a higher socioeconomic status than the women in our study. Compared to our sample at baseline, their sample was older (23 vs. 27.5 years), more likely to be married (32% vs. 88% married), more likely to be working outside the home (25% vs. 81% working), and fewer experienced elevated depressive symptoms (73% vs. 20% elevated). Additionally, 98% of the women in their study were white. They did not provide descriptive statistics for gestational age or birth weight, so it is unclear how the offspring in their sample compared to ours with respect to fetal growth.

Despite a number of studies suggesting otherwise, birth weight failed to have a significant effect on offspring internalizing scores at 22 years in our sample. Wojcik and colleagues (2013) recently published a systematic review and meta-analysis of the literature examining the association between low birth weight, defined as <2.5kg, and later depression, considered as a binary outcome. They identified 18 studies that met their inclusion criteria and performed a random effects meta-analysis to calculate a pooled estimate of the effect size. They found evidence for a weak association, with the odds of depression or psychological distress being 1.15 times greater for those of low birth weight compared to those of normal birth weight

(95% CI: 1.00-1.32). However, this association became non-significant when they employed a trim-and-fill correction to adjust for publication bias (OR: 1.08, 95% CI: 0.92-1.27).

Although prenatal substance use was common in this sample and has been linked to smaller size at birth (N. Day et al., 1992; N. L. Day & Richardson, 2004), offspring in our sample had birth outcomes comparable to the general population at that time. Data from the National Center for Health Statistics shows that 10% of births in the United States in 1985 were preterm and 6.8% were low birth weight, compared to 8.5% preterm births and 10% low birth weight in our sample (Martin et al., 2012). Additionally, we took prenatal substance use into account in our analysis by controlling for prenatal alcohol exposure.

Assuming that birth weight is not a mediator, these results suggest that prenatal depressive symptoms have a direct effect on offspring internalizing scores at 22 years. However, alternate explanations should be considered as well. It is possible that birth weight is a mediator, but our sample size may not have been large enough to detect the effect. Fritz and Mackinnon estimate that a sample size of at least 530 is needed for .80 power to detect a small effect size (β=0.14 or 2% of the variance) using the Baron and Kenny test, 667 for the Sobel test, and 558 for the percentile bootstrap method (Fritz & Mackinnon, 2007). Considering that the estimated effect sizes in our analysis were below the small effect size level, our sample may have been too small to detect an effect despite falling within the sample size range suggested by Fritz and Mackinnon. On the other hand, the association between prenatal depressive symptoms and internalizing scores may be mediated by a variable that we failed to consider in this analysis.

This study has several strengths. First, this was a longitudinal study with excellent follow-up rates. As subject loss was independent of baseline maternal depressive symptoms and offspring size at birth, our results are generalizable to the original birth cohort. Additionally, the

prospective nature of data collection helped to minimize memory and recall bias. Second, we had a large sample with equal proportions of African Americans and Caucasians. This diversity allowed us to examine potential interactions with race in our analysis. Third, we had reliable data on offspring growth measures. Trained study nurses abstracted birth weights from medical records and directly assessed gestational age using the Dubowitz method.

Several methodological limitations also need to be discussed. First, our sample is a homogeneous cohort with regard to their education and income. Consequently, these results may not be generalizable to women of a higher socio-economic status. Also, much occurs between a prenatal exposure and an outcome assessed 22 years later. While we had data available for other experiences and exposures during the offspring's life, we chose to focus on birth weight and prenatal exposures for this analysis. Future analyses will take into consideration exposures at other times during the offspring's life and explore their effect on internalizing symptoms.

Prenatal depressive symptoms are associated with higher offspring internalizing symptoms at 22 years and this effect was not mediated by birth weight. Since the introduction of the fetal origins of disease hypothesis, many researchers have explored the effects of birth weight on adult diseases. However, the findings with regards to psychopathology have been conflicting and few studies adequately controlled for predictors of birth weight. In our sample, birth weight did not significantly predict internalizing symptoms while controlling for prenatal depressive symptoms. Perhaps it is time for researchers to take a step back and start focusing on the specific prenatal causes of low birth weight that may be influencing adult disease. At this point, additional studies strictly exploring the effect of birth weight on psychopathology are unlikely to settle the conflicts within the existing literature.

2.3 PAPER 3: LONGITUDINAL COURSE OF MATERNAL DEPRESSIVE SYMPTOMS AND OFFSPRING INTERNALIZING SYMPTOMS AT 22 YEARS

2.3.1 Abstract

Background: Studies have revealed significant heterogeneity in the course of maternal depressive symptoms over time. We examined whether first trimester maternal depressive symptoms and the rate of change in maternal depressive symptoms over time predicted offspring internalizing scores at 22 years in the Maternal Health Practices and Child Development cohort study.

Methods: Latent growth curve modeling was used to examine the effect of the trajectory of maternal depressive symptoms from the first trimester through 16 years postpartum on offspring internalizing symptoms at 22 years. Multi-group structural equation modeling was performed to explore whether trajectories differed by race and a mediation analysis was conducted to determine whether any associations were mediated by offspring history of child abuse and neglect.

Results: There was significant variation in first trimester maternal depressive symptoms (mean CES-D score=21.1, $p<.001$; $\sigma^2=46.5$, $p<.01$) and borderline variance in the rate of change in maternal depressive symptoms through 16 years postpartum (mean slope= -0.894, p=.004; $\sigma^2=3.5$, p=.067). However, there were not enough significant differences between trajectories to justify analyzing the groups separately by race. Controlling for significant covariates, first trimester maternal depressive symptoms were marginally predictive of offspring internalizing scores (b=.126, p=.070), but change in maternal depressive symptoms was not (b= -.149, p=.621). Offspring history of child abuse and neglect mediated the marginal effect of first

trimester maternal depressive symptoms on offspring internalizing scores (indirect effect p-value=<.001).

Conclusions: Although first trimester maternal depressive symptoms were marginally associated with offspring internalizing scores, this effect was significantly mediated by childhood maltreatment. Nevertheless, detection of depression during pregnancy may identify mothers of offspring who are at increased risk for child maltreatment and elevated internalizing symptoms.

2.3.2 Introduction

Longitudinal studies have demonstrated that the offspring of prenatally depressed mothers are at an increased risk for negative infant reactivity (Davis et al., 2007), greater anxiety symptoms (Gerardin et al., 2011), and higher rates of depression at 16 years (Pawlby et al., 2009). Likewise, we found an association between prenatal depressive symptoms and offspring internalizing scores at 22 years in previous analyses, but the exact nature of this relationship is unclear. Depression is often chronic with women experiencing depression at one point in their child's lives being at an increased risk for subsequent depression (Coleman, Ghodsian, & Wolkind, 1986; Seto et al., 2005). However, studies have shown considerable variation in the patterns of depressive symptoms experienced over time (Mora et al., 2009; Nandi et al., 2009; Skipstein, Janson, Stoolmiller, & Mathiesen, 2010). Researchers have begun to investigate the effect that changes in maternal depressive symptoms over time may have on offspring mental health.

In a systematic review of the literature, Gunlicks and Weissman examined the effects of improvement in parental depression on child psychopathology (Gunlicks & Weissman, 2008).

They identified ten studies for inclusion in their review. Most of the studies reviewed showed a positive effect of treating parental depression on child psychopathology, where treatment of depression was associated with fewer internalizing and externalizing symptoms as well as improvements in child behavior and functioning. A few of the studies failed to find an effect of treatment, but this may be a result of the considerable variation in study design, samples, and treatments under investigation.

Within the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, researchers found a significant decrease in child psychiatric symptoms for women whose depression had remitted, regardless of whether the remission occurred early (within the first 3 months of treatment) or late (after the first 3 months but within the first year) (Pilowsky et al., 2008). In contrast, children of mothers whose depression had not remitted did not show significant improvement in psychiatric symptoms during the 1 year of follow-up. A similar study among 60 pairs of low-income women with MDD and their children ages four to 11 years found that children of mothers whose depression had remitted, regardless of their treatment assignment, had fewer behavior problems than children of mothers who remained depressed (Coiro, 2012).

