BIOLOGICAL AND PSYCHOSOCIAL INFLUENCES ON THE ASSOCIATIONS BETWEEN PRENATAL MATERNAL STRESS AND CHILDREN'S MENTAL HEALTH OUTCOMES

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ABSTRACT

Mental disorders are highly prevalent and represent an increasingly important public health priority in Canada and globally. Extensive research suggests that exposure to prenatal maternal stress can negatively impact offspring neurodevelopment and mental health. However, the factors that influence the development of mental disorders are varied, and do not occur in isolation. As a result, ascertaining which variables may drive or influence the associations between prenatal stress and mental disorders in children is particularly important, given the substantial burden that is attributed to poor mental health. The overarching aim of this doctoral thesis is to examine how biological and psychosocial factors influence the relationships between prenatal maternal stress and children's mental health outcomes. Four longitudinal studies were conducted to address this aim, using data from three international prospective birth cohort studies. Analyses comprised of structural equation modelling techniques, including latent moderated structural equation models and mediation analyses.

The first two studies utilized data from a Norwegian birth cohort study to examine how parenting and maternal positive mental health, respectively, modified the associations between prenatal maternal stress and children's internalizing and externalizing symptoms. Broadly, these results demonstrated that positive influences attenuated the associations between prenatal maternal stress and children's internalizing and externalizing symptoms, whereas negative influences strengthened the associations. The final two studies utilized data from Dutch and British birth cohorts. These studies sought to examine whether maternal and child inflammatory marker concentrations mediated the associations between prenatal maternal stress and children's mental health outcomes. There was no significant mediation through maternal levels of C-reactive

protein during pregnancy, however, the association between prenatal maternal stress and generalized anxiety disorder in adolescence was mediated by children's levels of interleukin-6. Prenatal maternal stress was consistently associated with children's mental health across all four studies.

This doctoral thesis has identified several important factors that influence the associations between prenatal maternal stress and children's mental health. Findings can serve to facilitate further research in this area, and ultimately, impact both health policy and clinical practice by stimulating the provision of tailored prevention and intervention efforts that may potentially reduce the burden of poor mental health.

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DEDICATION

This thesis is dedicated to my grandmother (*ayeeyo*), Marian Gure, who is the glue that holds my family together. You are the portrait of resilience – a trait that has guided me through this PhD, even when I thought I could not bear to continue. Thank you for teaching your daughters and your granddaughters about what it means to be strong.

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Chapter 1

INTRODUCTION

Mental health disorders are highly prevalent and represent an increasingly important public health issue in Canada and globally (1). Depression is particularly pervasive; conservative prevalence estimates suggest approximately 12.6% of Canadians will meet criteria for major depression at some point in their lives (2). Generalized anxiety disorder is also common, with an estimated lifetime prevalence of 8.7% (2). Although the lifetime risk of experiencing a psychotic disorder (e.g., schizophrenia) is comparatively lower, at an estimated 1 to 2% (3), psychotic disorders also represent a major cause of disability (4,5). Finally, externalizing disorders, including attention-deficit hyperactivity disorder and conduct disorder, have estimated prevalences of 3.4%, and 2.1%, respectively (6). In Canada alone, mental health disorders cost the economy at least $51 billion per year (7); this includes cost of health care services, lost productivity, and reduced quality of life.

Importantly, mental health disorders are often chronic and manifest early in life. In the case of depressive disorders, almost half of adults who report a lifetime history of depression cite initial onset in childhood or adolescence (8). Experiencing the onset of a mental health disorder early in life is particularly detrimental, and has the potential to disrupt the important developmental processes that take place in this period. In the long-term, experiencing poor mental health can potentially impact one's socioeconomic standing, relationships, and physical health, with earlier onset often leading to poorer prognosis (9–11). For example, experiencing depression in adolescence has been associated with increased risk of depression recurrence in adulthood, lower

odds of completing secondary school, and increased odds of unemployment and earlier pregnancy and parenthood (9,12). The consequences of poor mental health are staggering at both the individual- and societal-levels, underscoring the need to prioritize both the prevention and treatment of mental health disorders worldwide.

The etiology of poor mental health is unclear, highly complex, and varies considerably across mental health disorders. The factors that can influence one's mental health are biological, social, and behavioural in nature, and many can operate together to positively or negatively influence long-term risk. For example, risk factors associated with chronic depression include younger age at onset, family history, substance abuse, and negative social interactions (13), and risk factors towards externalizing behaviours include parental depression and negative parenting behaviours (14). Of particular interest in the recent literature is the impact that stress experienced in-utero can impart on offspring development. Exposure to environmental stressors can lead to permanent physiological and structural alterations in the fetus, which in turn, may predispose offspring towards experiencing a number of negative physical and mental health outcomes later in life (15,16). Common environmental stressors described in the literature include maternal psychopathology (17,18), stressful events experienced by the mother (19,20), prenatal infection (21,22), malnutrition (23), and substance use during pregnancy (24). Broadly, this notion that exposure to environmental stressors in utero can "program" offspring in such a manner that increases their susceptibility towards experiencing specific health outcomes later in development is framed as the fetal programming hypothesis, or the developmental origins of health and disease (DOHaD) hypothesis (25). Several studies have demonstrated the importance of prenatal

environmental influences on later risk of depression (17,26), schizophrenia (21), externalizing disorders (27), and other mental health disorders (28).

With mounting evidence supporting the relationships between prenatal maternal stress and offspring mental health outcomes, there has been a shift within the recent literature towards understanding factors that may explain or impact these relationships. For example, it has been hypothesized that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the immune system in mothers and offspring may partially mediate the associations (29–32); however, most studies evaluating biological mechanisms between prenatal maternal stress and offspring mental health have been carried out in animals (33,34). Investigations into long-term offspring immunity and inflammation are particularly scarce, and are often limited by small sample size or study design (29,35,36). Furthermore, there is growing interest in ascertaining the additional impacts of postnatal environmental influences, given that offspring risk towards later adverse health outcomes continues to be dynamically influenced by exposure to factors after birth (37), and also, that many of the factors that influence mental health do not occur in isolation (24). Examples of postnatal influences that offspring may encounter include parental stress and psychopathology, parental wellbeing, maltreatment, neglect, harsh parenting, parental warmth, and community-level social processes including cohesion, deprivation, and exposure to violence. In all, when paired with our understanding of the detrimental impacts that poor mental health can impart on the individual and on society, there is a growing need for studies examining how these factors can influence the relationships between prenatal maternal stress and offspring mental health outcomes.

1.1 Prenatal maternal stress: the need for comprehensive measurement

Pregnancy can present as a challenging time for many women, with a multitude of potential stressors ranging from work and family obligations to their financial situation or mental state. Ascertaining the impacts of prenatal maternal stress can be particularly challenging for researchers, given that stress itself is a multidimensional concept (38), which typically refers to one or a series of event(s), classified as the stressor(s); the stress response (e.g., distress, or potential symptoms of anxiety or depression following exposure to a stressor); and the interaction between stressor and response (39). A variety of measures are commonly used to describe prenatal maternal stress within the literature, including stressful or traumatic events (e.g., illness, death in one's family, natural disasters); depressive symptoms; generalized or pregnancy-specific symptoms of anxiety; and other sources of chronic stress, including discrimination, work-related stress, and abuse (38). These measures have demonstrated significant associations with a number of poor maternal-child health outcomes including preterm birth, low birth weight, and postpartum depression (38,40–44). Prenatal maternal stress has also been measured beyond the individual level, and studies have characterized the impacts of common neighbourhood stressors including poverty, high noise levels, and high rates of violent crime, on negative outcomes including postpartum depression, preterm birth, and low birth weight (45–49). Several studies also use birth outcomes as proxies to represent offspring exposure to environmental stressors in utero, including preterm birth and low birth weight (50–54), as these outcomes have been associated with prenatal maternal stress (55). In particular, it has been hypothesized that these birth outcomes may be explained by dysregulation of the HPA axis following stress exposure. For example, increased maternal cortisol can lead to increased

production of placental corticotrophin-releasing hormone (56), which in turn has been associated with reduced fetal growth and size at birth (57).

It has been suggested that these varying conceptualizations of prenatal maternal stress may be problematic, because these measures may operate on child outcomes through different mechanisms (38). For example, pregnancy-related anxiety may be more predictive of negative child outcomes than global measures of anxiety (58,59). Prenatal depression may act on the maternal serotoninergic system and HPA axis in a different manner when compared to other stress measures (39), and is often categorized separately from other measures of prenatal maternal stress. However, given that experiencing depression in itself may be stressful, many studies utilize measures of prenatal depression to represent experiencing prenatal stress. Chronic and prolonged exposures to stress may also elicit different physiological and emotional responses when compared to acute stressors, which can have differential impacts on the fetus (39). As a result, some researchers suggest incorporating several measures of prenatal maternal stress, and/or utilizing comprehensive representations of prenatal maternal stress in studies to bring consistency and generalizability into the current evidence base (60,61). Recent reviews have further suggested that studies empirically test for whether composite or general measures of stress are appropriate in analyses (38,62). To date, longitudinal studies examining relationships between comprehensive prenatal maternal stress measures and offspring inflammation and mental health have been lacking. However, in recent studies examining epigenome-wide associations between prenatal maternal stress and neonatal differential DNA methylation in two prospective birth cohorts, a cumulative measure of prenatal maternal stress was constructed using confirmatory factor analysis – this measure demonstrated good model fit (60,63). This

global measure of prenatal maternal stress encompassed a number of domains that have been examined in the prenatal maternal stress literature and that share substantial conceptual overlap, including life stress (i.e., stressful events), contextual stress (e.g., financial and housing problems), personal stress (e.g., depression and substance use), and interpersonal stress (e.g., relationship difficulties). As a result, these recent studies demonstrate the feasibility of creating and employing comprehensive measures of prenatal maternal stress exposure in DOHaD research.

1.2 The "programming" of mental health disorders

Within the past several years, a growing body of research has examined associations between prenatal maternal stress and mental health outcomes in offspring. Several studies demonstrate consistent associations between prenatal depression and risk of offspring depression in later development (17,64,65). Findings have been similar for studies using prenatal anxiety, stressful life events, and neighbourhood-level stressors as exposure variables (19,20,33,66). There is also emerging evidence of associations between prenatal maternal stress and other mental health disorders in offspring. Prenatal depression, prenatal anxiety, and stressful life events during pregnancy have all been associated with risk of generalized anxiety disorder and other anxiety disorders in offspring (67,68). Acute and chronic stress in pregnancy has been associated with offspring risk of schizophrenia (21,69). Antenatal anxiety has been linked to externalizing problems in offspring (19,20,33,66). Low birth weight has been associated with increased risks of schizophrenia and depression in offspring, and is often used as a proxy for fetal exposure to stress in utero, given associations between prenatal maternal stress and birth weight, as well as associations between low birth weight and offspring neurodevelopmental outcomes (52,70). As

evidence supporting the prenatal programming of mental health disorders continues to grow, there is a need for studies describing potential variables that may explain or impact these relationships, including further analysis into the additional impacts of postnatal stress exposures, as well as added examination into the biological mechanisms that support the maternal-fetal embedding of vulnerability towards poor mental health.

1.3 Postnatal influences

Although associations between the prenatal environment and offspring psychopathology are well-established, offspring continue to be exposed to a number of environmental influences after birth and throughout the lifespan. Most research to date has focused on broader associations between prenatal maternal stress and offspring neurodevelopmental and mental health outcomes. However, emerging evidence suggests that the relationships between prenatal maternal stress and offspring outcomes may be conditional on the postnatal environment, whereby prenatal maternal stress promotes postnatal "developmental plasticity" (71,72). This hypothesis, known as the differential susceptibility hypothesis (37,72), suggests that exposure to prenatal maternal stress may increase offspring sensitivity to both positive and negative influences in the postnatal environment, thus either reducing or amplifying offspring risk towards adverse outcomes later in development. By comparison, the common diathesis-stress (or dual-risk) model suggests that offspring with biological, behavioural, or genetic susceptibilities who are exposed to environmental stressors are more likely to experience poor outcomes (e.g., mental disorders)(73,74). The notion that vulnerable individuals are disproportionately more likely to be adversely impacted by negative environmental influences is central to both models (74);

however, the differential susceptibility model further suggests that vulnerable individuals are also susceptible to positive influences and can experience positive outcomes (see Figure 1.1).

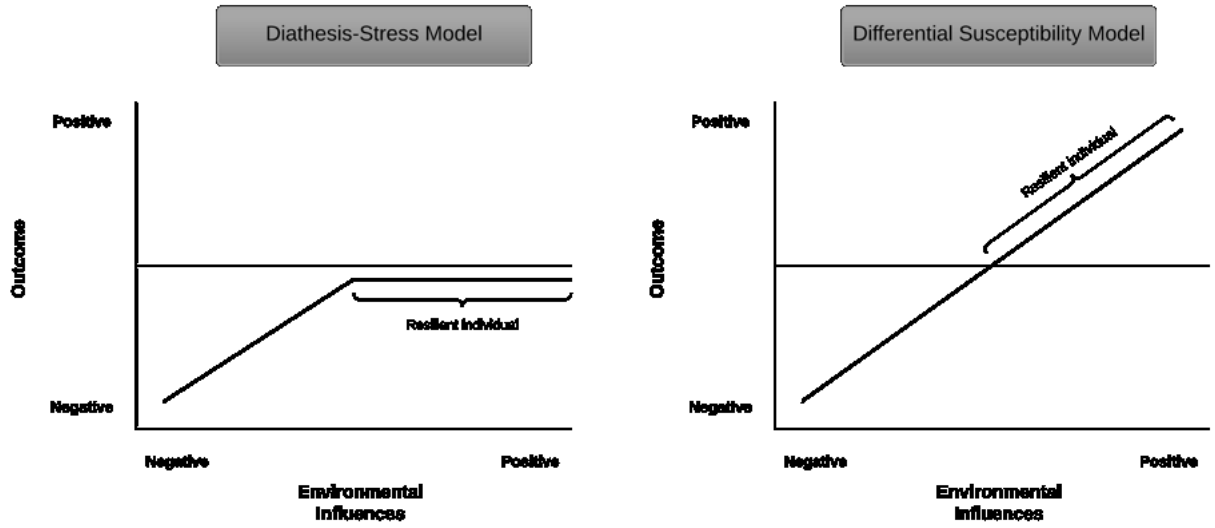

Figure 1.1. A comparison of outcomes for prenatally stressed individuals exposed to positive and negative environmental influences under the diathesis-stress and differential susceptibility models. Resilient individuals are those who do not experience negative outcomes despite predisposition or vulnerability. (Adapted from Belsky et al., (75))

A considerable number of studies support the potential role of the postnatal environment on the relationships between prenatal maternal stress and offspring mental health disorders. First, a growing body of research demonstrates links between prenatal maternal stress and higher risks of experiencing maltreatment, harsh discipline, and/or adverse experiences in childhood (76–78). Associations between these variables and later onset of mental health disorders, including depression, have been repeatedly demonstrated (79,80). Second, mothers who experience

prenatal depression, prenatal anxiety, or stressful life events during pregnancy are at an increased risk of experiencing psychopathology or additional stress in the postpartum period (42,81). Postpartum psychopathology and stressful events have subsequently been linked to altered stress reactivity and onset of mental health disorders in offspring (82–86). Postpartum depression experienced by fathers is also associated with offspring mental health outcomes (87,88). Third, protective factors, including positive parenting, wellbeing, coping skills, resiliency, and social support, although understudied, can also impact offspring mental health. Positive parenting practices, for example, have been linked to lower risk of depression, and higher ratings of self-esteem and optimism in offspring (89,90). In addition, higher levels of positive mental health indicators including high self-efficacy and positive affect are associated with positive parenting behaviours (91,92), as well as positive cognitive and socioemotional outcomes in children (93,94). Finally, factors beyond the individual level, including neighbourhood deprivation, and community-level social processes (e.g., neighbourhood cohesion), have also demonstrated robust associations with offspring mental health outcomes (95–98).