While these types of treatment studies are informative, they suffer from limitations that should be taken into account. Since the studies were designed to examine the effects of various treatments on maternal depression, researchers could only explore the effects of improvements in maternal depressive symptoms because only depressed mothers were selected into the studies. These studies fail to provide information about the natural course of maternal depressive symptoms and also could not examine the effect that increasing maternal depressive symptoms in previously non-depressed mothers may have on offspring outcomes. Follow-up in these

studies tended to be short and none considered offspring outcomes beyond adolescence. Additionally, because most of these studies had few and short follow-up assessments (range: 1-3 follow-up assessments), they were limited in the statistical techniques available to examine change.

Recently, more sophisticated methodologies for studying change have emerged, including trajectory analyses and, more specifically, latent growth curve modeling (LGCM). Traditional longitudinal studies that have followed depressive symptoms over time yield developmental trajectories of population means of depressive symptoms. However, LGCM focuses on individual development of and change in depressive symptoms over time. Latent growth curve modeling is further appealing for a number of reasons. Compared to repeated measures analysis of variance methods employed by some of the treatment studies, LGCM offers better methods for the treatment of missing data, they provide individual and group-level statistics, and there is a greater ability to examine change in more complex causal models, in which change can be considered as a predictor, mediator, or outcome within the same model (Duncan, Duncan, & Strycker, 2006).

While a number of studies have utilized trajectory analyses to describe the development of maternal depressive symptoms (Kuo, Yang, Kuo, Tseng, & Tzeng, 2012; Mora et al., 2009; Skipstein, Janson, Kjeldsen, Nilsen, & Mathiesen, 2012; Skipstein et al., 2010), few have used the trajectories themselves to predict offspring outcomes and those that have utilized growth mixture modeling methods (Ashman, Dawson, & Panagiotides, 2008; Glasheen et al., In press). Growth mixture modeling (GMM) identifies a number of homogeneous subpopulations, or classes, from the total sample with class membership determined by specific model parameters (Duncan et al., 2006). Studies employing GMM use class membership as a categorical variable

to predict offspring outcomes; consequently, these analyses have less power than studies that use LGCM parameters as continuous variables in the prediction of outcomes. However, considering that no LGCM studies predicting offspring outcomes were uncovered, the results of GMM studies are worth considering.

Only a single study was identified that utilized trajectory analysis to examine the effects of depression patterns on offspring psychopathology beyond childhood. Glasheen and colleagues used GMM to identify 2 distinct trajectories of maternal depressive symptoms from the first trimester of pregnancy through 18 months postpartum: low depressive symptoms (16.5%) and high depressive symptoms (83.5%) (Glasheen et al., In press). They also identified 3 trajectories of maternal anxiety symptoms during this time: low anxiety (12%), medium anxiety (52.6%), and high anxiety (35.4%). Depressive symptom trajectory group membership did not significantly predict MDD, anxiety, or conduct disorder among the adolescents at 16 years, but exposure to anxiety trajectories was associated with risk for conduct disorder. This association was moderated by sex, with females exposed to medium or high anxiety having lower odds of conduct disorder and males exposed to the medium and high anxiety having greater odds of conduct disorder. It is possible that the effects of maternal depressive symptoms on offspring depression may have been latent at the 16-year assessment and could emerge later on. Furthermore, they only considered depressive symptoms through 18 months postpartum in their trajectory analysis, while the course of maternal depressive symptoms during childhood and adolescence may influence the development of offspring depression.

Despite evidence supporting the heterogeneous development of depressive symptoms over time, few studies have explored the effect that the course of maternal depressive symptoms may have on offspring mental health. In this study, we used LGCM to examine the influence

that baseline maternal depressive symptoms and the subsequent change in those symptoms over time had on offspring internalizing scores. While GMM represents another analysis option that has been employed in previous trajectory studies of maternal depressive symptoms, we chose to perform LGCM to estimate baseline prenatal symptoms and change in symptoms because we were more interested in using these parameters to estimate offspring internalizing symptoms than we were in describing the trajectories of maternal symptoms. We hypothesized that higher maternal depressive symptoms at baseline would be associated with higher offspring internalizing scores at 22 years and that decreasing maternal depressive symptoms over time would be associated with lower internalizing scores. Additionally, considering evidence suggesting that depressive symptoms differ by race (Mora et al., 2009), we performed a multi-group structural equation modeling analysis stratified by race to explore racial differences in trajectories.

Lastly, we investigated whether offspring history of child abuse or neglect mediated any associations between trajectories of maternal depressive symptoms and offspring internalizing scores. Numerous studies have shown an association between depression and history of childhood maltreatment (Bifulco, Moran, Baines, Bunn, & Stanford, 2002; Cicchetti & Toth, 1995; Danese et al., 2008; Fergusson et al., 2013; Widom et al., 2007). Furthermore, a sizable body of research supports the intergenerational transmission of child maltreatment (Belsky, 1993; Oliver, 1993; Pears & Capaldi, 2001). For mothers, a history of neglect has been shown to lead to poor parenting and a history of abuse has been associated with an aggressive parenting style (Newcomb & Locke, 2001). In another analysis, families where at least one of the parents had a history of child abuse were more likely to be referred for maltreating their own children by a community health nurse visitor compared to families where neither parent had a history of

abuse (Dixon, Hamilton-Giachritsis, & Browne, 2005). This association was mediated by poor parenting styles and history of mental illness or depression in the parents. Given these associations, we hypothesized that offspring reports of child maltreatment would significantly mediate the associations between trajectories of maternal depressive symptoms and offspring internalizing scores.

2.3.3 Methods

2.3.3.1 Sample Selection and Study Design

Data for these analyses come from two cohorts within the Maternal Health Practices and Child Development (MHPCD) project, which was designed to examine the long-term effects of prenatal substance use on offspring. Between 1982 and 1985, a sequential sample of adult, English-speaking women in their fourth or fifth prenatal month was recruited from a prenatal clinic. Fifteen percent of the women approached refused participation, resulting in an initial sample of 1,360 women. Two groups were selected from this sample. The first cohort was selected based on first trimester alcohol use and included all women who drank at least 3 alcoholic drinks per week in the first trimester and a random sample of 1/3 of those who drank less or abstained. The second cohort was selected based on first trimester marijuana use and included all women who smoked two or more joints per month in the first trimester and a random sample of 1/3 of those who smoked less or abstained. Sampling was done with replacement, so a woman could be selected for either or both cohorts. Because these studies were conducted simultaneously, had considerable overlap, and used the same protocol, instruments, and personnel, the two cohorts can be combined for this analysis. The combined birth cohort consisted of 763 women with live singleton infants.

To date, the cohorts have completed 11 assessments. Women were assessed at their fourth or fifth prenatal month (first trimester), seventh prenatal month (second trimester), and with their offspring at delivery, 8 and 18 months postpartum, and at offspring ages 3, 6, 10, 14, 16, and 22 years. These analyses will use data from all of the assessments. Mothers were interviewed about demographic factors, substance use, psychological status, medical history, and current home environment at the initial visit and each follow-up, while offspring growth, cognitive and physical development, mental health, and behaviors were measured at each of the follow-up times. Mothers and offspring were interviewed separately at the 22-year assessment.

Follow-up rates for all study phases were high, with the lowest rate of 76% occurring at the 14-year assessment. Since we used methods that were capable of handling missing data, only those who did not have internalizing scores available for the 22-year assessment were excluded from the analysis. At the 22-year phase, 80% (n=608) of the birth cohort was interviewed. Missing were 30 offspring who refused to participate, 3 were adopted, 18 were institutionalized (jail or rehabilitation center), 56 were lost to follow-up, 29 moved out of the Pittsburgh area, 11 died, and 8 were unable to participate due to low cognitive functioning. One offspring did not complete the behavioral assessment, resulting in a sample of 607 offspring for this analysis. There were no significant differences between those included in the 22-year analysis and those who were not when baseline, defined as the first assessment, maternal education, race, depression, and alcohol, marijuana, or cigarette use were considered (Table 3, Paper 1). Missing offspring were more likely to be male, but the effect size was negligible suggesting that the results should be generalizable to the original birth cohort.

2.3.3.2 Measures

Outcome. Offspring completed the Adult Self Report (ASR) at the 22-year interview (Achenbach & Rescorla, 2003). This instrument is an adult continuation of the Child Behavior Checklist (Achenbach, 1991) and has subjects self-report on their behavioral, emotional, and social problems. It consists of 126 items that assess eight syndromes and has been shown to be reliable and valid (Achenbach & Rescorla, 2003). These eight syndromes can be grouped and summed to produce internalizing and externalizing scores. The internalizing grouping consists of problems that are mainly within the self and includes all items from the Anxious/Depressed, Withdrawn, and Somatic Complaints syndrome scales. The internalizing problem score was computed by summing the scores of the three internalizing syndrome scales. This score was then standardized based on a normative sample. The T-scores indicate how elevated the individual's internalizing score is in relation to the normative sample, with higher scores indicating more internalizing symptoms. The clinical cut-point for internalizing scores is a T-score>63, with T-scores in the 60-63 range considered borderline. A Cronbach's alpha of 0.93 was found for the internalizing items on the ASR (Achenbach & Rescorla, 2003).

Exposure. Maternal depressive symptoms were assessed at each visit with the CES-D Scale (Radloff, 1977), a widely used 20-item instrument with a 4-point Likert response scale that measures the frequency of depressive symptoms. Scores range from 0-60 with higher scores indicating greater depressive symptoms. The scale has been shown to be both reliable and valid (Radloff, 1977) and has frequently been used in studies of pregnant women (Gaynes et al., 2005). Within our cohort, the Cronbach's alpha for the CES-D was 0.89 at the 18-month assessment (Seto et al., 2005). We used the ten CES-D scores from the first-trimester through the 16-year assessment to estimate trajectories of maternal depressive symptoms.

Prenatal Covariates. Unless otherwise noted, prenatal covariates considered in this analysis were from the first trimester assessment. Mothers reported their age, race, marital status, education, household income, and employment status. Substance use measures were designed specifically for this study and have been shown to be both reliable and valid (N. L. Day & Robles, 1989; Robles & Day, 1990). For alcohol, women reported their usual, minimum, and maximum quantity and frequency of beer, wine, liquor, and beer and wine coolers. From this, ADV was calculated. Marijuana use was similarly assessed and converted into ADJ. Tobacco use was considered as the average number of cigarettes smoked per day. Other illicit drug use (cocaine, barbiturates, prescription drug abuse, etc.) in the first trimester was combined and dichotomized as any versus none. The PERI Life Events Scale was adapted to measure the number of stressful life events (Dohrenwend et al., 1978). Thirty-four events from the past year were assessed at the delivery interview and summed to create a total score. The social support measure was adapted from the Alameda County Health Study and had women report how many close friends they have (Berkman & Syme, 1979).

Maternal Covariates at 16-Years. We examined the same maternal covariates at 16-years as we did for the prenatal period to control for subsequent exposure to these variables as postnatal environmental exposures. Additionally, we considered maternal lifetime diagnoses of psychiatric disorders other than depression assessed at the 16-year phase. Maternal psychiatric diagnoses were assessed using the Diagnostic Interview Schedule (DIS-IV) (Robins, Bucholz, Comtpon, North, & Rourke, 2000), which is a structured diagnostic interview that elicits psychiatric diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, 1994). For this analysis, women who received a lifetime diagnosis of any of the following disorders

were categorized as having other psychiatric diagnoses, excluding Major Depressive Disorder and Dysthymia: Generalized Anxiety Disorder, Posttraumatic Stress Disorder, Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, Separation Anxiety, Oppositional Defiant Disorder, Conduct Disorder, Antisocial Personality Disorder, Alcohol Abuse and Dependence, and Drug Abuse and Dependence.

Offspring Covariates at 22 Years. Offspring education, personal income, marital status, employment, number of children, and living situation (lives with mother or not) were assessed at the 22-year interview. Offspring substance use at 22 years, including alcohol, marijuana, tobacco, and other illicit drug use, was assessed using the same instrument that was used for the mothers.

Mediator. Child maltreatment among the offspring was assessed at the 16-year interview using the revised Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998). The CTQ is a reliable and validated retrospective self-report inventory of physical, emotional, and sexual abuse, and physical and emotional neglect (Scher, Stein, Asmundson, McCreary, & Forde, 2001). The instrument consists of 25 statements about experiences during childhood and respondents rate the statements on a 5-point Likert scale ranging from (1) for *Never True* through (5) for *Very Often True*. The total CTQ score was calculated by summing the responses for all of the items, with scores ranging from 25-125 with higher scores indicating more severe levels of maltreatment. For this analysis, we used the continuous total CTQ score.

2.3.3.3 Analysis

Descriptive analyses were performed using Stata to summarize sample characteristics. The distributions of substance use (maternal and offspring alcohol and marijuana use) were positively skewed and log-transformed to reduce skewness. Pearson correlation coefficients were

calculated to examine associations between the maternal CES-D scores at each of the assessments and the offspring internalizing score at 22 years.

Latent growth curve modeling (LGCM), a longitudinal analysis technique used to examine change over time within the structural equation modeling framework, was used to identify trajectories of maternal depressive symptoms (Duncan et al., 2006). Within LGCM, the latent variables of interest are the intercept, representing the initial value, and slope, representing the rate of change, which are estimated using the observed maternal CES-D scores across the first 10 assessments of the study. For this analysis, the intercept and slope of the trajectories of maternal depressive symptoms were the exposures under investigation, as we were interested in examining the effect of prenatal depressive symptoms and changes in maternal depressive symptoms on offspring internalizing scores at 22 years. Full information maximum likelihood procedures were employed to account for missing data and parameters in the model were estimated by applying the maximum likelihood estimator with robust standard errors (MLR) (Yuan & Bentler, 2000). The MLR estimator produces robust standard errors that are not sensitive to non-normally distributed data. All LGCM analyses were performed using Mplus (Muthen & Muthen, 1998-2007).

We began by fitting an unconditional LGCM, which estimated the trajectories using only the CES-D scores without introducing any covariates into the model. The time intervals were fixed, or explicitly specified, for the first four assessments (first trimester, second trimester, delivery, and 8 months postpartum), and freely estimated for the subsequent assessments (18 months, 3 years, 6 years, 10 years, 14 years, and 16 years). Freely estimating the time intervals for the later assessments allowed us to examine non-linear growth in maternal depressive symptoms. The mean intercept of this model represents the average maternal CES-D score at the

first trimester assessment and the mean slope represents the average rate of change in maternal depressive symptoms across the study. Additionally, variance of the intercept and slope parameters were estimated, indicating whether there was significant variation in first trimester maternal depressive symptoms or change in symptoms, respectively. Model fit was assessed with the following fit indices: χ^2, comparative fit index (CFI$\geq$.95), and root mean square error approximation (RMSEA$\leq$.06) (Hu & Bentler, 1999).

Before the effects of the trajectories on offspring internalizing symptoms were explored, we tested whether there were any significant differences between the trajectories of African Americans and Caucasians that would justify running the analyses separately by race. A multi-group structural equation modeling (MSEM) analysis was carried out in three steps: (1) a model was fit within each racial group and model modifications were made until an acceptable fit was achieved, (2) a baseline model was calculated by analyzing the groups simultaneously without imposing any constraints, and (3) various structural parameters were constrained to be equal across the groups and this constrained model was compared to the baseline model from step (2) by performing a chi-square difference test. A significant chi-square test statistic indicates structural variance between the groups for the constrained parameter being tested. If no significant differences are found, then there is no need to stratify and the groups can be combined for the analysis. For step three, structural invariance was examined by constraining the following eight parameters in separate models: (3a) mean intercept, (3b) intercept variance, (3c) mean slope, (3d) slope variance, (3e) intercept predicting internalizing scores, (3f) slope predicting internalizing scores, (3g) intercept and slope predicting internalizing scores, and (3h) overall trajectory.