1.3.1 ***Overview of studies examining postnatal influences.*** Robust animal research has demonstrated that the negative impacts of prenatal stress exposure on offspring can be reversed by postnatal factors. For example, studies in rats have demonstrated that although prenatal stress exposure enhances HPA axis reactivity in offspring, this hypersensitivity is reversed by postnatal influences including adoption by a caring mother (99), and exposure to enriched physical environments (100). In addition, a recent animal study conducted in prairie voles demonstrated that prenatally stressed voles were more responsive to postnatal rearing environments than non-stressed voles (101). Voles exposed to prenatal maternal stress and raised in high-quality environments displayed lower behavioural and physiological reactivity to postnatal stressors,

while those raised in low-quality environments experienced higher stress reactivity (101). Emerging epidemiological research also supports the moderating role of postnatal environmental influences on relationships between prenatal maternal stress and offspring behaviour and mental health. A study by Bergman *et al.* demonstrated that the relationship between maternal glucocorticoid levels and offspring socio-emotional development was significant only for infants with insecure attachment to their mothers (102). Research by Costello *et al.* reported that girls born with low birth weight were at an increased risk of depression, and further, that each additional postnatal adversity increased risk for depression in girls born at a low birth weight to a greater degree than normal weight girls (71). Another study by Sharp *et al.* suggested that among offspring born to mothers with higher prenatal anxiety, exposure to postnatal maternal stroking (a measure of tactile stimulation and caregiving) in the first few weeks of life imparted a protective effect on internalizing symptoms measured at 2.5 years of age (103). Finally, findings from a study by Bolten *et al.* demonstrated that the associations between prenatal maternal stress and persistent infant crying were modified by self-efficacy, such that higher levels of self-efficacy reduced the strength of the association between prenatal maternal stress and persistent infant crying (104). Taken together, this highlighted body of evidence underscores the importance of considering postnatal influences when examining relationships between prenatal maternal stress and offspring mental health outcomes. Studies that consider both the prenatal and postnatal environment are particularly necessary in order to better identify and serve those who are most vulnerable towards experiencing poor mental health.

1.4 Proposed biological mechanisms

It has been hypothesized that alterations to the maternal and fetal HPA axes and immune systems are candidate mechanisms for the transmission of stress reactivity and vulnerability towards psychopathology from mother to child (30,31,105). This has been supported by several animal studies and a growing number of human studies, which have demonstrated that: (1) both mothers who are prenatally stressed, and their offspring, demonstrate abnormalities in HPA axis functioning, and in innate or adaptive immunity (29,35,36,106); and (2) higher levels of circulating cortisol and pro-inflammatory markers, particularly interleukin-6 (IL-6) and C-reactive protein (CRP), have demonstrated bidirectional associations with depression, anxiety, externalizing behaviours, and psychotic disorders (107–112). Some evidence exists to support the potential mediating role of HPA axis dysregulation in relations between prenatal maternal stress and offspring mental health (34,106). Only two studies, to our knowledge, have examined the mediating role of immune dysregulation in offspring on the associations between prenatal maternal stress and offspring mental health. The first study used DNA methylation data as a proxy measure for inflammation to examining potential mediation of associations between pre- and post-natal adversity and offspring mental health outcomes; associations were only significant for postnatal stress exposures (113). The second study used offspring inflammation data at age 9 to examine mediation of the associations between prenatal and postnatal stressful life events and offspring depression; mediation was not significant for prenatal maternal stressful life events (114). In addition, few studies have examined the mediating role of maternal inflammation during pregnancy on the associations between prenatal maternal stress and offspring development. One study suggested that maternal levels of CRP during pregnancy mediated the associations between prenatal environmental adversities (including mood and anxiety disorders,

overweight/obesity, diabetes and hypertension) and offspring neurodevelopmental delay (115); another study suggested that maternal levels of CRP during pregnancy mediated the associations between prenatal maternal depression and infant negative affect (116).Thus, given this limited evidence base with contrasting findings, further study of these associations is needed to elucidate the potential role of maternal and offspring inflammation in the prenatal programming of offspring mental health disorders.

1.4.1 ***Stress and the immune response*****.** Several studies demonstrate relationships between psychosocial stressors and immune functioning (117–119). In response to stress, the HPA axis releases cortisol, which can impact both adaptive immunity and innate immunity (i.e., inflammation). Under normal conditions, cortisol is considered anti-inflammatory – a negative feedback loop exists between the HPA axis and the immune system, which serves to maintain an appropriate allostatic load (120). However, when an individual experiences chronic stress, cortisol starts to become less effective at suppressing inflammation (121,122). Increased inflammation can act upstream to increase levels of serotonin and catecholamines (i.e., epinephrine, norepinephrine), which can further stimulate the release of cortisol and pro-inflammatory cytokines (123,124). Brief increases in circulating levels of proinflammatory cytokines in response to stress are physiologically appropriate; however, prolonged immune responses, which result from these poorly regulated interactions between the HPA axis and immune system, are maladaptive (125). Inflammation can also negatively act on the placental barrier enzyme 11β-hydroxysteroid dehydrogenase Type II (11βHSD2)(126), which typically breaks down cortisol and limits maternal-fetal transfer of cortisol in normal conditions (127).

This can lead to glucocorticoid resistance in offspring (126), and may also impact offspring immunity via glucocorticoid-mediated immune suppression (128,129).

1.4.2 ***Prenatal maternal stress and maternal and offspring inflammation.*** As pregnancy progresses, pregnant women exhibit elevated serum levels of pro-inflammatory markers, including IL-6 and CRP (130–133); this is because increased inflammation represents an important causal mechanism in the initiation of labour (134,135). Nonetheless, several studies demonstrate that women who experience high levels of prenatal maternal stress, including experiencing stressful life events, symptoms of depression, and/or symptoms of anxiety during pregnancy, exhibit significantly higher pro-inflammatory marker levels compared to pregnant women who report lower levels of stress during pregnancy (122,132,136). It has been suggested that particular pro-inflammatory markers, including IL-6 and CRP, can demonstrate maternal-fetal and fetal-maternal transfer in utero (137,138), which supports the notion that prenatal maternal stress can alter cytokine expression in offspring. This is further supported by an emerging body of literature demonstrating associations between prenatal maternal stress and offspring inflammation (29,35,36,139). Existing studies support associations between objective prenatal maternal stress measures (e.g., stressful events), subjective prenatal maternal stress measures (e.g., maternal distress), and offspring outcomes including elevated levels of CRP (29), and higher levels of pro-inflammatory cytokines including IL-1ß, IL-6, IL-10, and tumor necrosis factor alpha (TNF-α)(35,139). However, limitations of the existing evidence base include study design, as some existing studies employ retrospective or cross-sectional designs; inconsistent definitions of prenatal maternal stress; and small sample sizes, which limit statistical power, and thus the ability to adjust for important confounding variables, as well as the

opportunity to investigate for moderation by sex or postnatal variables of potential interest. Nonetheless, these data are promising in supporting the link between prenatal maternal stress and maternal and offspring inflammation, and thus suggest that these associations warrant further examination.

1.4.3 ***Inflammation and mental health*****.** Several studies demonstrate robust associations between inflammation and mental health outcomes, lending further support for inflammation as a potential mechanism underlying the associations between prenatal maternal stress exposure and offspring mental health. For example, inflammation has been implicated as a particularly important mechanism in the pathogenesis of depression. This is supported by multiple meta-analyses demonstrating longitudinal associations between pro-inflammatory markers including IL-1ß, IL-6, and CRP, and major depressive disorder (109–111), with further evidence supporting the notion that these relationships are bidirectional (140). Mendelian randomization studies have also suggested that IL-6 and CRP are likely causal risk factors for depression (141). Inflammation has further been implicated as a shared mechanism for the link between mental health disorders and poor physical health outcomes, ranging from type 2 diabetes to cardiovascular disease (141–146). Within the developmental literature, large-scale prospective studies have also demonstrated associations between levels of IL-6 and CRP measured in childhood and onset of depression, psychotic disorders, and generalized anxiety disorders in adolescence (107,108).

1.5 Conceptual model and summary

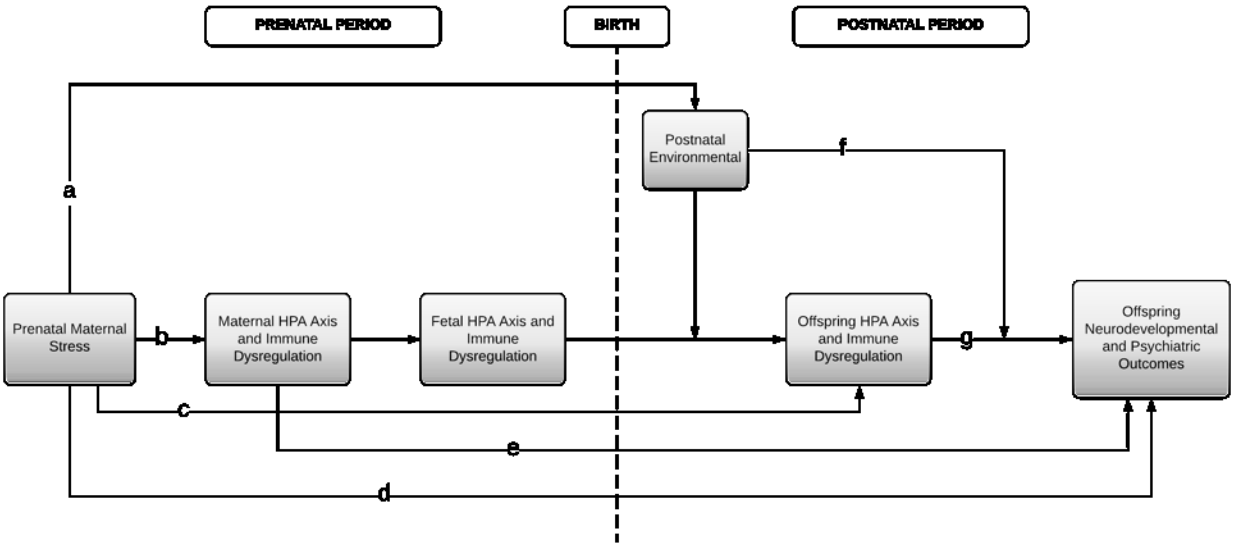

Figure 1.2. A conceptual model highlighting the roles of biological mechanisms in mediating the associations between prenatal maternal stress and offspring neurodevelopmental outcomes, as well as the role of the postnatal environment in modifying these associations.

There is a large body of evidence supporting relationships between prenatal maternal stress and a range of mental health outcomes in offspring, as well as emerging evidence demonstrating associations between prenatal maternal stress and maternal and offspring inflammation, and associations between maternal and offspring inflammation and offspring mental health. There is also emerging evidence that supports the potential moderating role of the postnatal environment in these associations, as well as growing interest in examining the potential biological mechanisms of the associations between prenatal maternal stress and offspring mental health. Figure 1.2 highlights a conceptual model that illustrates potential mediation of the associations between prenatal maternal stress and offspring neurodevelopmental and psychiatric outcomes

through maternal, fetal, and offspring HPA axis and immune system dysregulation, as well as moderation of these associations by the postnatal environment – this conceptual model forms the underlying objectives of this doctoral research. In addition, this thesis will aim to address some of the primary limitations that exist within the current evidence base. For example, studies often operationalize prenatal maternal stress using different definitions, which calls for research that examines stress in accordance to its multidimensional nature. There is also increasing need for large-scale, prospective analyses that are sufficiently powered to address the areas highlighted in the proposed conceptual model, including: (1) the interactive role of postnatal environmental influences on the associations between prenatal maternal stress and offspring mental health; (2) the associations between prenatal maternal stress and markers of maternal and offspring inflammation; and (3) the role of maternal and offspring inflammation in mediating the associations between prenatal maternal stress and offspring mental health outcomes. Through the use of large-scale, longitudinal birth cohort data to address these areas, this thesis aims to both support and extend the current evidence base that describes the developmental origins of mental health disorders.

1.6 Dissertation objectives

This thesis aims to identify important biological and psychosocial influences of the associations between prenatal maternal stress and a range of children's mental health outcomes, including internalizing and externalizing symptoms, using complex statistical methods such as structural equation modelling. Four studies were conducted to answer the following research questions:

1. Is a comprehensive measure of prenatal maternal stress associated with later mental health outcomes in children? (Figure 1.2, path d)
2. Are the associations between prenatal maternal stress and children's mental health outcomes moderated by parenting behaviours? (Figure 1.2, paths a and f)
3. Are the associations between prenatal maternal stress and children's mental health outcomes moderated by indicators of maternal positive mental health? (Figure 1.2, paths a and f)
4. Does maternal inflammation during pregnancy mediate the associations between prenatal maternal stress and children's mental health outcomes? (Figure 1.2, paths b and e)
5. Are the associations between prenatal maternal stress and children's mental health outcomes mediated by children's inflammation? (Figure 1.2, paths c and g)

1.7 Dissertation organization

This thesis is organized in an article format following the University of Ottawa doctoral thesis guidelines. A brief overview of each chapter is provided below:

- Chapter 1 provides an introduction and rationale for the thesis topic
- Chapter 2 represents the first article of the thesis, titled "Prenatal maternal stress, child internalizing and externalizing symptoms, and the moderating role of parenting: Findings from the Norwegian Mother, Father, and Child Cohort Study". This article is published in *Psychological Medicine.*
- Chapter 3 represents the second article of the thesis, titled "Positive maternal mental health attenuates the associations between prenatal maternal stress and children's

internalizing and externalizing symptoms". This article is under peer review at *European Child & Adolescent Psychology.*

- Chapter 4 represents the third article of this thesis, titled "Associations between prenatal maternal stress, maternal inflammation during pregnancy, and children's internalizing and externalizing symptoms throughout childhood". This article has been prepared for submission to *Brain, Behavior, and Immunity*.
- Chapter 5 represents the fourth and final article of this thesis, titled "The mediating role of childhood inflammation in the associations between prenatal maternal stress and adolescent mental health disorders". This article has been prepared for submission to *Biological Psychiatry.*
- Chapter 6 provides a summary and discussion of key findings from Chapters 2 through 5, discusses strengths and limitations of the thesis, and comments on the potential implications of the thesis research.

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Chapter 2

Prenatal maternal stress, child internalizing and externalizing symptoms, and the moderating role of parenting: Findings from the Norwegian Mother, Father, and Child Cohort Study

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Article preface: The aims of this study were to examine the sex-specific associations between prenatal maternal stress and child internalizing and externalizing symptoms at 8 years of age, and to assess the moderating effects of parenting behaviors on these associations.

Contribution statement: I am the first author on this article. I designed the study and its objectives, with guidance from my co-authors. I conducted all study analyses, prepared the first draft of the manuscript, submitted the manuscript for publication, and led subsequent revisions.

ABSTRACT

Background: Few studies have examined how parenting influences the associations between prenatal maternal stress and children's mental health. The objectives of this study were to examine the sex-specific associations between prenatal maternal stress and child internalizing and externalizing symptoms, and to assess the moderating effects of parenting behaviors on these associations.

Methods: This study is based on 15,963 mother-child dyads from the Norwegian Mother, Father and Child Cohort Study (MoBa). A broad measure of prenatal maternal stress was constructed using 41 self-reported items measured during pregnancy. Three parenting behaviors (positive parenting, inconsistent discipline, positive involvement) were assessed by maternal report at child age 5 years. Child symptoms of internalizing and externalizing disorders (depression, anxiety, attention deficit hyperactivity disorder, conduct disorder, oppositional defiant disorder) were assessed by maternal report at age 8. Analyses were conducted using structural equation modeling techniques.

Results: Prenatal maternal stress was associated with child internalizing and externalizing symptoms at age 8; associations with externalizing symptoms differed by sex. Associations between prenatal maternal stress and child depression, and conduct disorder and oppositional defiant disorder in males, became stronger as levels of inconsistent discipline increased. Associations between prenatal maternal stress and symptoms of attention-deficit hyperactivity disorder in females were attenuated as levels of parental involvement increased.

Conclusions: This study confirms associations between prenatal maternal stress and children's mental health outcomes, and demonstrates that these associations may be modified by parenting

behaviors. Parenting may represent an important intervention target for improving mental health outcomes in children exposed to prenatal stress.

Keywords: prenatal stress, internalizing, externalizing, parenting, fetal programming, MoBa

INTRODUCTION

According to the developmental origins of health and disease hypothesis, exposure to maternal stress during critical developmental windows can lead to enduring alterations of fetal endocrine, nervous, and immune systems, which can have long-term consequences for children's health and development (1,2). In line with this hypothesis, maternal stress during pregnancy is associated with children's risk of depression, externalizing disorders, and other mental health disorders (3–5).