Pearson correlation coefficients were calculated to examine the bivariate associations between covariates and offspring internalizing scores at 22 years. Significant covariates correlated with internalizing scores with a $p<.10$ were entered into the model predicting internalizing symptoms with the trajectory parameters of intercept and slope. Covariates with a $p>.10$ were removed from the model. This was done in three separate models with the significant covariates from each phase (maternal prenatal covariates, maternal 16-year covariates, and offspring 22-year covariates). The final model was built by combining the significant covariates from the three phases into a single model predicting internalizing scores. Non-significant covariates with a $p>.10$ were removed to arrive at a final model predicting offspring internalizing scores with the first trimester depressive symptoms and the rate of change of the maternal depressive symptoms.

Lastly, we explored whether offspring child abuse and neglect as measured by the CTQ score mediated the association between first trimester maternal depressive symptoms and change in maternal depressive symptoms and offspring internalizing score. This was achieved by entering the CTQ score as a mediator in the LGCM final model containing all of the significant covariates of internalizing scores. The total indirect effect was calculated with its p-value indicative of the significance of the mediation effect of the CTQ score. The results are presented in accordance with Baron and Kenny's mediation criteria: (1) the independent variable is associated with the dependent variable, (2) the independent variable is associated with the proposed mediator, (3) the mediator is associated with the dependent variable, and (4) the effect of the independent variable on the dependent variable should be diminished when controlling for the mediator (Baron & Kenny, 1986). Steps 3 and 4 are tested within the same equation.

2.3.4 Results

2.3.4.1 Descriptive Statistics

Descriptive statistics for the mothers at the first trimester assessment can be found in Table 4 (Paper 1). The mean age of the mothers at the first assessment was 23 years (range: 18-42). Forty-eight percent of the women were white, 25% worked or attended school, and 32% were married. They had, on average, 11.8 years of education, a median monthly household income of $300-400 in 1982-1985 currency, experienced 2 life events (range: 0-9) during the year prior to delivery, and reported having 5 close friends (range: 0-10). Sixty-four percent reported alcohol use with an ADV of 0.9 among users, 41% reported marijuana use with an ADJ of 0.9 among users, 11% reported other illicit drug use, and 53% reported cigarette use with an average of 15.4 cigarettes daily among users.

Descriptive statistics for the offspring at birth are presented in Table 10 (Paper 2). At birth, 48% of the offspring were male, 10% were low birth weight (<2.5kg), 9% were preterm (<37 weeks gestation), and 11% were small for gestational age (birth weight $\leq 10^{th}$ percentile for gestational age). The average birth weight in the sample was 3.2 kg (range: 1.04-4.99), with a mean gestational age of 40 weeks (range: 28-44). Few offspring had major anomalies (1%) and only 8% had 2 or more minor physical anomalies.

Descriptive statistics for the mothers at the 16-year assessment can be found in Table 13. At the 16-year assessment, the mothers had a mean education of 12.2 years, a median monthly household income of $1,700 in 1998-2001 currency, reported three life events, and had four close friends for social support. Thirty-nine percent were married, 74% were employed or in school, and 44% were diagnosed as having any other lifetime psychiatric disorder excluding depression. Women who used substances reported an ADV of 1.1, an ADJ of 0.6, and 14.7

Table 13. Maternal characteristics at the 16-year assessment

Maternal at 16 years	Mean (range)
Education (years)	12.2 (7-18)
Household income (median $/month)	1,700 (0-18,000)
Marital status (% married)	38.6
Work/school status (% working/in school)	73.8
Life events (#)	2.9 (0-12)
Social support (# of close friends)	3.6 (0-9)
Alcohol use among users (avg. daily volume)	1.1 (<.1-13.1)
Marijuana use among users (avg. daily joints)	0.6 (<.1-6.1)
Cigarette use among users (avg. daily cigs)	14.7 (.5-60)
Any other illicit drug use (%)	4.9
Other psychiatric disorder* (%)	44.4
*Excluding Major Depressive Disorder and Dysthymia	

average daily cigarettes, respectively. Roughly 5% of the women reported any other illicit drug use.

Descriptive statistics for the offspring at 22 years are presented in Table 4 (Paper 1). At 22 years, 6% of the offspring were married, 37% had at least one child, 38% live with their mother, and 60% worked or attended school. On average, they were 22.8 years old, had 12.8 years of education and earned a median personal monthly income of $800 in 2004-2007 currency. Ninety-two percent reported alcohol use with an ADV of 2.1 among users, 50% reported any marijuana use with 1.6 ADJ among users, 44% reported cigarette use with 9.9 average daily cigarettes among users, and 17% reported other illicit drug use. At the 16-year assessment, the offspring had a mean CTQ score of 35 (range: 25-96).

Correlations between the maternal CES-D scores at each phase of the study and offspring internalizing scores are presented in Table 14. Maternal depressive symptoms at the three prenatal assessments and at the 10-, 14-, 16-, and 22-year assessments were correlated with offspring internalizing scores at 22 years, while maternal depressive symptoms from 8 months through 6 years were not. Maternal depressive symptoms at each assessment were correlated

Table 14. Correlations between maternal depressive symptoms at each assessment and offspring internalizing symptoms at 22 years

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
1. Offspring internalizing	1.00											
Maternal CES-D Scores												
2. First trimester	.11**	1.00										
3. Second trimester	.08*	.68**	1.00									
4. Delivery	.07*	.60**	.72**	1.00								
5. 8 months	.07	.55**	.57**	.58**	1.00							
6. 18 months	.06	.54**	.61**	.59**	.69**	1.00						
7. 3 years	.07	.47**	.50**	.46**	.59**	.62**	1.00					
8. 6 years	.02	.40**	.44**	.36**	.48**	.56**	.59**	1.00				
9. 10 years	.08*	.38**	.45**	.36**	.43**	.54**	.53**	.61**	1.00			
10. 14 years	.09**	.37**	.42**	.33**	.46**	.45**	.47**	.52**	.57**	1.00		
11. 16 years	.10**	.37**	.35**	.32**	.35**	.39**	.41**	.45**	.55**	.62**	1.00	
12. 22 years	.11**	.36**	.36**	.32**	.35**	.39**	.41**	.49**	.52**	.58**	.60**	1.00
* p<.10 **p<.05												

with depressive symptoms at all other assessments, with the highest correlations between proximal assessments. In general, the more distant the assessments, the weaker the correlations became.

2.3.4.2 Latent Growth Curve Model Results

Multi-group Structural Equation Modeling

Preliminary LGCM analysis revealed significant variation in first trimester maternal depressive symptoms and the rate of change in maternal depressive symptoms, so we performed an MSEM analysis to examine differences in trajectories by race. The results of the MSEM are presented in Table 15. After achieving good model fit within the African American and Caucasian women separately (1a. CFI=.978, RMSEA=.042; 1b. CFI=.940; RMSEA=.068, respectively), a baseline model without restraints was produced (2. CFI=.961; RMSEA=.056). A series of eight subsequent models were run, each constraining a different parameter, and then compared to the baseline model by performing a chi-square difference test (Table 16). Significant differences were found when constraining the variance of first trimester maternal depressive symptoms (4b) and constraining the overall trajectory (4h). While this suggests that there were significant differences in the intercept variance and overall trajectory between African Americans and Caucasians, no other significant differences emerged. Particularly worth noting is that there were no differences when constraining parameters in the prediction of offspring internalizing symptoms. Since the main goal of this analysis was to predict internalizing symptoms with the trajectories of depressive symptoms, we chose not to stratify by race and all results that follow are for the total sample.

Table 15. Multi-group structural equation models by race

Step	Model	χ^2	df	CFI	RMSEA
1a	Blacks	80.97	50	.978	.042
1b	Whites	113.41	50	.940	.068
2	Baseline	194.38	100	.961	.056
3a	Structural Invariance (constrain mean intercept)	194.64	101	.961	.055
3b	Structural Invariance (constrain intercept variance)	204.36	101	.957	.058
3c	Structural Invariance (constrain mean slope)	194.26	101	.962	.055
3d	Structural Invariance (constrain slope variance)	194.02	101	.962	.055
3e	Structural invariance (constrain intercept predicting ASR)	195.02	101	.961	.055
3f	Structural invariance (constrain slope predicting ASR)	194.83	101	.961	.055
3g	Structural invariance (constrain intercept and slope predicting ASR)	195.83	102	.961	.055
3h	Structural invariance (constrain trajectory)	169.91	97	.970	.050

Table 16. Chi-square difference tests for multi-group structural equation models by race

Model	$\Delta\chi^2$	Δdf	p
2 vs 3a	.077	1	.781
2 vs 3b	11.945	1	<.001
2 vs 3c	.352	1	.553
2 vs 3d	.016	1	.899
2 vs 3e	.506	1	.477
2 vs 4f	.295	1	.587
2 vs 3g	1.191	2	.551
2 vs 3h	39.778	5	<.001

First Trimester Depressive Symptoms and Rate of Change in Maternal Depressive Symptoms Predicting Internalizing Scores

Figure 2 shows the trajectory of maternal depressive symptoms across time during the study. In the unadjusted LGCM, the mean first trimester CES-D score was 21.1 ($p<.001$) with a significant variance of 46.5 ($p<.001$). Additionally, higher CES-D scores were significantly associated with higher offspring internalizing scores ($b=.211$, $p=.005$). The mean change in maternal depressive symptoms was -0.894 ($p=.004$) with a variance of 3.5 ($p=.067$). On average, maternal CES-D scores decreased by -0.894 points during the study (from the first assessment through 16 years) and there was only borderline variation in the change in depressive symptoms over time. The change in depressive symptoms was not significantly associated with offspring internalizing scores ($b=.233$, $p=.506$). The mean first trimester CES-D score and change in depressive symptoms significantly covaried with one another (covariance=-4.581), with higher baseline depressive symptoms associated with a greater decrease in symptoms over the study.

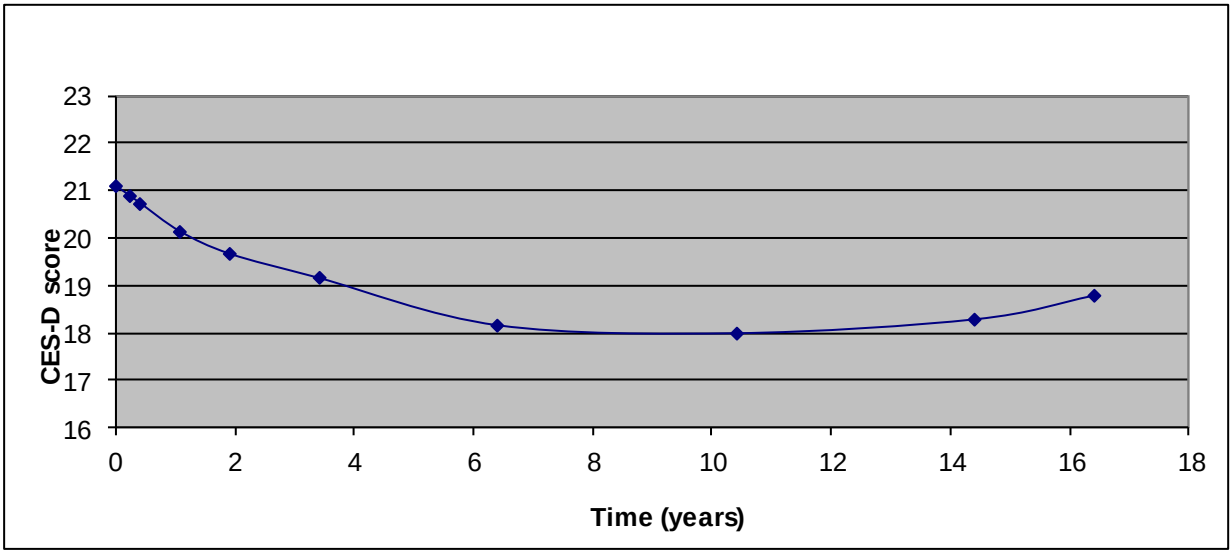

Figure 2. Trajectory of maternal depressive symptoms from the first trimester through 16 years

Tables 17, 18, and 19 show the correlations between the prenatal covariates, maternal 16-year covariates, and offspring 22-year covariates and the offspring internalizing scores at 22 years, respectively. Prenatal covariates that were correlated with offspring internalizing scores included maternal race, education, work status, life events, alcohol, cigarettes, and other drug use. Maternal 16-year covariates that were associated with internalizing scores included education, work status, alcohol and marijuana use, and any other psychiatric diagnoses. Significant offspring covariates at 22 years associated with internalizing scores included sex, age, education, work status, income, alcohol, cigarette, and any other illicit drug use. After combining the significant covariates from each phase and eliminating the non-significant ones ($p>.10$), the final adjusted LGCM model controlled for prenatal alcohol use, maternal education and marijuana use at 16 years, offspring sex, personal income at 22 years, and cigarette and other illicit drug use at 22 years.

Table 20 presents the results of the fully adjusted LGCM model predicting offspring internalizing symptoms at 22 years and Table 21 shows correlations between the covariates in the model. Controlling for significant covariates, first trimester depressive symptoms were marginally predictive of offspring internalizing scores ($\beta=.078$, $p=.070$), however the change in maternal depressive symptoms was not ($\beta=-.026$, $p=.621$). The model had a decent fit with a CFI=.961 and RMSEA=.040. Also, prenatal alcohol exposure, maternal marijuana use at 16 years, and offspring cigarette and other illicit drug use were associated with higher internalizing scores, while higher maternal education at 16 years, being male, and higher offspring personal income at 22 years were associated with lower internalizing scores. Figure 3 provides a visual representation of these results controlling for significant covariates.

Table 17. Correlations between prenatal covariates and offspring internalizing scores at 22 years

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
1. Internalizing core	1.00												
2. Race	.09**	1.00											
3. Age	-.02	.03	1.00										
4. Education	-.10**	-.11**	.19**	1.00									
5. Work status	-.07*	-.09**	.02	.20**	1.00								
6. Income	-.05	.22**	.21**	.17**	.14**	1.00							
7. Marital status	.02	.36**	.11**	.07*	-.09**	.36**	1.00						
8. Life events	.07*	.06	-.09**	.06	.04	-.09**	-.02	1.00					
9. Social support	-.04	.04	.02	.05	.01	.10**	.09**	.02	1.00				
10. Alcohol	.13**	.01	.04	.01	-.02	-.03	-.10**	.09**	-.02	1.00			
11. Marijuana	.04	-.18**	-.01	-.06	-.10**	-.08**	-.12**	.01	-.07	.09**	1.00		
12. Cigarettes	.10**	.33**	.06	.22**	-.09**	.06	.09**	.01	.01	.16**	.04	1.00	
13. Other illicit drugs	-.01	.14**	.02	-.07*	-.01	.01	.05	.01	-.02	.10**	.11**	.15**	1.00

* p<.10
**p<.05

Table 18. Correlations between maternal covariates at 16 years of offspring internalizing scores at 22 years