Sex differences in the consequences of exposure to prenatal maternal stress are well-documented (6). Animal studies demonstrate sex-specific alterations to neural structures and the hypothalamic–pituitary–adrenal (HPA) axis in response to prenatal maternal stress (7). Evolutionary explanations posit that female fetuses adapt to intrauterine stress exposures through growth modulation and greater stress responsiveness, which can improve viability but give rise to depressed or anxious phenotypes (7,8). Conversely, male fetuses tend to prioritize growth and physical development in response to adversity; after birth, males may be better adapted to explore new environments and compete with other males, but these adaptations can lead to greater aggression (7,8). These differences are reflected in the developmental literature, as several studies demonstrate stronger associations between prenatal maternal stress and internalizing symptoms in females and externalizing symptoms in males (6), emphasizing the need to evaluate sex-specific effects of prenatal maternal stress on children's development.

A wide range of stressors can activate the maternal stress response system. In line with this, the measurement of maternal stress during pregnancy varies substantially among existing studies;

measures ranging from adverse events to maternal depression have been used to assess stress (9), and have demonstrated associations with children's mental health (10,11). Several studies have examined these stressors in isolation; however, co-occurrence is common, and experiencing multiple forms of stress can further amplify children's risk of adverse outcomes (12). Many stress measures overlap conceptually and phenotypically (13), thus, it may be more valuable to focus on broad representations of prenatal maternal stress that capture the shared variance across stress measures (9). This view is supported by recent studies that have found associations between broad conceptualizations of prenatal maternal stress and children's intelligence, autistic traits, and callous-unemotional behaviors (14–16).

The long-term burden of early life stress exposure on mental health is not limited to exposures during fetal life. Emerging research has examined the impacts of postnatal exposures, including attachment and adversity, on the development of mental disorders in light of prenatal maternal stress exposure (17,18); this has broad implications given that several aspects of the postnatal environment may be modifiable (19). In particular, parenting behaviors may be a target of intervention, as positive and negative parenting behaviors are associated with prenatal stress and children's mental health (20,21). For example, positive parental involvement has been associated with lower risk of incident depression in early adulthood (22), whereas harsh parenting and inconsistent discipline have been associated with increased externalizing problems and depressive symptoms (23,24). To our knowledge, few studies have examined whether parenting behaviors moderate the effects of prenatal maternal stress on developmental outcomes. As a result, there is a need for research that investigates the moderating role of parenting behaviors on these associations.

The aims of our study were two-fold. Our first aim was to examine the associations between a broad measure of prenatal maternal stress and children's internalizing and externalizing symptoms in a longitudinal sample, and to ascertain potential sex differences of the associations. Our second aim was to examine the moderating roles of positive parenting, positive parental involvement, and inconsistent discipline on these associations.

METHODS

Sample

The current study utilizes data from the Norwegian Mother, Father and Child Cohort Study (MoBa), a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from across Norway between 1999 and 2008, and women consented to participation in 41% of pregnancies. The cohort now includes over 114,500 children, 95,200 mothers and 75,200 fathers (25). Maternal questionnaire response rates at the 17th and 30th week of gestation, and at 18 months and 5 years after birth were 95.1%, 91.4%, 87.0% and 54.0%, respectively (26). The current study is based on version 12 of the quality-assured data files released for research in 2020. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act. This study includes 15,963 participants with available data on study exposure and outcome variables (see Figure S2.1). This study was approved by The Regional Committees for Medical and Health Research Ethics (#2013/2061).

Measures

Prenatal Maternal Stress. A total of 41 items, collected via maternal questionnaire at 17 and/or 30 weeks' gestation, were used to create a broad measure of prenatal maternal stress. This measure was constructed using methods developed by Cecil et al. (15), which uses confirmatory factor analysis to account for the shared variance across prenatal stress measures, and has been implemented with good model fit in other studies (14,16). The prenatal stress measure categorizes items in relation to four domains that account for different manifestations of stress: life stress, contextual stress, personal stress, and interpersonal stress. Items from each domain were summed and divided by the number of items to generate mean scores, which were used as indicators to extract a single, latent prenatal maternal stress factor. We excluded maternal education from the personal stress domain, because maternal education may impact child development by pathways independent of maternal prenatal stress (16). We included occupational stress-related items into the contextual stress domain, and removed maternal hospitalizations during pregnancy from the life stress domain to improve fit of the measurement model, and required participants to have complete data on at least two out of four stress domains to improve stability of the latent variable. A list of included items is provided in the Appendix.

Parenting Behaviors. Maternal parenting behaviors at child age 5 years were examined using the Alabama Parenting Questionnaire 9-item short-form version (APQ-9), which was developed to assess parenting practices in clinical and research settings (27). The APQ-9 was collected in version B of the 5 year questionnaire, which was provided to 64.3% of study participants (remaining participants received version A and thus were not eligible for study inclusion). The

APQ-9 measures three dimensions of parenting that are relevant to the etiology and treatment of child internalizing and externalizing problems, including positive parenting (e.g., "you let your child know when they are doing a good job with something"), inconsistent discipline (e.g., "you threaten to punish your child and then do not actually punish him/her"), and positive parental involvement (e.g., "you have a friendly talk with your child"). All answers were scored on a 5-point Likert scale ranging from 1 (never) to 5 (always), with mean scores generated for each dimension. The APQ-9 demonstrates good construct and convergent validity, and is strongly correlated with scores from the complete APQ scale (27). Scores from the APQ have also demonstrated moderate to strong correlations with observational data (28).

Child Mental Health Outcomes

Internalizing symptoms. Mother-reported symptoms of child depression and anxiety were examined using total scores from short versions of the Mood and Feelings Questionnaire (SMFQ) and the Screen for Child Anxiety Related Disorders (SCARED) at child age 8 years (29,30). The SMFQ comprises 13 items assessing depressive symptoms experienced over the past two weeks, rated from 0 (not true) to 2 (true), resulting in a total sum score of 0–26, with higher scores representing increased depressive symptoms. The SCARED comprises five items rated on a 3-point Likert scale from 1 (not true) to 3 (true). Total scores were calculated by summing values of all items, resulting in a possible score range of 5–15, with higher scores representing increased symptoms of anxiety. Both the SMFQ and SCARED measures have demonstrated high internal consistency in several population-based studies (29,31).

Externalizing symptoms. Mother-reported symptoms of attention deficit hyperactivity disorder, conduct disorder, and oppositional defiant disorder were assessed using the Parent/Teacher Rating Scale for Disruptive Behavior Disorders (RS-DBD) at child age 8 years (32). The scale consists of 34 items describing the child's behavior during the last six to twelve months. This includes 18 items reflecting symptoms of attention deficit hyperactivity disorder (e.g., "Has difficulty sustaining attention in tasks or play activities"), 8 items related to conduct disorder (e.g., "Initiates physical fights"), and 8 items related to oppositional defiant disorder (e.g., "Argues with adults"). Items were rated on a 4-point Likert scale from 1 (never/rarely) to 4 (very often). For each disorder, item scores were summed into total scores, with higher scores representing increased symptoms. Items included in the RS-DBD reflect those presented in the Diagnostic and Statistical Manual of Diseases – 4th revision (DSM-IV-TR), and the measure demonstrates good construct and instrument validity when compared to other parent- and teacher-rated measures of externalizing symptoms (32).

Covariates. Child sex (male or female) was examined as a potential stratification variable and used as a covariate where sex differences were not statistically significant. A number of potential confounding variables were also identified a priori based on the existing literature and investigated in analyses. This included maternal and paternal education (postsecondary and above, high school and below); smoking during the first trimester of pregnancy (yes or no); drinking during the first trimester of pregnancy (never, 1-3 times per month, 1 time per week or more); and parity (no prior births, 1+ prior births). Maternal symptoms of depression at child age 5, measured using the Hopkins Symptom Checklist-8 (33), and cumulative maternal adverse events up to child age 5, were adjusted for in sensitivity analyses.

Statistical Analyses

Reporting of participant characteristics and attrition analyses comparing those included and excluded from the study sample on key study variables were performed using Stata version 15 (StataCorp, College Station, TX). Remaining analyses were conducted using MPlus version 8 (Muthén & Muthén, Los Angeles, CA). Estimation of the associations between prenatal maternal stress and child internalizing and externalizing symptoms was performed using structural equation modelling, with multiple group analyses performed to ascertain potential sex differences. Next, interaction terms were added to the structural equation models to assess moderation by positive parenting, positive parental involvement, and inconsistent discipline. To account for potential non-normality of data and missing values on prenatal stress items and covariates, all models were estimated using full information maximum likelihood estimation (FIML) with robust standard errors (MLR), which is a valid analytic approach to dealing with missing data and is robust to the assumption that data are missing at random (34). Sensitivity analyses were then conducted by adjusting for cumulative maternal stressful life events and maternal depression at child age 5 years for all interaction analyses. Examples of the models assessed in this study are provided in Figures S2.2 and S2.3, and details on main analyses conducted are presented below.

Associations between prenatal maternal stress and child internalizing and externalizing symptoms. Confirmatory factor analysis was used to estimate a latent factor of prenatal maternal stress using mean scores from the four calculated prenatal stress domains as indicators, and analyses of the associations between latent prenatal maternal stress and child internalizing and

externalizing symptoms were performed simultaneously. Latent prenatal maternal stress was standardized by scaling its variance to 1, with standardized parameter estimates reported representing changes in the standard deviations of child mental health variables per one standard deviation increase in latent prenatal maternal stress. Unstandardized parameter estimates are also reported, and represent changes in child mental health variables per one unit increase in the latent prenatal maternal stress variable. Unadjusted and adjusted models were estimated. Measures examining internalizing and externalizing disorders were allowed to correlate in all models. Fit of the measurement and structural models were assessed using the comparative fit index (CFI) and the root mean square error of approximation (RMSEA), where good fit was categorized as a value of 0.90 and above or 0.06 and below (35,36), respectively.

Sex differences were ascertained through multiple group analyses, whereby models examining the associations between prenatal maternal stress and child internalizing or externalizing symptoms were stratified by sex and examined simultaneously. Constrained (all factor loadings held equal) and unconstrained (free estimation of paths between prenatal stress and child internalizing or externalizing symptoms) models were compared using likelihood ratio tests to ascertain whether or not unconstrained estimates significantly differed by sex ($p < .05$); if significant, analyses were stratified by sex.

Moderating effects of parenting. To examine moderation by parenting measures, interaction terms were created between prenatal maternal stress and each parenting measure using the *XWITH* procedure in MPlus, in accordance with the latent moderated structural equations approach (37). We considered moderation to be present if interaction terms were significantly

associated with symptoms of internalizing or externalizing disorders at a threshold of $p < .05$. Statistically significant interactions were probed using the Johnson-Neyman technique in MPlus (38), which plots the unstandardized effect (slope) of latent prenatal maternal stress on symptoms of internalizing or externalizing disorders and their 95% confidence intervals (CI) on the y-axis, against the complete range of values for the moderator variables on the x-axis. For continuous moderators, the Johnson-Neyman technique in MPlus provides a visual representation of the values of the moderating variables (on the X-axis) at which the associations between prenatal maternal stress and child internalizing and externalizing symptoms are statistically significant (i.e., where the effect line and its 95% CI do not overlap with zero on the Y-axis), and highlight the strength of the associations across values of the moderating variables.

RESULTS

The majority of mothers included in the sample were married or cohabiting, had some level of post-secondary education, and were pregnant with their first child. Approximately 3.5% of women reported smoking (sometimes or daily), and 8% of women reported alcohol use (1 drink per month or greater) at 17 weeks' gestation. Descriptive characteristics of the sample, including information on missing data, are summarized in Table 2.1.

Associations between prenatal maternal stress and child internalizing and externalizing symptoms

The measurement model for latent prenatal maternal stress (Figure S2.4) had excellent fit (RMSEA = .000, 90% CI = .000, .014; CFI = 1.000), and all stress domains and outcomes were

significantly correlated (Table S2.1). The likelihood-ratio test to assess for sex differences was not statistically significant for symptoms of internalizing disorders, $\chi^2(2) = 3.614$, $p = .16$, suggesting that the associations between prenatal maternal stress and symptoms of depression and anxiety were similar for males and females. The associations between prenatal maternal stress and symptoms of depression and anxiety were statistically significant prior to and after adjustment for covariates including sex (Table 2.2), and model fit was good (RMSEA = .043, 90% CI = .040, .045; CFI = 0.901).

For the associations between prenatal maternal stress and symptoms of externalizing disorders, the likelihood-ratio test to assess for sex differences was statistically significant, $\chi^2(3) = 37.966$, $p < .001$, and analyses were sex-stratified. Prenatal maternal stress was associated with symptoms of all externalizing disorders in males and females. However, the associations with symptoms of conduct disorder and oppositional defiant disorder appeared slightly stronger for males compared to females (Tables 2.3 and 2.4), and associations with symptoms of attention deficit hyperactivity disorder appeared stronger for females compared to males. Model fit was excellent for both male (RMSEA = .036, 90% CI = .032, .039; CFI = 0.963) and female (RMSEA = .039, 90% CI = .036, .043; CFI = 0.945) models.

Moderation by parenting behaviors

The interaction term between prenatal maternal stress and inconsistent discipline was small but statistically significant and positively associated with symptoms of depression (β =.063, 95% CI: .032, .094). The association between prenatal maternal stress and symptoms of depression was

significant at all values of inconsistent discipline (i.e., the effect and 95% confidence intervals were above 0 across values of inconsistent discipline), however, the strength of the association increased with increasing levels of inconsistent discipline (Figure 2.1A). Interaction terms between prenatal maternal stress and positive parenting and positive parental involvement in structural models examining symptoms of depression or anxiety were not statistically significant (Table 2.2).

For males and females, interactions between prenatal maternal stress and positive parenting were not significantly associated with symptoms of externalizing disorders (Tables 2.3 and 2.4). For males, the interaction terms between prenatal maternal stress and inconsistent discipline were small but positively associated with higher symptoms of conduct disorder (β = .049, 95% CI = .014, .085) and oppositional defiant disorder (β =.049, 95% CI = .014, .085); interaction terms were not significant for females. The association between prenatal maternal stress and symptoms of conduct disorder was significant at most values of inconsistent discipline, and not statistically significant at the lowest values of inconsistent discipline (Figure 2.1B). The association between prenatal maternal stress and symptoms of oppositional defiant disorder in males was significant at all values of inconsistent discipline (Figure 2.1C). Strength of the associations between prenatal maternal stress and symptoms of conduct disorder and oppositional defiant disorder increased as levels of inconsistent discipline increased. For females, the interaction between prenatal maternal stress and positive parental involvement was small but negatively associated with symptoms of attention-deficit hyperactivity disorder (β = -.053, 95% CI: -.093, -.013); interaction terms were not significant for males. The association between prenatal maternal stress and symptoms of attention-deficit hyperactivity disorder in females was significant at all values

of positive parental involvement, however, strength of the association was attenuated as positive parental involvement increased (Figure 2.1D).

Attrition and sensitivity analyses

Comparisons between those included in the study sample and those excluded from analysis are presented in Table S2.2, as well as detailed information on missing data. Excluded participants, on average, were younger, were less likely to have postsecondary education, and were more likely to have at least one child, smoke during pregnancy, report higher levels of all four prenatal stress domains, and report higher internalizing and externalizing symptoms for children at age 5. Sensitivity analyses adjusting for maternal stressful life events from birth to child age 5 years, and symptoms of depression at child age 5 years are presented in Tables S2.3 to S2.5; all interaction effects remained statistically significant after these additional adjustments.

DISCUSSION

Our prospective study of almost 16,000 mother-child dyads demonstrates associations between a broad measure of prenatal maternal stress and subsequent symptoms of internalizing and externalizing disorders in children at 8 years of age; associations between prenatal maternal stress and externalizing disorders also differed by sex. Our findings further demonstrate that several of these associations are moderated by parenting behaviors. Higher levels of inconsistent discipline indicated stronger associations between prenatal maternal stress and child depression in both sexes, and conduct disorder and oppositional defiant disorder in males, and higher levels of positive parental involvement attenuated the association between prenatal maternal stress and

symptoms of attention-deficit hyperactivity disorder in girls. These effects also persisted after adjustment for postnatal maternal depression and stressful life events.

Our findings are in line with prior studies on prenatal maternal stress and children's internalizing and externalizing disorders (5), and expand the evidence base by demonstrating the effects of a broad measure of prenatal maternal stress. We tested for potential sex differences, and in line with the extant literature (6), observed sex differences in the associations between prenatal maternal stress and symptoms of externalizing disorders. Contrary to expectations, we did not observe any statistically significant sex differences for models with internalizing symptoms. A potential explanation for this finding is that these sex differences may appear later in development. Animal models suggest that prenatal maternal stress may disrupt sex-specific development of the prefrontal cortex during adolescence, which differentially influences vulnerability to psychiatric disorders among males and females (39); several observational studies demonstrate that females are at greater risk for internalizing disorders compared to males into adolescence and adulthood (40).