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
1. Internalizing score	1.00											
2. Education	-.17**	1.00										
3. Work status	-.08*	.24**	1.00									
4. Income	-.01	.28**	.29**	1.00								
5. Marital status	.04	.09*	.04	.42**	1.00							
6. Life events	.04	.05	-.04	-.13**	-16**	1.00						
7. Social support	-.01	.04	.14**	.08*	.07	.07	1.00					
8. Alcohol	.10**	-.03	-.02	-.08*	-.09	-.09**	.01	1.00				
9. Marijuana	.09*	.01	-.09**	-.10**	-.08*	-.08*	-.01	.11**	1.00			
10. Cigarettes	.01	-.11**	-.07	-.04	.04	.07	-.07	.11**	.07*	1.00		
11. Other illicit drugs	-.03	-.01	-.04	-.06	-.03	-.03	-.01	.11**	.19**	.08*	1.00	
12. Other psychiatric diagnosis	.12**	-.01	-.09**	.01	-.05	.27**	-.03	.10**	.12**	.15**	.10**	1.00

* p<.10
**p<.05

Table 19. Correlations between offspring covariates at 22 years and offspring internalizing scores at 22 years

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
1. Internalizing score	1.00												
2. Sex	-.08*	1.00											
3. Age	-.09**	.11**	1.00										
4. Education	-.09**	-.06	.01	1.00									
5. Work status	-.07*	.05	-.05	.21**	1.00								
6. Income	-.11**	.15**	.15**	.18**	.60**	1.00							
7. Marital status	-.03	.01	.10**	.02	.06	.15**	1.00						
8. Has children	-.03	-.17**	.01	-.30**	-.20**	-.12**	.07*	1.00					
9. Lives with mom	-.01	.06	-.05	.02	-.06	-.15**	-.12	.-.15**	1.00				
10. Alcohol	.10**	.17**	.05	-.05	-.07*	.01	.07*	.02	-.03	1.00			
11. Marijuana	.05	.14**	-.06	-.11**	-.10**	-.06	-.04	.05	-.02	.21**	1.00		
12. Cigarettes	.16**	.08*	.01	-.31**	-.13**	-.07	-.02	.03	.02	.30**	.21**	1.00	
13. Other illicit drugs	.17**	.19**	.01	-.11**	-.05	-.01	.03	.01	-.02	.33**	.19**	.27**	1.00
14. CTQ score	.28**	-.01	-.04	-.16**	-.11**	.01	.01	.08*	-.05	.01	-.02	.15**	.01

* p<.10
**p<.05

Table 20. Predicting offspring internalizing scores at 22 years with first trimester depressive symptoms and rate of change in symptoms while controlling for significant covariates

	b	β	p-value
Maternal depressive symptoms			
First trimester symptoms	.126	.078	.070
Rate of change in symptoms	-.149	-.026	.621
Prenatal alcohol use	1.051	.122	.000
Maternal education at 16 years	-.693	-.131	.002
Maternal marijuana use at 16 years	2.047	.088	.005
Offspring sex	-1.875	-.082	.043
Offspring personal income at 22 years	-1.031	-.078	.035
Offspring cigarette use at 22 years	.187	.114	.004
Offspring other illicit drug use at 22 years	4.463	.135	.001
β =standardized coefficient χ^2 (106, 607) = 209.868 CFI=.961 RMSEA=.040			

Table 21. Correlations between covariates in final model predicting offspring internalizing scores at 22 years

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
1. Offspring internalizing score	1.00							
2. Prenatal alcohol use	.13**	1.00						
3. Maternal education at 16 years	-.17**	.02	1.00					
4. Maternal marijuana use at 16 years	.09*	-.03	<.-01	1.00				
5. Offspring sex	-.08*	-.02	.11**	<.01	1.00			
6. Offspring personal income at 22 years	-.11**	-.02	.10**	.02	.15**	1.00		
7. Offspring cigarette use at 22 years	.16**	.02	-.10**	<.01	.08*	-.07*	1.00	
8. Offspring other illicit drug use at 22 years	.17**	.07*	-.07	.03	.19	<-.01	.27**	1.00
* p<.10 **p<.05								

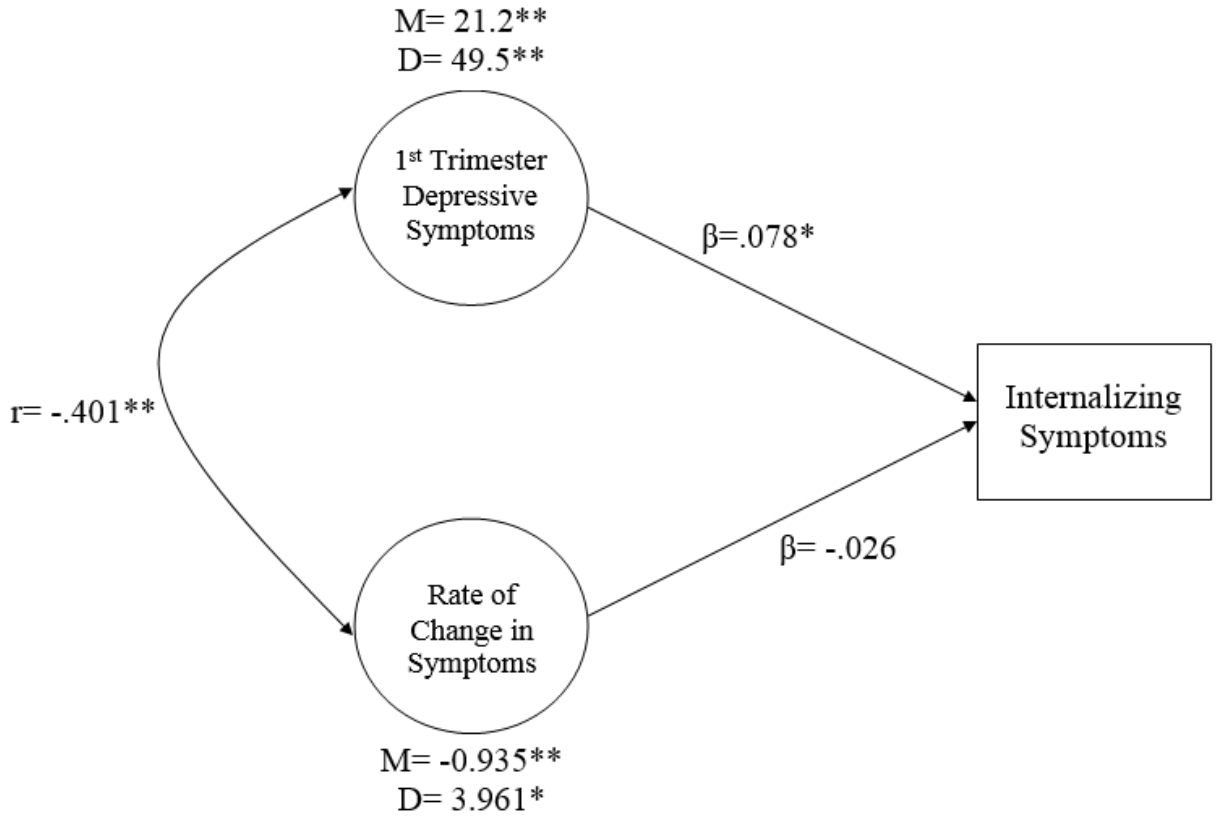

Figure 3. First trimester depressive symptoms and rate of change in symptoms predicting internalizing scores at 22-years controlling for significant covariates (*p<.10, **p<.05, β=standardized coefficient, r=correlation, M=mean, D=variance)

Child Maltreatment Mediation Analysis

While first trimester depressive symptoms were only marginally associated with internalizing symptoms, we examined whether child maltreatment mediated this relationship. Correlations between the CTQ score and offspring internalizing scores and other covariates at 22 years can be found in Table 17. The CTQ score was significantly correlated with offspring internalizing scores (r=.28, p<.001), with higher CTQ scores predicting higher internalizing scores. Results of the mediation analysis are presented in Table 22. First trimester depressive symptoms significantly predicted CTQ scores (b=.254, p<.001), and the effect of first trimester symptoms on internalizing scores was greatly diminished when controlling for the CTQ scores (b=.060,