Emerging evidence further suggests that the associations between prenatal stress and offspring outcomes may be conditional on the postnatal environment, whereby prenatal stress promotes postnatal "developmental plasticity" (18,41). This hypothesis of differential susceptibility suggests that exposure to prenatal stress can increase offspring sensitivity to positive and negative postnatal influences, thus either reducing or amplifying risk towards adverse outcomes. A growing number of experimental and observational studies support the role of postnatal environmental factors in moderating the associations between prenatal stress exposure and

children's development in line with differential susceptibility. For example, research suggests that among offspring born to prenatally anxious mothers, higher exposure to postnatal maternal stroking in the first few weeks of life imparts a protective effect on internalizing symptoms at 2.5 years of age, whereas lower exposure is associated with increased internalizing symptoms (42). In addition, research conducted in prairie voles suggests that prenatally stressed voles are more responsive to postnatal rearing environments than non-stressed voles (43).

There has been limited research examining the moderating role of parenting behaviors in the associations between prenatal maternal stress and child developmental outcomes; among existing studies, findings have been inconsistent (44–46). Our findings support small interaction effects of inconsistent discipline and positive parental involvement in a manner such that the strength of the associations between prenatal maternal stress and internalizing and externalizing outcomes are amplified when levels of inconsistent discipline are high (or levels of positive parental involvement are low), and vice versa. Elucidating how parenting behaviours moderate these associations based on differential susceptibility can have substantial public health implications (47). Parenting behaviors are potentially modifiable (48), and child regulation of stress hormones and other physiological systems implicated in the later onset of psychiatric disorders are responsive to parenting and other psychosocial interventions (49,50). Intervention research also suggests that children who have been affected by adversity tend to benefit most from supportive interventions targeting parenting, in line with models of differential susceptibility (51). Research by Pitzer et al. (52) examining interactions between temperament, parenting, and externalizing problems also partially supports differential susceptibility, and suggests that the influence of parenting behaviours among fearful-inhibited children may be gender-specific (i.e., boys may be

more responsive to sensitive parenting, whereas girls may respond more to restrictive parenting). Thus, parenting behaviors may represent a valuable target of intervention in order to enhance resilience among children exposed to early adversity (49).

Findings from the current study should be interpreted in light of a number of limitations. First, measures were collected by maternal report, and reporting bias cannot be ruled out. However, many of the included measures have been validated and widely used in epidemiological and psychiatric research (see Appendix for prenatal stress items). Second, parenting behaviors were only reported for mothers, and the role of paternal parenting was not examined. Paternal parenting has demonstrated effects on child behaviour, and paternal involvement may moderate the association between maternal depression and child internalizing symptoms (53); thus, paternal parenting may benefit from further study. Third, we were limited to the parenting measures collected in the MoBa study, however, other parenting behaviours, including parental sensitivity, have demonstrated associations with children's mental health (54), and warrant further analysis. Furthermore, the associations between parenting and children's behaviour are often bidirectional and parenting can vary throughout childhood depending on both parent and child factors (55,56); future researchers may seek to examine the moderating effects of parenting throughout development, and to examine how parenting and children's behaviour interact over time. Fourth, we did not include genetic information in analyses, and cannot rule out the potential for genetic confounding; more research is needed to determine the role that genetics may play in the observed associations. Fifth, over 99% of MoBa participants report European ancestry, and most are of higher socioeconomic status. Our findings may not generalize to regions with greater socioeconomic or ethnic diversity, and highlight the need to further examine

these associations in diverse samples. Sixth, although the assessed stress domains loaded onto a single latent factor, their intercorrelations were small-to-moderate; thus, it may be of interest for future researchers to measure the effects of these domains separately to ascertain the specific effects of early-life stress exposure on children's development. Finally, substantial attrition was observed over the study follow-up period, which may potentially bias observed associations; however, prior MoBa analyses suggest that this attrition may not substantially impact general estimates of exposure-outcome associations (57).

These limitations are offset by strengths. The construction of a broad prenatal stress measure addresses limitations inherent to many previous developmental programming studies (9), and directly incorporates the shared variance across stress domains; thus, this measure may be of relevance for public health (12). In addition, the use of data from a prospective study with a large sample size allowed for the adjustment of several confounding variables, including measures reflective of postnatal adversity, with sufficient statistical power to evaluate sex differences and the moderating role of parenting behaviors on several children's behavioural outcomes.

CONCLUSIONS

The current study provides evidence of associations between a broad measure of prenatal maternal stress and symptoms of internalizing and externalizing disorders in children, and highlights the role of positive and negative parenting behaviors in amplifying and reducing the effects of prenatal maternal stress on these outcomes respectively, partly supporting differential susceptibility. Findings may have implications for public health and research, and reinforce the need to develop and promote strategies aimed at reducing stress and reinforcing positive

parenting in expecting and new mothers in order to cultivate intergenerational resilience and wellbeing.

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Ethical Standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 2.1. Descriptive characteristics of sample at 17 weeks' gestation (N = 15,963)

Characteristic	Mean ± SD or n (%)
Maternal age	30.48 ± 4.37
Parity	
0	8,080 (50.62)
1+	7,753 (48.57)
Missing	130 (0.81)
Marital status	
Married	7,722 (48.37)
Cohabiting	7,820 (48.99)
Single	354 (2.22)
Missing	67 (0.42)
Maternal education	
> High school	11,960 (74.92)
High school and below	3,306 (20.71)
Missing	697 (4.37)
Paternal education	
> High school	9,076 (56.86)
High school and below	5,668 (35.51)
Missing	1,219 (7.64)
Smoking	
None	15,025 (94.12)
Sometimes	250 (1.57)
Daily	312 (1.95)
Missing	376 (2.36)
Alcohol use	
None	12,836 (80.41)
1-3 drinks per month	1,257 (7.87)
1+ drinks per week	50 (0.31)
Missing	1,820 (11.40)

Note. SD = standard deviation

Table 2.2. Models of associations between prenatal maternal stress, parenting behaviours at age 5, and their interactions, and symptoms of internalizing disorders at age 8 (N = 15,963)

	Symptoms of Depression		Symptoms of Anxiety	
	b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Individual models				
Prenatal maternal stress (unadjusted)	21.039 (1.318)***	.291 (.268, .31416)	6.104 (.505)***	.166 (.144, .189)
Prenatal maternal stress (adjusted)	20.383 (1.344)***	.301 (.276, .327)	6.147 (0.514)***	.179 (.154, .203)
Positive parenting model				
Prenatal maternal stress	38.760 (11.064)***	.576 (.260, .891)	10.687 (4.234)*	.313 (.073, .553)
Positive parenting	-.421 (.044)***	-.077 (-.092, -.061)	-.078 (.022)***	-.028 (-.044, -.012)
Prenatal maternal stress x Positive parenting	-4.073 (2.389)	-.026 (-.056, .004)	-1.009 (.918)	-.013 (-.036, .010)
Inconsistent discipline model				
Prenatal maternal stress	5.463 (3.593)	.080 (-.024, .192)	3.741 (1.486)*	.108 (.024, .192)
Inconsistent discipline	.366 (.030)***	.094 (.078, .109)	.048 (.016)**	.024 (.009, .040)
Prenatal maternal stress x Inconsistent discipline	**7.099 (1.878)*** **	**.064 (.032, .095)**	1.094 (.693)	.019 (-.005, .043)
Positive parental involvement model				
Prenatal maternal stress	40.511 (11.218)***	.600 (.282, .919)	10.865 (4.913)*	.317 (.039, .594)
Positive parental involvement	-.476 (.051)***	-.072 (-.088, -.057)	-.110 (.026)***	-.033 (-.048, -.018)
Prenatal maternal stress x Positive parental involvement	-4.593 (2.486)	-.025 (-.051, .001)	-1.078 (1.103)	-.011 (-.034, .011)

Note. *p < .05, **p < .01, ***p < .001. Significant moderation effects also bolded. b = unstandardized regression coefficient, SE = standard error, β = standardized regression coefficient, CI = confidence interval. Symptoms of depression and anxiety were included together in models. Models were adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, parity, and sex.

Table 2.3. Models of associations between prenatal maternal stress, parenting behaviours at age 5, and their interactions, and symptoms of externalizing disorders at age 8 (males, *n* = 8,083)

	Symptoms of Attention-Deficit Hyperactivity Disorder		Symptoms of Conduct Disorder		Symptoms of Oppositional Defiant Disorder	
	b (SE)	β (95% CI)	b (SE)	β (95% CI)	b (SE)	β (95% CI)
Individual models						
Prenatal maternal stress (unadjusted, full sample)	47.336 (3.143)***	.234 (.211, .256)	5.305 (.536)***	.125 (.102, .148)	17.438 (1.296)***	.192 (.170, .214)
Prenatal maternal stress (adjusted, full sample)	44.776 (3.207)***	.234 (.208, .259)	5.075 (.564)***	.126 (.101, .152)	17.385 (1.335)***	.202 (.177, .227)
Prenatal maternal stress (unadjusted, males)	48.375 (3.561)***	.231 (.202, .259)	6.713 (.738)***	.141 (.112, .170)	17.686 (1.490)***	.195 (.167, .223)
Prenatal maternal stress (adjusted, males)	45.560 (3.647)***	.229 (.198, .260)	6.454 (.774)***	.143 (.111, .175)	17.881 (1.554)***	.208 (.176, .240)
Positive parenting model						
Prenatal maternal stress	52.511 (35.388)	.266 (-.084, .617)	22.416 (8.555)**	.501 (.127, .875)	30.369 (13.993)*	.356 (.035, .677)
Positive parenting	-1.409 (.193)***	-.083 (-.105, -.060)	-.422 (.044)***	-.109 (-.131, -.087)	-.758 (.081)***	-.103 (-.124, -.081)
Prenatal maternal stress x Positive parenting	-1.602 (7.785)	-.004 (-.037, .030)	-3.500 (1.831)	-.034 (-.069, .001)	-2.814 (3.081)	-.014 (-.045, .017)
Inconsistent discipline model						
Prenatal maternal stress	22.649 (12.397)	.114 (-.009, .236)	-1.535 (2.570)	-.034 (-.145, .077)	1.643 (5.160)	.019 (-.099, .137)
Inconsistent discipline	1.606 (.136)***	.132 (.110, .154)	.353 (.030)***	.128 (.107, .148)	.898 (.059)***	.171 (.149, .192)
Prenatal maternal stress x Inconsistent discipline	10.222 (5.931)	.032 (-.004, .067)	**3.763 (1.367)****	**.051 (.016, .087)**	**7.345 (2.644)****	**.053 (.017, .088)**
Positive parental involvement model						
Prenatal maternal stress	103.318 (47.399)*	.521 (.059, .982)	20.670 (11.221)	.459 (-.029, .947)	24.603 (17.277)	.286 (-.107, .680)
Positive parental involvement	-2.649 (.236)***	-.129 (-.152, -.107)	-.626 (.236)***	-.135 (-.157, -.113)	-1.118 (.099)***	-.126 (-.148, -.104)
Prenatal maternal stress x Positive parental involvement	-13.240 (10.509)	-.024 (-.062, .013)	-3.248 (2.469)	-.024 (-.062, .013)	-1.556 (3.902)	-.007 (-.039, .026)

Note. *$p < .05$, **$p < .01$, ***$p < .001$. Significant moderation effects also bolded. b = unstandardized regression coefficient, SE = standard error, β = standardized regression coefficient, CI = confidence interval. Symptoms of attention deficit hyperactivity disorder,

conduct disorder, and oppositional defiant disorder were included together in models. Models were adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, and parity.

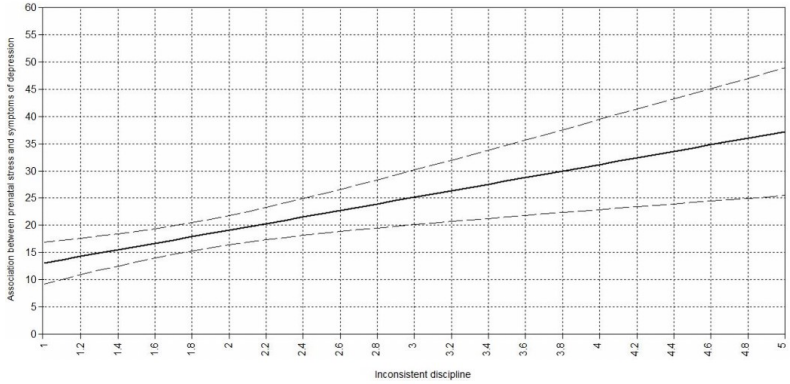
Table 2.4. Models of associations between prenatal maternal stress, parenting behaviours at age 5, and their interactions, and symptoms of externalizing disorders at age 8 (females, *n* = 7,754)

	Symptoms of Attention-Deficit Hyperactivity Disorder		Symptoms of Conduct Disorder		Symptoms of Oppositional Defiant Disorder	
	b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Individual models						
Prenatal maternal stress (unadjusted, full sample)	47.336 (3.143)***	.234 (.211, .256)	5.305 (.536)***	.125 (.102, .148)	17.438 (1.296)***	.192 (.170, .214)
Prenatal maternal stress (adjusted, full sample)	44.776 (3.207)***	.234 (.208, .259)	5.075 (.564)***	.126 (.101, .152)	17.385 (1.335)***	.202 (.177, .227)
Prenatal maternal stress (unadjusted)	45.903 (3.542)***	.248 (.218, .278)	3.601 (.539)***	.109 (.078, .141)	16.938 (1.608)***	.188 (.158, .219)
Prenatal maternal stress (adjusted)	43.636 (3.603)***	.250 (.217, .284)	3.400 (.561)***	.110 (.075, .144)	16.618 (1.655)***	.196 (.162, .230)
Positive parenting model						
Prenatal maternal stress	35.582 (37.712)	.208 (-.224, .641)	15.907 (9.677)	.522 (-.099, 1.144)	20.288 (15.924)	.244 (-.133, .621)
Positive parenting	-1.328 (.159)***	-.094 (-.116, -.072)	-.251 (.030)***	-.100 (-.122, -.078)	-.794 (.077)***	-.116 (-.138, -.094)
Prenatal maternal stress x Positive parenting	1.569 (8.263)	.004 (-.037, .045)	-2.689 (2.005)	-.038 (-.094, .018)	-.815 (3.485)	-.046 (-.040, .031)
Inconsistent discipline model						
Prenatal maternal stress	23.474 (13.426)	.134 (-.017, .285)	-2.099 (3.017)	-.067 (-.255, .121)	4.769 (6.084)	.056 (-.084, .196)
Inconsistent discipline	1.292 (.116)***	.128 (.106, .151)	.188 (.020)***	.105 (.083, .126)	.860 (.056)***	.176 (.154, .199)
Prenatal maternal stress x Inconsistent discipline	8.329 (6.518)	.029 (-.015, .073)	2.611 (1.694)	.051 (-.013, .115)	4.910 (2.968)	.035 (-.006, .077)
Positive parental involvement model						
Prenatal maternal stress	157.264 (44.195)***	.910 (.412, 1.407)	16.018 (13.459)	.523 (-.343, 1.388)	33.560 (19.281)	.400 (-.055, .854)
Positive parental involvement	-2.110 (.183)***	-.125 (-.146, -.104)	-.336 (.033)***	-.112 (-.133, -.091)	-1.085 (.091)***	-.132 (-.154, -.110)
Prenatal maternal stress x Positive parental involvement	**-25.909 (9.695)****	**-.054 (-.094, -.014)**	-2.841 (2.889)	-.034 (-.101, .034)	-3.919 (4.295)	-.017 (-.053, .020)

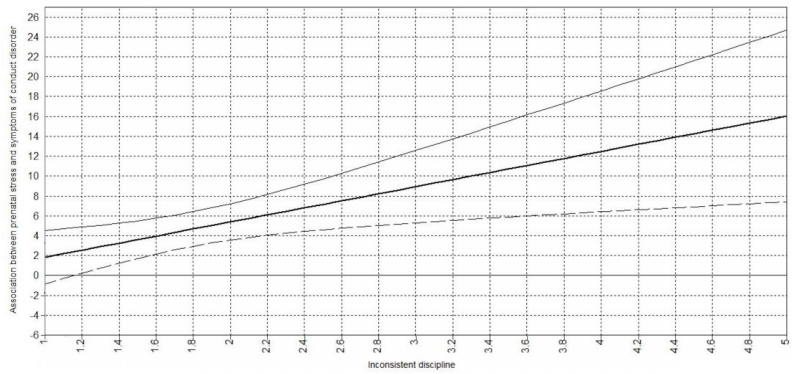
Note. *$p < .05$, **$p < .01$, ***$p < .001$. Significant moderation effects also bolded. b = unstandardized regression coefficient, SE = standard error, β = standardized regression coefficient, CI = confidence interval. Symptoms of attention deficit hyperactivity disorder,

conduct disorder, and oppositional defiant disorder were included together in models. Models were adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, and parity.

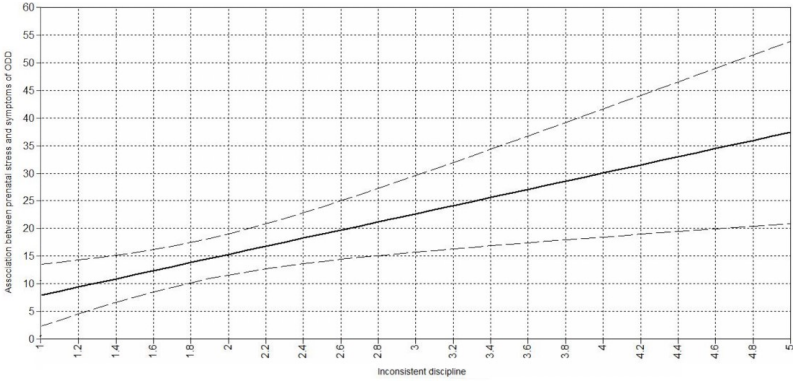
A


Association between prenatal stress and symptoms of depression
Inconsistent discipline

B


Association between prenatal stress and symptoms of conduct disorder
Inconsistent discipline

C


Association between prenatal stress and symptoms of ODD
Inconsistent discipline

D

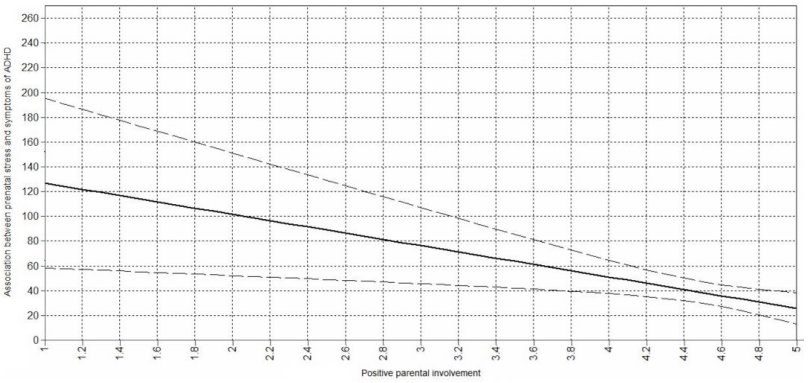

Association between prenatal stress and symptoms of ADHD
Positive parental involvement

Figure 2.1. Johnson-Neyman plots of significant interactions between prenatal maternal stress and parenting behaviours at age 5 on child internalizing and externalizing symptoms at age 8. A) Moderating role of inconsistent discipline on the association between prenatal maternal stress and symptoms of depression. B) Moderating role of inconsistent discipline on the association between prenatal maternal stress and symptoms of conduct disorder in males. C) Moderating role of inconsistent discipline on the association between prenatal maternal stress and symptoms of oppositional defiant disorder (ODD) in males. D) Moderating role of positive parental involvement on the association between prenatal maternal stress and symptoms of attention deficit hyperactivity disorder (ADHD) in females. Plot lines represent effect (solid line) and 95% confidence interval of effect (dashed lines).

Appendix 2.1: MoBA items included in prenatal maternal stress exposure variable

Life Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Adverse events – Have you lost someone close to you?	30 weeks	Dichotomous (yes/no)	(1,2,3)
Adverse events – Child, partner, or relative was seriously ill	30 weeks	Dichotomous (yes/no)	(1,2,3)
Adverse events – You were ill	30 weeks	Dichotomous (yes/no)	(1,2,3)
Adverse events – Robbery, fire	30 weeks	Dichotomous (yes/no)	(1,2,3)
Unplanned pregnancy	17 weeks	Dichotomous (yes/no)	N/A
Worried about health of baby	30 weeks	Dichotomous (yes/no)	N/A
Dissatisfied with antenatal care	30 weeks	Dichotomous (yes/no)	N/A
Experienced vaginal bleeding during pregnancy	30 weeks	Dichotomous (yes/no)	N/A
Test to see if baby was abnormal (amniocentesis or biopsy)	30 weeks	Dichotomous (yes/no)	N/A

Contextual Stress Domain

Scale/Item	Time of Assessment	Variable Type	References
Adverse events – problems at school or work	30 weeks	Dichotomous (yes/no)	(1,2,3)
Adverse events – major financial problems	30 weeks	Dichotomous (yes/no)	(1,2,3)
Financial difficulties – can your family manage without your income?	17 weeks	Dichotomous (yes/no)	N/A
Employment – lost job since start of pregnancy (fired, laid off)	30 weeks	Dichotomous (yes/no)	N/A
Employment – work stress scale	17 weeks	Dichotomous (median split)	(4,5)
- I have physically heavy work [R]			-
- My work is very stressful [R]			-
- I learn a lot at work			-
- My work is very monotonous [R]			-
- My work demands a lot of me [R]			-
- I am able to decide how my work is to be carried out			-
- There is a good team spirit at my place of work			-
- I enjoy my work			-
Income – low income (< 300,000 NOK per year)	17 weeks	Dichotomous (yes/no)	(6,7)

Note. [R] Item reverse coded

Personal Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Early parenthood (maternal age 18 and under)	17 weeks	Dichotomous (yes/no)	N/A
Feeling fearful	30 weeks	Dichotomous (yes/no)	(8,9)
Nervousness or shakiness inside	30 weeks	Dichotomous (yes/no)	(8,9)
Feeling hopeless about the future	30 weeks	Dichotomous (yes/no)	(8,9)
Feeling blue	30 weeks	Dichotomous (yes/no)	(8,9)
Worrying too much about things	30 weeks	Dichotomous (yes/no)	(8,9)
Feeling everything is an effort	30 weeks	Dichotomous (yes/no)	(8,9)
Feeling tense or keyed up	30 weeks	Dichotomous (yes/no)	(8,9)
Suddenly scared for no reason	30 weeks	Dichotomous (yes/no)	(8,9)
Maternal substance use	17 weeks	Dichotomous (yes/no)	N/A

Interpersonal Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
> 3 children under 18 in household	17 weeks	Dichotomous (yes/no)	N/A
I have a close relationship with my spouse/partner [R]	17 weeks	Dichotomous (yes/no)	(10)
My partner and I have problems in our relationship	17 weeks	Dichotomous (yes/no)	(10)
I am very happy with our relationship [R]	17 weeks	Dichotomous (yes/no)	(10)
My partner is generally understanding [R]	17 weeks	Dichotomous (yes/no)	(10)
I often consider ending our relationship	17 weeks	Dichotomous (yes/no)	(10)
I am satisfied with my relationship with my partner [R]	17 weeks	Dichotomous (yes/no)	(10)
We frequently disagree on important decisions	17 weeks	Dichotomous (yes/no)	(10)
I have been lucky in my choice of a partner [R]	17 weeks	Dichotomous (yes/no)	(10)
We agree on how our child should be raised [R]	17 weeks	Dichotomous (yes/no)	(10)
I believe my partner is satisfied with our relationship [R]	17 weeks	Dichotomous (yes/no)	(10)
Adverse Events – Arguments with family or friends	30 weeks	Dichotomous (yes/no)	(1,2,3)
Adverse Events – Recent separation or divorce	30 weeks	Dichotomous (yes/no)	(1,2,3)
Social Support scale	17 weeks	Dichotomous (median split)	(11)
- Do you have anyone other than your husband/partner you can ask for advice in a difficult situation		Dichotomous (median split)	-
- How often do you meet or talk on the telephone with your family (other than your husband/partner and children) or close friends?			-
- Do you often feel lonely			-

Notes. [R]Item reverse coded

Table S2.1. Pearson correlations between stress domains and child internalizing and externalizing disorders

	Prenatal Contextual Stress	Prenatal Interpersonal Stress	Prenatal Life Stress	Prenatal Personal Stress	Depressive Symptoms, Age 8	Anxiety Symptoms, Age 8	Conduct Disorder Symptoms, Age 8	ADHD Symptoms, Age 8	ODD Symptoms, Age 8
Prenatal Contextual Stress	-	-	-	-	-	-	-	-	-
Prenatal Interpersonal Stress	0.17***	-	-	-	-	-	-	-	-
Prenatal Life Stress	0.15***	0.16**	-	-	-	-	-	-	-
Prenatal Personal Stress	0.25***	0.28***	0.27***	-	-	-	-	-	-
Depressive Symptoms, Age 8	.13***	.10***	.09***	.20***	-	-	-	-	-
Anxiety Symptoms, Age 8	.05***	.05***	.05***	.12***	.23***	-	-	-	-
Conduct Disorder Symptoms, Age 8	.07***	.07***	.03***	.08***	.35***	.03***	-	-	-
ADHD Symptoms, Age 8	.11***	.10***	.08***	.16***	.49***	.10***	.41***	-	-
ODD Symptoms, Age 8	.08***	.08***	.04***	.14***	.50***	.16***	.52***	.53***	-

Note. ADHD = attention-deficit hyperactivity disorder, ODD = oppositional defiant disorder. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

Table S2.2. Comparison between included and excluded mothers on study variables

	Included (n = 15,963)		Excluded (n = 94,158)		
Characteristic	**n**	**Mean (SD) or %**	**n**	**Mean ± SD or %**	**p-value[a]**
Maternal age	15,963	30.48 ± 4.37	86,180	29.63 (4.63)	< .0001
Parity					
0	8,080	50.62	37,732	40.07	< .0001
1+	7,753	48.57	46,408	49.29	
Missing	130	0.81	10,018	10.64	
Marital status					
Married	7,722	48.37	41,325	43.89	< .0001
Cohabiting	7,820	48.99	41,346	43.91	
Single	354	2.22	3,059	3.25	
Missing	67	0.42	8,428	8.95	
Maternal education					
> High school	11,960	74.92	50,163	53.28	< .0001
High school and below	3,306	20.71	31,475	33.43	
Missing	697	4.37	12,520	13.30	
Paternal education					
> High school	9,076	56.86	37,936	40.29	< .0001
High school and below	5,668	35.51	40,174	42.67	
Missing	1,219	7.64	16,048	17.04	
Smoking					
None	15,025	94.12	66,900	71.05	< .0001
Sometimes	250	1.57	2,567	2.72	
Daily	312	1.95	5,313	5.64	
Missing	376	2.36	19,378	20.58	
Alcohol use					
None	12,836	80.41	62,089	65.94	< .0001
1-3 drinks per month	1,257	7.87	9.389	9.97	
1+ drinks per week	50	0.31	464	0.49	
Missing	1,820	11.40	22,216	23.59	

Prenatal stress (mean scores)					
Life stress	15,222	.11 (.11)	66,874	.12 (.11)	< .001
Contextual stress	14,005	.17 (.17)	61,361	.21 (.19)	< .001
Personal stress	15,015	.16 (.19)	66,587	.18 (.20)	< .001
Interpersonal stress	14,828	.04 (.09)	67,481	.05 (.10)	< .001
Child mental health, age 5 (mean scores)					
Internalizing symptoms	15,732	1.21 (.25)	25,227	1.22 (.26)	.046
Externalizing symptoms	15,642	1.30 (.28)	24,845	1.32 (.29)	< .001

Note. [a]Differences between included and excluded groups examined using *t*-tests for continuous variables, and χ^2 tests for categorical variables.

Table S2.3. Models of interactions between prenatal maternal stress and parenting behaviours at age 5 and symptoms of internalizing disorders at age 8 after additional adjustment (N = 15,963)

	Symptoms of Depression		Symptoms of Anxiety	
	b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Positive parenting model				
Prenatal maternal stress	37.575 (10.821)**	.547 (.244, .850)	11.366 (4.215)**	.326 (.091, .561)
Positive parenting	-.413 (.043)***	-.075 (-.091, -.060)	-.075 (.022)***	-.027 (-.042, -.011)
Prenatal maternal stress x Positive parenting	3.957 (2.339)	-.025 (-.054, .004)	-1.181 (.912)	-.015 (-.037, .008)
Inconsistent discipline model				
Prenatal maternal stress	7.041 (3.530)*	.102 (.001, .202)	3.422 (1.494)*	.098 (.015, .181)
Inconsistent discipline	.367 (.031)***	.094 (.079, .109)	.049 (.016)**	.025 (.009, .040)
Prenatal maternal stress x Inconsistent discipline	6.030 (1.820)**	.053 (.023, .083)	1.174 (.691)	.020 (-.003, .044)
Positive parental involvement model				
Prenatal maternal stress	37.032 (11.282)**	.538 (.223, .853)	10.826 (4.977)*	.309 (.033, .585)
Positive parental involvement	-.470 (.050)***	-.071 (-.087, -.056)	-.108 (.026)***	-.032 (-.048, -.017)
Prenatal maternal stress x Positive parental involvement	-3.931 (2.506)	-.021 (-.047, .005)	-1.089 (1.116)	-.011 (-.034, .011)

Note. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$. β = standardized regression coefficient, CI = confidence interval. Symptoms of depression and anxiety were included together in models. Models were adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, parity, sex, stressful life events from birth to age 5, and maternal depression at age 5.

Table S2.4. Models of interactions between prenatal maternal stress and parenting behaviours at age 5 and symptoms of internalizing disorders at age 8 after additional adjustment (males, *n* = 8,083)

	Symptoms of Attention-Deficit Hyperactivity Disorder		Symptoms of Conduct Disorder		Symptoms of Oppositional Defiant Disorder	
	b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Positive parenting model						
Prenatal maternal stress	43.065 (35.134)	.212 (-.127, .551)	20.560 (8.555)**	.446 (.096, .796)	28.619 (14.260)*	.326 (.008, .644)
Positive parenting	-1.392 (.192)***	-.082 (-.104, -.059)	-.418 (.044)***	-.108 (-.130, -.085)	-.751 (.081)***	-.102 (-.123, -.080)
Prenatal maternal stress x Positive parenting	-.303 (7.729)	-.001 (-.033, .032)	-3.242 (1.753)	-.031 (-.064, .002)	-2.679 (3.140)	-.013 (-.044, .017)
Inconsistent discipline model						
Prenatal maternal stress	22.484 (12.433)	.111 (-.009, .231)	-1.726 (2.561)	-.037 (-.146, .071)	.558 (5.124)	.006 (-.108, .121)
Inconsistent discipline	1.601 (.136)***	.131 (.110, .153)	.355 (.030)***	.128 (.108, .149)	.895 (.059)***	.170 (.149, .192)
Prenatal maternal stress x Inconsistent discipline	8.706 (5.856)	.026 (-.008, .061)	3.553 (1.344)**	.047 (.013, .082)	7.366 (2.596)**	.052 (.017, .086)
Positive parental involvement model						
Prenatal maternal stress	68.085 (46.379)	.335 (-.110, .780)	15.635 (10.723)	.339 (-.118, .796)	13.272 (17.277)	.151 (-.234, .536)
Positive parental involvement	-2.634 (.237)***	-.129 (-.152, -.106)	-.622 (.053)***	-.134 (-.157, -.112)	-1.112 (.099)***	-.125 (-.147, -.103)
Prenatal maternal stress x Positive parental involvement	-6.023 (10.285)	-.011 (-.047, .025)	-2.265 (2.357)	-.018 (-.055, .019)	.768 (3.904)	.003 (-.029, .035)

Note. *$p < .05$, **$p < .01$, ***$p < .001$. β = standardized regression coefficient, CI = confidence interval. Symptoms of depression and anxiety were included together in models. Models were adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, parity, stressful life events from birth to age 5, and maternal depression at age 5.