Table 22. Childhood maltreatment mediation analysis

Baron & Kenny Mediation Steps	Outcome	Predictor	b	β	*p*	Test of Indirect Effect
3. IV predicts DV	Internalizing symptoms	Maternal depressive symptoms First trimester symptoms Rate of change in symptoms	 .129 -.149	 .078 -.026	 .064 .621	
4. IV predicts mediator	CTQ score	Maternal depressive symptoms First trimester symptoms Rate of change in symptoms	 .254 .348	 .172 .066	 <.001 .342	b=.069 *p*=.001 Proportion of effect mediated=53.5%
3&4. IV, mediator predict DV	Internalizing symptoms	Maternal depressive symptoms First trimester symptoms Rate of change in symptoms	 .060 -.224	 .037 -.039	 .371 .457	
		CTQ score	.270	.247	<.001	

*Controlling for prenatal alcohol use, maternal education at 16 years, maternal marijuana use at 16 years, offspring sex, offspring personal income at 22 years, offspring cigarette and other illicit drug use at 22 years
b=unstandardized coefficient
β=standardized coefficient
Model χ^2=222.430, df=117, p=.000
CFI=.961
RMSEA=.039

p=.371). The CTQ scores also significantly predicted internalizing scores (b=.270, p<.001), resulting in a significant test of the indirect effect (p=.001). Figure 4 provides a visual representation of these results.

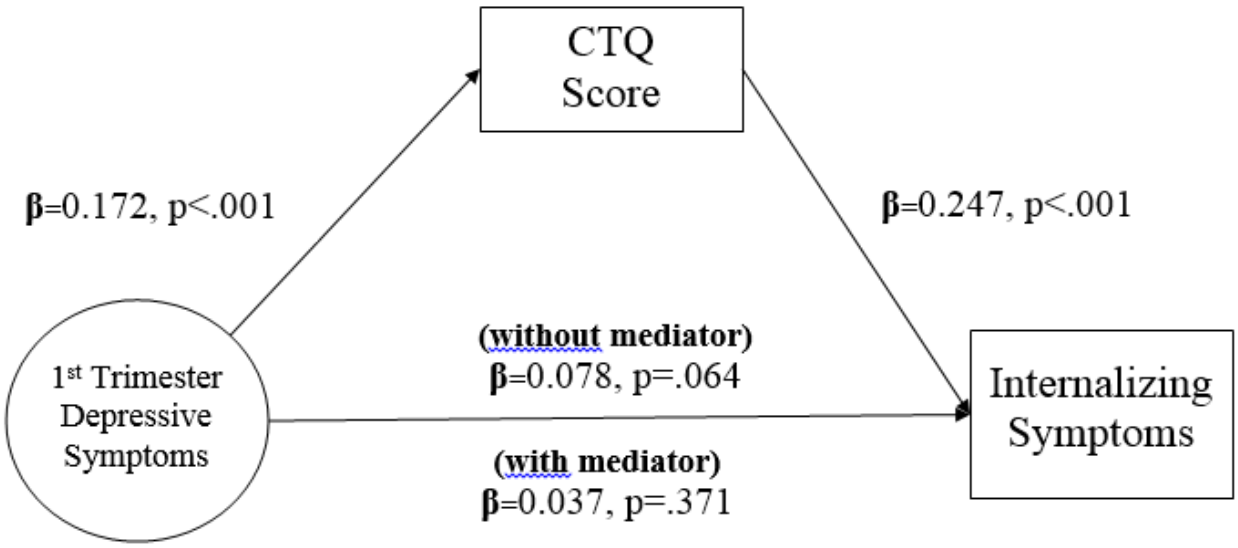

Figure 4. Childhood maltreatment mediation model controlling for significant covariates (β=standardized coefficient)

2.3.5 Discussion

Using a novel approach, we demonstrated that first trimester maternal depressive symptoms had a marginal effect on offspring internalizing scores at 22-years, with higher CES-D scores at the first trimester assessment predicting higher offspring internalizing scores. In our sample, the rate of change in maternal depressive symptoms over time did not significantly affect offspring internalizing scores. Previous literature suggests that improvements in maternal depression result in improvements in offspring psychopathology (Coiro, Riley, Broitman, & Miranda, 2012; Pilowsky et al., 2008). However, these were treatment studies that employed different statistical techniques in their analyses. It should be noted that these studies examined the effects of remission of major depression among mothers with a diagnosis, while our study examined

continuous depressive symptoms. In general, maternal depressive symptoms in our sample were relatively stable, only decreasing an average of roughly 2 points during the 16 years. Although not statistically significant, the nature of the association was in the direction we had anticipated with decreasing depressive symptoms associated with lower internalizing scores. The magnitude of the change in depressive symptoms may not have been large enough to significantly affect internalizing scores. Furthermore, there may not have been enough variation in the rate of change in maternal depressive symptoms over time (σ^2=3.5, p=.067) for it to explain any of the variance in internalizing scores.

Depressive symptoms were common in this sample, with an average first trimester CES-D score of 21.1. Throughout the study, the average CES-D score never dropped below the typical cut-point of 16 used to indicate elevated depressive symptoms. However, our higher rates of depression are consistent with estimates from other studies of urban low-income women (Chung, McCollum, Elo, Lee, & Culhane, 2004; Kurtz Landy, Sword, & Ciliska, 2008; Orr & James, 1984) and for African American women (Orr, Blazer, & James, 2006; Stewart, Dean, Gregorich, Brawarsky, & Haas, 2007). Furthermore, a number of studies have advocated using higher cut-points for the CES-D, ranging from 23-25 points (Husaini, Neff, Harrington, Hughes, & Stone, 1980; Seto et al., 2005; Weissman, Sholomskas, Pottenger, Prusoff, & Locke, 1977)

The mediation analysis revealed that offspring reports of child maltreatment significantly mediated the marginal association between first trimester depressive symptoms and offspring internalizing scores. A previous study by Pawlby and colleagues (2011) within the South London Child Development Study did not find evidence of a mediation effect, but instead reported a significant interaction between childhood maltreatment and exposure to prenatal depression in the prediction of offspring psychopathology. Although prenatal depression

increased the risk for both childhood maltreatment and offspring psychopathology, only those offspring who were exposed to both prenatal depression and childhood maltreatment had an increased risk of psychopathology in their study. Offspring who were exposed to only one of the individual risk factors were not at greater risk of developing psychopathology. Considering this, we tested for an interaction between first trimester maternal depressive symptoms and offspring CTQ score, but the interaction term was not significant (p=.364).

There was not sufficient evidence of distinct trajectories of maternal depressive symptoms by race. While most studies have not had the racial diversity to explore differential effects by race, the study by Mora and colleagues found that women in the chronic depressed group were more likely to be African American compared to women in the never depressed group (2009). However, Mora and colleagues used growth mixture modeling to identify classes of latent trajectories of depressive symptoms to which women were assigned based on their highest estimated posterior probabilities. Conversely, we chose to perform LGCM to estimate baseline symptoms and change in symptoms because we were more interested in using these parameters to estimate offspring internalizing symptoms than we were in describing the trajectories of maternal symptoms. Additionally, only one-quarter of the women in the Mora study fell into a class of high depressive symptoms, defined as a CES-D<16, at any of the assessments. This is in contrast to our study, where 95% of the women had elevated depressive symptoms at least one time using the same cut-point. Similar to the women in our study, their sample was young, low-income, inner-city, and multi-ethnic, but had fewer Caucasians and included Hispanics.

This study has a number of strengths. To our knowledge, it is the first study to utilize trajectories of maternal depressive symptoms to predict an offspring outcome in adulthood.