Table S2.5. Models of interactions between prenatal maternal stress and parenting behaviours at age 5 and symptoms of internalizing disorders at age 8 after additional adjustment (females, *n* = 7,754)

	Symptoms of Attention-Deficit Hyperactivity Disorder		Symptoms of Conduct Disorder		Symptoms of Oppositional Defiant Disorder	
	b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Positive parenting model						
Prenatal maternal stress	44.164 (37.634)	.253 (-.168, .674)	14.372 (8.999)	.462 (-.105, 1.028)	19.982 (15.451)	.235 (-.123, .593)
Positive parenting	-1.303 (.157)***	-.092 (-.114, -.070)	-.248 (.029)***	-.099 (-.121, -.077)	-.786 (.077)***	-.115 (-.137, -.093)
Prenatal maternal stress x Positive parenting	-.882 (8.222)	-.004 (-.038, .029)	-2.436 (1.850)	-.034 (-.084, .017)	-.853 (3.370)	-.004 (-.038, .029)
Inconsistent discipline model						
Prenatal maternal stress	23.697 (13.674)	.132 (-.018, .283)	-2.273 (2.886)	-.071 (-.248, .106)	6.656 (5.924)	.077 (-.057, .210)
Inconsistent discipline	1.302 (.116)***	.129 (.107, .152)	.189 (.020)***	.105 (.083, .126)	.861 (.056)***	.176 (.154, .199)
Prenatal maternal stress x Inconsistent discipline	6.893 (6.631)	.023 (-.020, .066)	2.533 (1.656)	.048 (-.013, .110)	3.786 (2.886)	.027 (-.013, .066)
Positive parental involvement model						
Prenatal maternal stress	152.146 (44.718)**	.860 (.365, 1.354)	14.729 (12.442)	.469 (-.312, 1.251)	32.211 (18.795)	.375 (-.057, .806)
Positive parental involvement	-2.105 (.182)***	-.125 (-.146, -.103)	-.335 (.033)***	-.112 (-.133, -.091)	-1.079 (.091)***	-.132 (-.153, -.110)
Prenatal maternal stress x Positive parental involvement	-25.270 (9.822)*	-.052 (-.091, -.012)	-2.627 (2.650)	-.030 (-.091, .030)	-3.693 (4.172)	-.016 (-.050, .019)

Note. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$. β = standardized regression coefficient, CI = confidence interval. Symptoms of depression and anxiety were included together in models. Models were adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, parity, stressful life events from birth to age 5, and maternal depression at age 5.

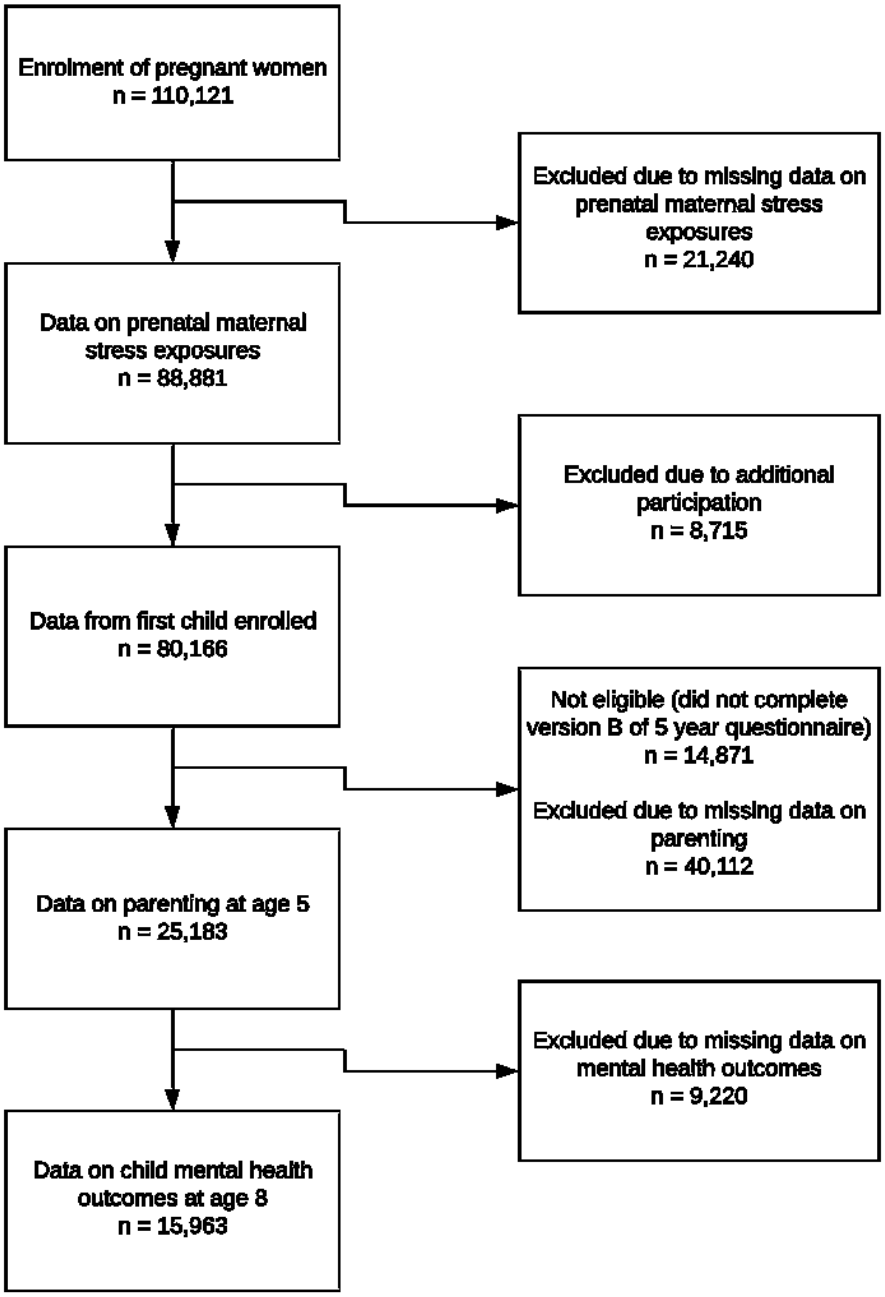


Figure S2.1. Flow chart of inclusion and exclusion criteria for participants included in complete MoBa cohort to sample included in current analysis

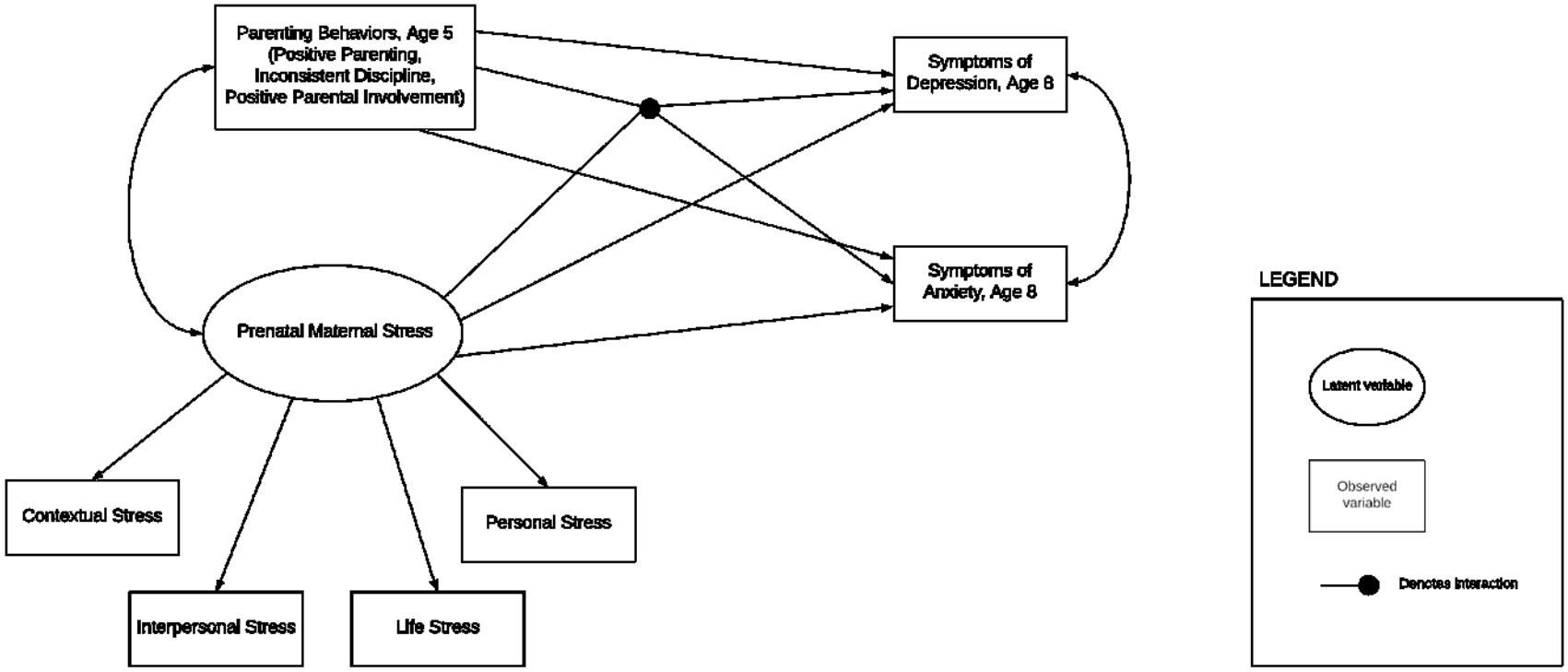


Figure S2.2. Conceptual path diagram of latent structural equations approach examining main effects and interaction effect between prenatal maternal stress and parenting behaviours on child internalizing symptoms (covariates not included, analyses stratified by sex)

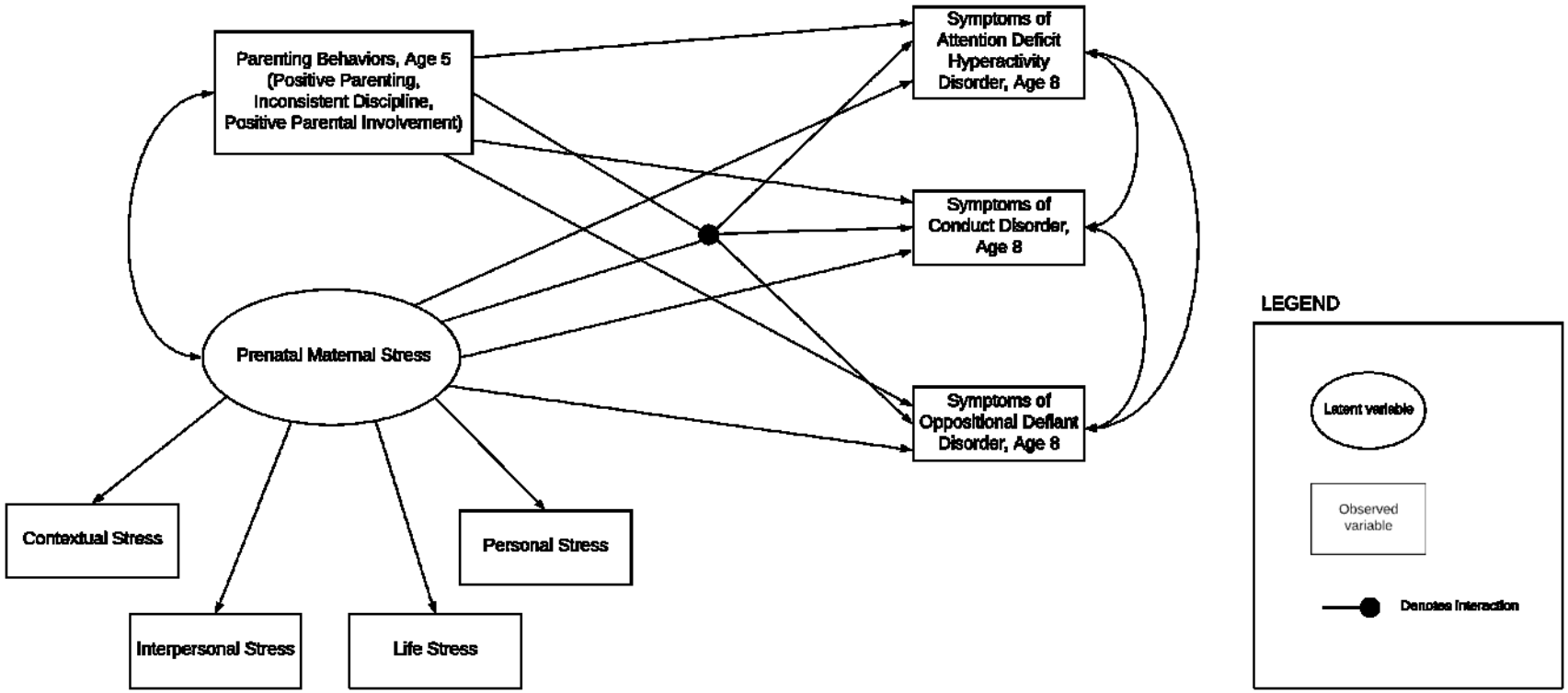


Figure S2.3. Conceptual path diagram of latent structural equations approach examining main effects and interaction effect between prenatal maternal stress and parenting behaviours on child externalizing symptoms (covariates not included, analyses stratified by sex)

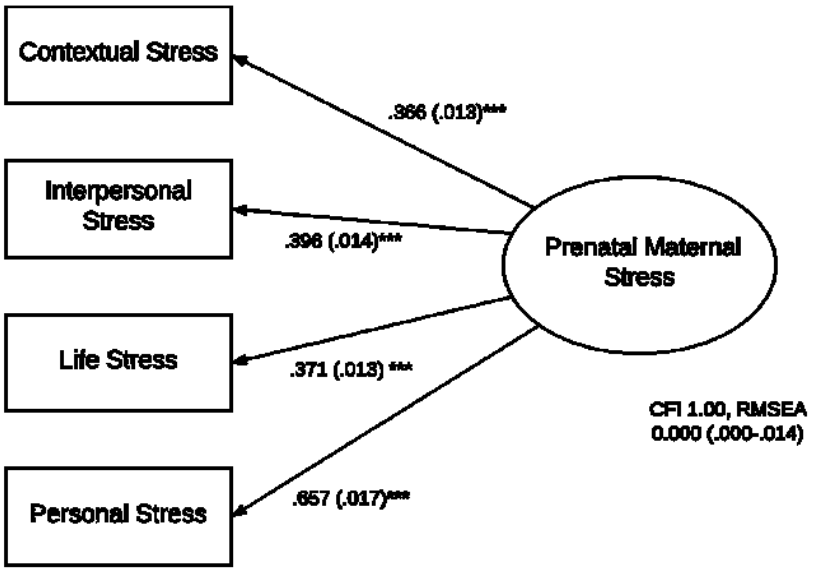


Figure S2.4. Path diagram of prenatal maternal stress latent variable and indicator variables with associated factor loadings. $^{***}p < .001$.

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Chapter 3

Positive maternal mental health attenuates the associations between prenatal stress and children's internalizing and externalizing symptoms

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The article presented in this chapter is under peer review at *European Child & Adolescent Psychiatry*. All tables and figures are numbered with two digits (chapter number followed by table or figure number). Supplementary materials are included as appendices at the end of this chapter, with tables and figures denoted with an "S" followed by two digits (chapter number followed by table or figure number).

Article preface: The aims of this study were to examine the associations between prenatal maternal stress, positive maternal mental health and children's internalizing and externalizing symptoms, and to ascertain whether indicators of positive maternal mental health moderated the associations between prenatal stress and children's internalizing and externalizing symptoms..

Contribution statement: I am the first author on this article. I designed the study and its objectives, with guidance from my co-authors. I conducted all study analyses, prepared the first draft of the manuscript, and submitted the manuscript for publication.

ABSTRACT

Background: Positive maternal mental health can improve perceptions of stressful situations and promote the use of adaptive coping strategies. However, few studies have examined how positive maternal mental health affects children's development. The aims of this study were to examine the associations between positive maternal mental health and children's internalizing and externalizing symptoms, and to ascertain whether positive maternal mental health moderated the associations between prenatal stress and children's internalizing and externalizing symptoms.

Methods: This study is based on the Norwegian Mother, Father, and Child Cohort Study (MoBa), and comprised 36,584 mother-child dyads. Prenatal stress was assessed using 41 self-reported items measured during pregnancy. Positive maternal mental health (self-efficacy, self-esteem, and enjoyment) was assessed by maternal report during pregnancy and postpartum. Child internalizing and externalizing symptoms were assessed by maternal report at age 5. Structural equation modeling was used for analysis.

Results: Maternal self-efficacy, self-esteem, and enjoyment were negatively associated with internalizing and externalizing symptoms in males and females. The association between prenatal stress and internalizing symptoms in males was stronger at low than at high levels of maternal self-esteem and enjoyment, whereas for females, the association was stronger at low than at high levels of maternal self-esteem and self-efficacy.

Conclusions: This study provides evidence of associations between positive maternal mental health and children's mental health, and suggests that higher positive maternal mental health may buffer against the impacts of prenatal stress. Positive maternal mental health may represent an important intervention target to improve maternal-child wellbeing and foster intergenerational resilience.

Keywords: stress, depression, mental health, behavior problems, epidemiology

INTRODUCTION

Distress and psychopathology are common among expecting and new mothers – for example, up to 20% of women report symptoms of depression in the prenatal and postnatal periods (1,2), and up to 60% report experiencing at least one stressful life event during pregnancy (3,4). In turn, it is well-established that maternal distress and mental health problems adversely impact children's development (5–7). However, many women report high levels of positive mental health during the prenatal and postnatal periods, including high self-rated mental health and high life satisfaction (8,9). Though inversely associated, it is possible to experience concurrently high levels of both positive mental health and distress or psychopathology (10), but few studies have examined associations between indicators of positive maternal mental health and children's development.

Positive mental health is typically viewed from hedonic and eudaimonic perspectives, which are related but have distinct psychosocial and biological correlates (11,12). For example, the hedonic perspective highlights the importance of pleasure, comfort, and positive mood in promoting happiness and wellbeing. By comparison, the eudaimonic perspective prioritizes meaning and self-actualization through promoting traits such as autonomy, self-esteem, engagement, and self-efficacy (13,14); these eudaimonic traits are strongly correlated with resilience (15). During the perinatal period, both hedonic and eudaimonic indicators of positive mental health can influence how women are affected by and cope with adversity. For example, women who report high levels of optimism during pregnancy report lower levels of depression and distress (16–18), and higher levels of mastery and self-esteem (18). Positive affect and optimism are positively associated with improved stress management and adaptive coping strategies and are inversely

associated with the use of avoidant coping strategies during pregnancy (19,20). In turn, positive stress appraisals and coping strategies can reduce levels of maternal distress and improve maternal wellbeing (21).

Given that higher positive maternal mental health can improve perceptions of stressful situations and promote the use of adaptive coping strategies, this implies that even in the context of prenatal distress and psychopathology it may be beneficial to target attributes of positive mental health in order to improve maternal and child health outcomes. Research suggests that positive mental health may buffer against the negative effects of prenatal distress (18,22). The potential buffering role of positive mental health is further supported by research which suggests that eudaimonic factors, such as self-esteem and self-efficacy, are associated with improved parenting behaviours, which can positively impact children's development (23). Hedonic factors including enjoyment and positive affect have also been linked to improvements in children's socio-emotional development among children (24). However, we are aware of only one small study that has examined the potential moderating role of positive maternal mental health on the relation between prenatal maternal distress and children's development. Findings from this study reported that infants of prenatally stressed mothers who reported higher self-efficacy during pregnancy cried less than the infants of prenatally stressed mothers who reported low levels of self-efficacy (25).

There is a need for research that examines whether indicators of positive maternal mental health are associated with children's mental health and development, and whether they can attenuate the associations between prenatal stress and adverse children's outcomes beyond infancy. Using a

large longitudinal sample of mothers and their children, we first examined the independent associations between prenatal maternal stress, three indicators of positive maternal mental health (self-efficacy, self-esteem, and enjoyment) measured during pregnancy and postnatally, and children's internalizing and externalizing symptoms at five years of age. We hypothesized that prenatal maternal stress and positive maternal mental health would be positively and negatively associated with children's internalizing and externalizing symptoms at five years of age, respectively. We then examined whether positive maternal mental health moderated the associations between prenatal maternal stress and children's internalizing and externalizing symptoms; we hypothesized that the associations would be attenuated at high levels of positive maternal mental health, and strengthened at lower levels of positive maternal mental health.

METHODS

Data and participants

This study used data from the Norwegian Mother, Father and Child Cohort Study (MoBa), a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from across Norway between 1999 and 2008, and women consented to participation in 41% of pregnancies. The cohort includes over 114,500 children, 95,200 mothers and 75,200 fathers (26). Maternal questionnaire response rates at 17 weeks' gestation, 30 weeks' gestation, 18 months, and 5 years after birth were 95.1%, 91.4%, 87.0% and 54.0%, respectively (26,27). The current study was based on version 12 of the quality-assured data files released for research in 2020. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional

Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations governed by Norwegian Health Registry Act. The study sample included 36,584 mother-child dyads with complete data on key study variables (Figure 3.1). This study was approved by The Regional Committees for Medical and Health Research Ethics (#2013/2061).

Measures

Prenatal maternal stress. A broad measure of prenatal maternal stress was constructed based on methods developed by Cecil and colleagues (28), which have also been adapted for use in other prospective birth cohort studies (29,30). The prenatal stress measure comprised 41 items collected by maternal questionnaire at 17 and 30 weeks' gestation that spanned four stress domains: life stress, contextual stress, personal stress, and interpersonal stress (see Appendix). Items from each domain were summed and divided by the total number of items to generate domain-specific mean scores. Next, scores from the four stress domains were used as indicators in a confirmatory factor analysis to extract a latent prenatal maternal stress factor that demonstrated excellent model fit according to fit indices (see Figure S3.1); development of the prenatal maternal stress measure included respondents who had complete data on at least two out of four stress domains. Relative to the original measure (28), we excluded maternal education from the personal stress domain given that prior research suggests maternal education may impact developmental outcomes through mechanisms independent of prenatal stress (30). We also added items from an occupational stress measure to the contextual stress domain, and removed maternal hospitalizations during pregnancy from the life stress domain to improve measurement model fit.

Positive maternal mental health. Three positive mental health measures encompassing both hedonic and eudaimonic perspectives were examined during pregnancy: self-efficacy (eudaimonic perspective), self-esteem (eudaimonic perspective), and enjoyment (hedonic perspective). Self-efficacy was measured at 30 weeks' gestation using a short-form, 5-item version of the General Self-Efficacy Scale (GSES) (31,32), which was designed to examine the belief in one's ability to cope with challenging life demands. Items were summed to generate total self-efficacy scores, with higher scores representing greater self-efficacy. The General Self-Efficacy Scale demonstrated good internal consistency in the study sample (Cronbach's alpha = 0.84). Self-esteem and enjoyment were examined at 30 weeks' gestation and at 6 months, 18 months, and 36 months postpartum using a short-form version of the Rosenberg Self-Esteem scale (33) and the enjoyment subscale of the Differential Enjoyment Scale (34). In line with scoring recommendations (33), total scores were generated for maternal self-esteem at each assessment point by summing across items, and mean scores for maternal enjoyment were generated by calculating total scores and dividing by the number of items (34). Given that the same self-esteem and enjoyment items were administered at all four assessment points of interest and were highly correlated, latent maternal self-esteem and enjoyment factors were generated by combining scores for each measure across all assessment points using confirmatory factor analysis. Generation of factor scores required complete data on maternal self-esteem and enjoyment at 30 weeks' gestation, as well as complete data on these measures during at least one postnatal assessment point. All scales used to measure positive maternal mental health in the current study have demonstrated high internal consistency (34–36), and the short-form versions

of the General Self Efficacy Scale and Rosenberg Self-Esteem Scale used in the current study correlate strongly with scores from the full versions (32).

Child internalizing and externalizing symptoms. Children's internalizing and externalizing symptoms at 5 years of age were examined using short-form versions of the Child Behavior Checklist (CBCL), a standardized, adult-reported scale commonly used to assess a broad range of neuropsychiatric outcomes in children (37). The short-form versions for the MoBa cohort were constructed by a team clinical and developmental psychologists. We used five items to assess internalizing symptoms and eight items to assess externalizing symptoms. Items were rated on a 3-point scale and summed to create total scores for internalizing and externalizing symptoms. The CBCL has demonstrated good predictive validity in distinguishing between children with and without psychiatric disorders in a Norwegian sample (38), and prior research demonstrates that the short form version of the externalizing scale used in the MoBa cohort is highly correlated with the full externalizing scale of the CBCL ($r = 0.92$), using data from the NICHD Study of Early Child Care and Youth Development (39). Factor analysis of the MoBa CBCL items load clearly onto two distinct internalizing and externalizing latent constructs (40).

Covariates. Child sex (male or female) was examined as a potential moderating variable given recommendations to examine sex-stratified associations where possible in the existing fetal programming literature (41). In addition, a number of potential confounding variables were selected a priori based on theoretical grounds and were adjusted for in analyses. These included maternal and paternal educational attainment (postsecondary and above; and high school and below); smoking during the first trimester of pregnancy (yes; no); alcohol consumption during

the first trimester of pregnancy (never; 1-3 times per month;1 time per week or more); and parity (no prior births; at least one prior birth). Cumulative stressful life events from birth to 5 years of age were adjusted for in sensitivity analyses.

Statistical Analyses

Examination of respondent characteristics was performed using Stata version 15 (StataCorp, College Station, TX); all remaining analyses were performed using MPlus version 8 (Muthén & Muthén, Los Angeles, CA). All models estimated in MPlus used full information maximum likelihood estimation with robust standard errors (MLR) to account for potential non-normality of data and missing values on covariates, a method which is valid under the assumption that missing data were missing at random (42).

We used structural equation modeling to examine the associations between prenatal maternal stress, positive maternal mental health measures, and child internalizing and externalizing symptoms; separate models were run for each positive mental health measure. Prenatal maternal stress, maternal self-esteem, and maternal enjoyment were standardized by scaling their variances to 1; thus, standardized parameter estimates (β) reported represent changes in child internalizing and externalizing symptoms per one standard deviation increase in these latent factors, and were used to ascertain effect size. Unstandardized parameter estimates are also reported (b), and represent changes in child internalizing or externalizing symptoms per one unit increase in predictor variables. To ascertain potential sex differences, multiple group analyses were conducted to test the equality of coefficients between males and females on associations of

interest (i.e., associations between prenatal maternal stress, positive maternal mental health, and child internalizing and externalizing symptoms). Likelihood ratio tests, with statistical significance set at a threshold of $p < .05$, were used to indicate whether or not parameter estimates significantly differed by sex; subsequent analyses were stratified by sex when likelihood-ratio tests were significant. The comparative fit index (CFI) and the root mean square error of approximation (RMSEA), with threshold values of ≥ 0.90 or ≤ 0.06 were used to indicate good model fit (43,44).

To test whether maternal self-efficacy, self-esteem, and enjoyment moderated the associations between prenatal maternal stress and child internalizing and externalizing symptoms, interaction terms were created between prenatal maternal stress and each positive mental health measure in separate models using the *XWITH* procedure in MPlus (45). Moderation was deemed to be present if interaction terms were significantly associated with child internalizing or externalizing symptoms, using a threshold of $p < .05$. The Johnson-Neyman technique was then used to visually examine statistically significant interactions (46,47). This involved plotting the standardized effect (slope) of latent prenatal maternal stress on child internalizing or externalizing symptoms, as well as their 95% confidence intervals (CI) on the y-axis, against the range of values of the positive mental health moderating variables on the x-axis, with maternal enjoyment and self-esteem plotted using the mean (zero) ± three standard deviations, and maternal self-efficacy plotted using the complete range of values. Johnson-Neyman plots indicate at which levels of the moderating variable the effect of interest is statistically significant (i.e., where the 95% CI of the effect does not cross zero (47), and provide a visual representation of the strength of the effect across values of the moderating variable. Fit of moderation models

was assessed using a log-likelihood difference test, as traditional fit indices (e.g., CFI, RMSEA) are not generated for moderation models using the *XWITH* procedure in MPlus. This test involved calculating the difference in -2*log likelihood values between nested (i.e., main effects) models and models containing interaction terms to generate a difference value that is approximately distributed as $\chi 2$, with degrees of freedom calculated as the difference in free parameters estimated between models. Significant log-likelihood difference tests ($p < .05$) indicated that models with interactions had better fit than the models without. Additional analyses included testing the moderating role of a comprehensive positive mental health measure (i.e., using a second-order latent variable including maternal self-efficacy, latent self-esteem, and latent enjoyment), and adjusting primary analyses for all maternal stressful events occurring from birth to 5 years of age.

RESULTS

Descriptive characteristics of the study sample are provided in Table 3.1. Almost all mothers included in the sample were married or cohabiting, and the majority had some level of post-secondary education. Mean age of mothers in the sample was 30.2 years ($SD = 4.36$). Approximately 4.8% of women reported smoking (sometimes or daily), and 9.8% of women reported alcohol use (1 drink per month or greater) at 17 weeks' gestation. 50.8% of the children in the study sample were males. Correlations between prenatal maternal stress, maternal self-esteem, maternal self-efficacy, maternal enjoyment, and child internalizing and externalizing symptoms (ranging between -0.43 and 0.58) are provided in Table S3.1. Correlations between all items included in positive mental health measures (ranging between 0.27 and 0.65) are provided

in Table S3.2. Given significant findings from multiple group analyses (p's < .05), all structural equation model analyses were stratified by sex (results not shown).

Across all models, higher prenatal maternal stress was associated with higher internalizing symptoms and higher externalizing symptoms in males and females prior to and after adjustment for covariates (unadjusted models not shown; see Tables 2 to 4). Higher maternal self-efficacy was associated with lower internalizing symptoms and lower externalizing symptoms in females, but not males. Both higher maternal self-esteem and higher maternal enjoyment, as well as a comprehensive measure of positive mental health involving all indicators (see Table S3), were associated with lower internalizing symptoms in females, and lower externalizing symptoms in both males and females. Model fit across all models was good.

The interaction between prenatal maternal stress and prenatal maternal self-efficacy was small but statistically significant for female internalizing symptoms (β = -.038, 95% CI = -.060, -.016); remaining interaction terms were not statistically significant. The log-likelihood test for this model was statistically significant ($\chi^2(8) = 960.880$, $p < .001$), indicating that the model with the interaction between prenatal maternal stress and prenatal self-efficacy had better fit than the main effects model. Figure 2A demonstrates that the association between prenatal maternal stress and internalizing symptoms in females was strongest at lower levels of maternal self-efficacy, and attenuated at higher levels of self-efficacy. Interactions between prenatal maternal stress and maternal self-esteem were small but statistically significant for internalizing symptoms in males (β = -.026, 95% CI = -.045, -.007) and females (β = -.017, 95% CI = -.034, .000); remaining interactions were not statistically significant. The log-likelihood tests for male ($\chi^2(5) = 330.793$,

$p < .001$) and female ($\chi^2(5) = 1294.042$, $p < .001$) models were significant, indicating that models with interactions between prenatal maternal stress and self-esteem had better fit than the models without. Figures 2B and 2C demonstrates that the associations between prenatal maternal stress and internalizing symptoms in males and females were stronger at lower levels of maternal self-esteem, and attenuated at higher levels of self-esteem. The interaction between prenatal maternal stress and maternal enjoyment was small but statistically significant for internalizing symptoms in males (β = -.023, 95% CI = -.046, -.001); the log-likelihood test for this model was also significant ($\chi^2(5) = 1635.908$, $p < .001$), indicating that the model with the interaction between prenatal maternal stress and maternal enjoyment had better fit than the model without. Remaining interaction terms that were tested were not statistically significant. Figure 2D demonstrates that the association between prenatal maternal stress and internalizing symptoms in males was strongest at lower levels of maternal enjoyment, and attenuated at higher levels of enjoyment.

Additional analyses including interactions between prenatal maternal stress and a comprehensive positive mental health measure were statistically significant for internalizing symptoms in males (β = -.029, 95% CI = -.049, -.009) and females (β = -.021, 95% CI = -.038, -.004), but not for externalizing symptoms. Findings across models remained statistically significant after additional adjustment for cumulative postnatal stressful events (Tables S4 to S6).

DISCUSSION

Findings from this study of over 36,000 mothers and their children suggest that prenatal maternal stress and indicators of positive maternal mental health are associated with children's

internalizing and externalizing symptoms at 5 years of age. Our findings further suggest that higher levels of positive maternal mental health during pregnancy may buffer the associations between prenatal maternal stress and child internalizing and externalizing symptoms Specifically, our findings suggest that the association between prenatal maternal stress and internalizing symptoms in males is stronger at low than at high levels of maternal self-esteem and maternal enjoyment. Findings also suggest that the association between prenatal maternal stress and internalizing symptoms in females may be stronger at low than at high levels of maternal self-esteem and maternal self-efficacy. These findings held after adjustment for postnatal maternal adversity.