While a number of studies have associated prenatal and postpartum depression with offspring mental health, few of these studies took into account the effects of subsequent exposure to depression and none specifically examined the impact that change in depressive symptoms had. Moreover, these trajectories began in the prenatal period and extended through 16-years postpartum. Among previous studies of maternal depression trajectories, the longest follow-up was 13 years. Rates of follow-up within our study were high and never dropped below 70% for any of the assessments. Racial differences could be examined because we had equal numbers of African Americans and Caucasians, and we were able to take a number of covariates from various phases of the offspring's life into account. Also, maternal depression, childhood maltreatment, and offspring internalizing symptoms were all assessed using reliable and valid instruments.

Several limitations should also be reviewed. First, our sample is homogeneous with regards to their education and income and these results may not be generalizable to women of a higher socio-economic status. Second, the assessments were conducted infrequently and the course of maternal depressive symptoms between interviews may not have been consistent. Third, there was not much variation in the course of depressive symptoms over time, thus limiting our ability to examine the effect that change in symptoms may have had on offspring health. Lastly, while we had maternal lifetime diagnoses of depression at the 16-year assessment, maternal diagnoses were not assessed at any of the previous phases. Consequently, we cannot make inferences regarding the effects of remission of diagnosed depression during the study.

In summary, we found a marginal effect of first trimester maternal depressive symptoms on offspring internalizing scores, but this was mediated by childhood maltreatment. Women

reported experiencing the highest level of depressive symptoms during pregnancy, and these symptoms tended to decrease over time. Regardless, decreases in depressive symptoms were not associated with improvements in internalizing symptoms among offspring. This study suggests that pregnancy represents an important time to screen for women with elevated depressive symptoms whose offspring are at elevated risk for childhood maltreatment and higher internalizing symptoms.

3.0 SUMMARY DISCUSSION

3.1.1 Summary of Findings

This dissertation used data from the Maternal Health Practices and Child Development birth cohort study to improve our understanding of the relationship between prenatal depressive symptoms and internalizing symptoms. Prenatal depressive symptoms were common and persistent in our sample. Nearly 70% of the women would be categorized as "Depressed" using the traditional cut-point of 16 on the CES-D for the first trimester. Other studies among comparable samples of low-income women have reported similarly high levels of depressive symptoms (Chung et al., 2004; Kurtz Landy et al., 2008; Orr & James, 1984). As expected, prenatal depressive symptoms were associated with higher internalizing symptoms at 22 years. This effect remained while controlling for current covariates of internalizing symptoms and, to our knowledge, this is the first study to extend these effects into adulthood.

Birth weight was explored as a potential mediator of this relationship. Despite prior research suggesting otherwise, prenatal depressive symptoms were not associated with birth weights in our sample. Consequently, birth weight failed to meet the criteria for mediation. Although our sample was recruited based on substance use, fetal growth characteristics were comparable to those of the general population. Additionally, we did not find evidence to support

moderation by sex or race, although the power to detect an effect was diminished when splitting our sample by these characteristics.

Latent growth curve modeling trajectory analysis revealed that the women in our sample had high levels of depressive symptoms at the first trimester assessment. These symptoms were relatively stable over time and only decreased slightly through the time when their offspring were 16 years old. Multi-group structural equation modeling did not uncover sufficient evidence to support analyzing the trajectories separately by race. Higher baseline depressive symptoms in the first trimester were associated with higher internalizing symptoms at 22 years, but the rate of change in maternal depressive symptoms during the course of the study was not. After controlling for significant covariates, the effect of prenatal depressive symptoms was marginally predictive of internalizing symptoms. This marginal effect was found to be mediated by childhood maltreatment. Baseline maternal depressive symptoms predicted higher childhood maltreatment scores in offspring, which subsequently predicted higher internalizing symptoms.

Given the racial diversity of our sample and previous research suggesting that rates of depression may differ by race, we stratified the analyses by race to explore possible moderation. However, race failed to emerge as a moderator in all of our analyses. One explanation for our lack of moderation by race is that race may be a more general marker of socioeconomic status (SES). African Americans generally have less education (Newburger & Curray, 2000) and are more likely to experience poverty (McKinnon, 2003) compared to Caucasians. These SES differences and experiences that accompany them (i.e., exposure to stressful life events) may actually be driving the observed racial differences in prior studies. The women in our study were recruited at a prenatal clinic characterized by a low SES population and, consequently, were relatively homogenous with regard to education and income.

3.1.2 Strengths and Limitations

Several issues should be considered when interpreting the findings of these results. First, this was a relatively homogeneous cohort with regard to education and income. Hence, our results may not be applicable to women of a higher socioeconomic status. Nevertheless, our findings are still valuable as they apply to a population of women that is generally underrepresented in research studies. While the sample was recruited based on prenatal substance use, we also included a random sample of women who abstained from alcohol and marijuana use in the first trimester. Additionally, we considered and controlled for the effects of prenatal substance use in all of our analyses. Although lifetime estimates of MDD diagnosis were available for the mothers at 16 years, we considered continuous CES-D scores of depressive symptoms as our exposure since these were available for each assessment. Consequently, these results may not be generalizable to women with a clinical diagnosis of depression.

Depressive symptoms were common in our sample and relatively stable over time. This lack of variation subsequently limited our ability to examine change in symptoms over time as risk factor. While prenatal anxiety has also been shown to have effects on offspring psychopathology, we did not include it in our analysis. Maternal depression and anxiety were highly correlated at all phases of the study (r=.70) and it was difficult to tease out the effects of one from the other. Finally, information on paternal psychopathology was unavailable, so we could not examine the effect or role of this potentially important exposure.

These limitations are offset by the strengths of the study. This was a longitudinal study with exposure data available from the first trimester of pregnancy to an outcome 22 years later. Therefore, we took advantage of novel latent growth curve modeling techniques to explore the effect that trajectories of maternal depressive symptoms had over the offspring's life course. To

our knowledge, this is first study to utilize trajectory analysis to examine the effect of a prenatal exposure on an outcome in adulthood. The prospective nature of the study minimizes memory and recall bias and also helps to establish temporality.

The sample is large and was not recruited based on mental health or from a psychiatric facility. Furthermore, antidepressant use was rare at the start of the study, with only five women endorsing use during pregnancy. Nevertheless, we reran all analyses excluding these women. Since their inclusion did not significantly change our results, we kept them in the analysis. Because there were equal numbers of African Americans and Caucasians, we were able to test for differential effects by race. This study has excellent follow-up rates and remains representative of the original cohort at 22 years. Additionally, subject loss was independent of baseline maternal depressive symptoms. The quality of the data in this study was high, as a number of highly validated and reliable instruments were used to assess exposures, outcomes, and covariates. Specifically, reliable and extensive data were available for maternal substance use during the course of the study.

3.1.3 Public Health Implications

These results have several important public health implications. While effective treatments exist for prenatal depression, choosing a treatment regimen during pregnancy is complicated by calculating the risks and benefits of each alternative to both the mother and the fetus. A critical question currently facing researchers and clinicians is whether the negative effects of antidepressant use during pregnancy on the fetus outweigh the negative effects of untreated prenatal depression. To help women make informed choices about their treatment options, more longitudinal studies like our own are needed to elucidate the long term effects of prenatal

depression on offspring. Although our study found that prenatal depressive symptoms were associated with offspring internalizing symptoms at 22 years, the size of this effect was small and it was largely mediated by childhood maltreatment. However, this finding has important public health implications of its own that are worth discussing.

Childhood maltreatment has been shown to have damaging effects on psychopathology and behavior. Our study suggests that identifying women with elevated depressive symptoms during pregnancy identifies a subgroup of children at increased risk of experiencing child abuse and neglect. Pregnancy is a unique time during which most women tend to have frequent contact with the health care system. This affords clinicians a valuable opportunity to screen and identify women whose offspring may benefit from targeted interventions to decrease exposure to childhood maltreatment.

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