The examined positive mental health indicators have been directly and indirectly associated with children's development. For example, similar to enjoyment, positive maternal affect has been associated with positive socioemotional and cognitive outcomes in children, as well as the development of children's positive affect (48,49). Broadly, research suggests that higher positive mental health lowers risk of onset and reduces symptom severity of mental health disorders (50,51). Positive maternal affect and self-efficacy have been associated with positive parenting behaviors (52,53), which, in turn, can protect against the development of mental health problems in children and promote their positive mental health (54–56). Maternal self-esteem has also been associated with improved mother-child relationships (57), and with improved self-esteem in children (58). Our findings contribute to this growing evidence base by suggesting that independent of prenatal maternal stress, higher maternal self-efficacy, self-esteem, and enjoyment are associated with lower internalizing and externalizing symptoms in children at 5 years of age. Given that a limited number of studies have directly examined the associations

between maternal self-efficacy, self-esteem, and enjoyment on children's outcomes, findings from this study contribute to this literature. Based on existing research, our findings may suggest that positive maternal mental health can play a protective role on the development of children's internalizing and externalizing symptoms through potential mechanisms including the promotion of positive parenting behaviors and by directly improving children's positive mental health and developmental outcomes.

Our findings highlight the potential for both hedonic and eudaimonic dimensions of positive maternal mental health to reduce the adverse effects of prenatal distress on children's development. In line with our findings regarding the potential protective role of positive maternal mental health following stress exposure, a longitudinal study by McDonald and colleagues found that the association between cumulative prenatal maternal stress and preterm birth was only significant for mothers who reported low levels of dispositional optimism (59). Longitudinal research also suggests that maternal self-efficacy reduces the impacts of prenatal maternal stress on infant crying behavior (25); persistent infant crying has been associated with negative mother-child interactions (60), and greater risk of children's behavioral and psychological difficulties later in childhood (61). To our knowledge, no other studies have examined the moderating role of positive maternal mental health on the associations between prenatal maternal stress and children's internalizing and externalizing symptoms. It is important to note that in the current study, moderation analyses were significant for internalizing, but not externalizing symptoms; this contrasts with other studies that have demonstrated associations between children's self-esteem and self-efficacy with both internalizing and externalizing symptoms during adolescence (62,63). Given that children in the current study were five years of age at outcome ascertainment,

these associations may benefit from further inquiry as children continue to develop through late childhood and adolescence. In addition, some sex differences were observed in moderation analyses; for example, maternal enjoyment buffered the association between prenatal maternal stress and boys' internalizing symptoms, whereas maternal self-efficacy buffered the association between prenatal maternal stress and girls' internalizing symptoms. In line with these findings, one study reported that male gender was negatively associated with mothers' parental self-efficacy, suggesting that mothers may be less likely to use positive parenting practices with boys than with girls (64); this may partially explain why interactions between prenatal maternal stress and maternal self-efficacy were significant for girls but not boys. In another study, mothers were more likely to encourage the expression of positive emotions in boys compared to girls (65), which may potentially address why maternal enjoyment moderated the association between prenatal maternal stress and boys', but not girls', internalizing symptoms. In all, coupling the current study's findings with the existing literature highlights the potential importance of higher positive maternal mental health in reducing the adverse effects of early stress exposure, but also emphasizes the need for additional inquiry into these associations throughout children's development.

Importantly, positive mental health may be modifiable (66,67), and research suggests that it is possible to develop personal strengths and resources (e.g., self-efficacy, mastery), cultivate a sense of meaning, and enhance positive feelings through positive psychological interventions (67). Meta-analyses of randomized controlled trials support the efficacy of psychological interventions in increasing subjective and psychological well-being and reducing symptoms of depression (67). Emerging research also supports the efficacy of positive psychological

interventions targeted at improving maternal mental health in the prenatal and postnatal periods. For example, interventions during pregnancy and after birth that integrate positive psychological components, including gratitude journaling and mindfulness, may reduce mothers' perceived stress and symptoms of depression and increase positive affect (68,69). Research further suggests that parenting interventions can increase levels of parental self-efficacy and positive affect (70). Higher parental self-efficacy has been associated with positive parenting behaviors including increased sensitivity, warmth, and responsiveness (71), which can protect against the development of children's mental health problems (54–56,71). Although research supporting the effects of these interventions on children's long-term mental health is scarce, this evidence highlights the importance of targeting the improvement of positive maternal mental health in promoting improved maternal wellbeing and positive parenting behaviors, and by extension, nurturing children's wellbeing.

These findings should be interpreted in consideration of several limitations. First, significant attrition occurred during the study follow-up period, which may have biased the reported associations. However, attrition analyses completed in the MoBa cohort suggest that participant attrition largely impacts prevalence estimates, and may not substantially bias exposure-outcome associations (72). Second, we did not examine other potentially important indicators of positive mental health. Although the measures included in our study encompass both hedonic and eudaimonic perspectives, other factors that span both perspectives (e.g., mastery, life satisfaction, and social wellbeing) would benefit from further inquiry given their limited exploration in the developmental literature. Third, over 99% of MoBa participants are White and most participants are of higher socioeconomic status; as a result, our findings may not generalize

to regions with greater socioeconomic or ethnic diversity, and further study of these associations in diverse samples is necessary. Fourth, our study measures were collected by maternal report, and reporting bias cannot be ruled out. However, to address this limitation, we adjusted for maternal adversity after birth, and findings remained largely unchanged. Fifth, since we did not correct for multiple comparisons, it is possible that some of the observed associations may be due to chance. Finally, we did not have data on paternal positive mental health or on genetic information, and thus could not examine how indicators of positive paternal mental health influence children's internalizing and externalizing symptoms, nor could we address potential genetic confounding (e.g., genetic factors may alter the impacts of prenatal maternal stress on the child (55), and subsequent risk towards poor mental health).

The current study has numerous strengths. The use of data from a large, prospective pregnancy cohort allowed for the adjustment of several confounding variables, and afforded sufficient statistical power to examine latent variable interactions and conduct sex-stratified analyses. The majority of measures included in the current study have been well-validated and extensively used in both psychiatric and epidemiological studies. Furthermore, in line with research suggesting that positive mental health demonstrates stability over time (73), repeated measurement of maternal enjoyment and self-esteem allowed for the construction of latent variables that examined these aspects of positive mental health from pregnancy up to three years postpartum. Finally, the prenatal maternal stress measure we used allowed for examination of a broad measure of stress that considers the shared variance across stress dimensions and further addresses concerns about variability of prenatal stress measurements highlighted in the extant literature (74).

CONCLUSIONS

This study suggests that higher maternal enjoyment, self-efficacy, and self-esteem are associated with lower internalizing and externalizing symptoms in children. Given the small interactions observed between prenatal maternal stress and positive mental health measures, findings also suggest that these aspects of positive maternal mental health may act as buffers in reducing some of the adverse effects of prenatal maternal stress on children's mental health outcomes. If replicated, these findings may have implications for future research and practice. Few studies have examined the impacts of positive maternal mental health on children's development, and few have directly examined the modifiability of positive maternal mental health through positive psychological and parenting interventions. Further integration of positive maternal mental health measures into the study of maternal mental health can contribute to a deeper understanding of children's development, and aid in the construction of effective interventions to improve maternal-child wellbeing and foster intergenerational resilience.

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Conflicts of Interest: None

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Table 3.1. Descriptive characteristics of sample at 17 weeks' gestation (N = 36,584)

Characteristic	Mean ± SD or n (%)
Maternal age	30.23 (4.36)
Parity	
0	17,845 (48.78)
1+	18,447 (50.42)
Missing	292 (0.80)
Marital status	
Married	18,059 (49.36)
Cohabiting	17,519 (47.89)
Single	861 (2.35)
Missing	145 (0.40)
Maternal education	
> High school	25,864 (70.70)
High school and below	9,066 (24.78)
Missing	1,654 (4.52)
Paternal education	
> High school	19.274 (52.68)
High school and below	14,384 (39.32)
Missing	2,926 (8.00)
Smoking	
None	34,005 (92.95)
Sometimes	659 (1.80)
Daily	1,087 (2.97)
Missing	833 (2.28)
Alcohol use	
None	28.753 (78.59)
1-3 drinks per month	3,437 (9.39)
1+ drinks per week	151 (0.41)
Missing	4,243 (11.60)
Child gender	
Male	18,596 (50.83)
Female	17,988 (49.17)

Note. SD = standard deviation

Table 3.2. Main effect and moderation models of associations between prenatal maternal stress, maternal self-efficacy, and internalizing and externalizing symptoms in males and females

		Males (n = 18,596)		Females (n = 17,988)	
		b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Internalizing symptoms	**Main effects model (unadjusted)**				
	Prenatal maternal stress	1.895 (.114)***	.251 (.229, .273)	1.675 (.107)***	.234 (.212, .256)
	Maternal self-efficacy	-.002 (.001)***	-.008 (-.012, -.003)	-.005 (.001)***	-.020 (-.025, -.015)
	Main effects model (adjusted)				
	Prenatal maternal stress	1.985 (.122)***	.270 (.245, .295)	1.765 (.115)***	.254 (.229, .279)
	Maternal self-efficacy	.001 (.001)	.016 (-.001, .032)	-.002 (.001)*	-.023 (-.040, -.007)
	Moderation model				
	Prenatal maternal stress	2.556 (.377)***	.347 (.250, .445)	2.994 (.420)***	.431 (.321, .540)
	Maternal self-efficacy	.001 (.001)*	.017 (.001, .033)	-.002 (.001)*	-.020 (-.036, -.004)
	Prenatal maternal stress x self-efficacy	-.041 (.025)	-.017 (-.037, .003)	-.087 (.027)**	-.038 (-.060, -.016)
Externalizing symptoms	**Main effects model (unadjusted)**				
	Prenatal maternal stress	1.916 (.116)***	.223 (.202, .245)	1.607 (.105)***	.215 (.193, .237)
	Maternal self-efficacy	-.004 (.001)**	-.015 (-.019, -.010)	-.005 (.001)***	-.020 (-.025, -.015)
	Main effects model (adjusted)				
	Prenatal maternal stress	1.812 (.121)***	.216 (.192, .240)	1.543 (.111)***	.213 (.188, .238)
	Maternal self-efficacy	-.001 (.001)	-.009 (-.026, .007)	-.002 (.001)**	-.027 (-.044, -.011)
	Moderation model				
	Prenatal maternal stress	1.678 (.387)***	.200 (.110, .291)	2.057 (.418)***	.283 (.174, .392)
	Maternal self-efficacy	-.001 (.001)	-.010 (-.026, .006)	-.002 (.001)**	-.026 (-.042, -.010)
	Prenatal maternal stress x self-efficacy	.012 (.026)	.003 (-.015, .022)	-.037 (.027)	-.015 (-.037, .006)
Model fit statistics		**CFI**	**RMSEA (95% CI)**	**CFI**	**RMSEA (95% CI)**
	Main effects model (adjusted)	.885	.046 (.044, .048)	.885	.045 (.042, .047)

Note. *$p < .05$, **$p < .01$, ***$p < .001$. b = unstandardized regression coefficient, SE = standard error, β = standardized regression coefficient, CI = confidence interval, CFI = comparative fit index, RMSEA = root mean square error of approximation. Models adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, and parity.

Table 3.3. Main effect and moderation models of associations between prenatal maternal stress, maternal self-esteem, and internalizing and externalizing symptoms in males and females

		Males (n = 18,596)		Females (n = 17,988)	
		b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Internalizing symptoms	**Main effects model (unadjusted)**				
	Prenatal maternal stress	1.859 (.138)***	.243 (.212, .273)	1.509 (.132)***	.205 (.174, .236)
	Maternal self-esteem	-.003 (.002)	-.020 (-.046, .006)	-.012 (.002)***	-.068 (-.094, -.042)
	Main effects model (adjusted)				
	Prenatal maternal stress	1.902 (.146)***	.257 (.223, .290)	1.549 (.138)***	.218 (.184, .253)
	Maternal self-esteem	-.002 (.002)	-.009 (-.035, .018)	-.010 (.002)***	-.058 (-.085, -.031)
	Moderation model				
	Prenatal maternal stress	1.825 (.143)***	.247 (.214, .280)	1.519 (.136)***	.214 (.181, .248)
	Maternal self-esteem	-.001 (.002)	-.006 (-.032, .020)	-.010 (.002)***	-.055 (-.082, -.028)
	Prenatal maternal stress x self-esteem	-.129 (.048)**	-.026 (-.045, -.007)	-.085 (.043)*	-.017 (-.034, .000)
Externalizing symptoms	**Main effects model (unadjusted)**				
	Prenatal maternal stress	1.570 (.142)***	.180 (.150, .210)	1.259 (.127)***	.164 (.133, .194)
	Maternal self-esteem	-.017 (.003)***	-.086 (-.111, -.060)	-.019 (.002)***	-.104 (-.129, .-.078)
	Main effects model (adjusted)				
	Prenatal maternal stress	1.420 (.147)***	.168 (.136, .200)	1.131 (.138)***	.153 (.120, .186)
	Maternal self-esteem	-.015 (.003)***	-.077 (-.103, -.051)	-.018 (.002)***	-.098 (-.125, -.072)
	Moderation model				
	Prenatal maternal stress	1.426 (.146)***	.169 (.137, .201)	1.115 (.131)***	.151 (.118, .183)
	Maternal self-esteem	-.015 (.003)***	-.077 (-.103, -.051)	-.018 (.002)***	-.097 (-.123, -.070)
	Prenatal maternal stress x self-esteem	-.004 (.047)	-.001 (-.017, .016)	-.052 (.049)	-.010 (-.029, .009)
Model fit statistics		**CFI**	**RMSEA (95% CI)**	**CFI**	**RMSEA (95% CI)**
	Main effects model (adjusted)	.968	.034 (.032, .035)	.967	.034 (.032, .035)

Note. *$p < .05$, **$p < .01$, ***$p < .001$. b = unstandardized regression coefficient, SE = standard error, β = standardized regression coefficient, CI = confidence interval, CFI = comparative fit index, RMSEA = root mean square error of approximation. Models adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, and parity.

Table 3.4. Main effect and moderation models of associations between prenatal maternal stress, maternal enjoyment, and internalizing and externalizing symptoms in males and females

		Males (n = 18,596)		Females (n = 17,988)	
		b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Internalizing symptoms	**Main effects model (unadjusted)**				
	Prenatal maternal stress	1.749 (.119)***	.259 (.230, .289)	1.465 (.112)***	.230 (.200, .259)
	Maternal enjoyment	.001 (.007)	.002 (-.022, .026)	-.021 (.007)**	-.039 (-.063, -.014)
	Main effects model (adjusted)				
	Prenatal maternal stress	1.753 (.127)***	.266 (.233, .298)	1.464 (.121)***	.235 (.202, .269)
	Maternal enjoyment	-.001 (.007)	-.001 (-.026, .024)	-.023 (.007)**	-.041 (-.067, -.015)
	Moderation model				
	Prenatal maternal stress	1.692 (.124)***	.256 (.224, .288)	1.430 (.119)***	.230 (.197, .263)
	Maternal enjoyment	.000 (.007)	-.001 (-.025, .024)	-.022 (.007)**	-.040 (-.065, -.014)
	Prenatal maternal stress x enjoyment	-.339 (.166)*	-.023 (-.046, -.001)	-.222 (.125)	-.016 (-.034, .001)
Externalizing symptoms	**Main effects model (unadjusted)**				
	Prenatal maternal stress	1.565 (.119)***	.204 (.176, .232)	1.290 (.109)***	.194 (.165, .223)
	Maternal enjoyment	-.040 (.008)***	-.061 (-.085, -.038)	-.042 (.007)***	-.073 (-.097, -.049)
	Main effects model (adjusted)				
	Prenatal maternal stress	1.348 (.128)***	.180 (.148, .211)	1.109 (.116)***	.171 (.138, .203)
	Maternal enjoyment	-.046 (.008)***	-.070 (-.095, -.046)	-.049 (.007)***	-.084 (-.109, -.059)
	Moderation model				
	Prenatal maternal stress	1.358 (.127)***	.180 (.149, .211)	1.102 (.114)***	.170 (.138, .202)
	Maternal enjoyment	-.046 (.008)***	-.071 (-.095, -.046)	-.048 (.007)***	-.084 (-.108, -.059)
	Prenatal maternal stress x enjoyment	.009 (.150)	.001 (-.017, .018)	-.064 (.130)	-.004 (-.022, .013)
Model fit statistics		**CFI**	**RMSEA (95% CI)**	**CFI**	**RMSEA (95% CI)**
	Main effects model (adjusted)	.957	.037 (.036, .039)	.957	.037 (.035, .039)

Note. *$p < .05$, **$p < .01$, ***$p < .001$. b = unstandardized regression coefficient, SE = standard error, β = standardized regression coefficient, CI = confidence interval, CFI = comparative fit index, RMSEA = root mean square error of approximation. Models adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, and parity

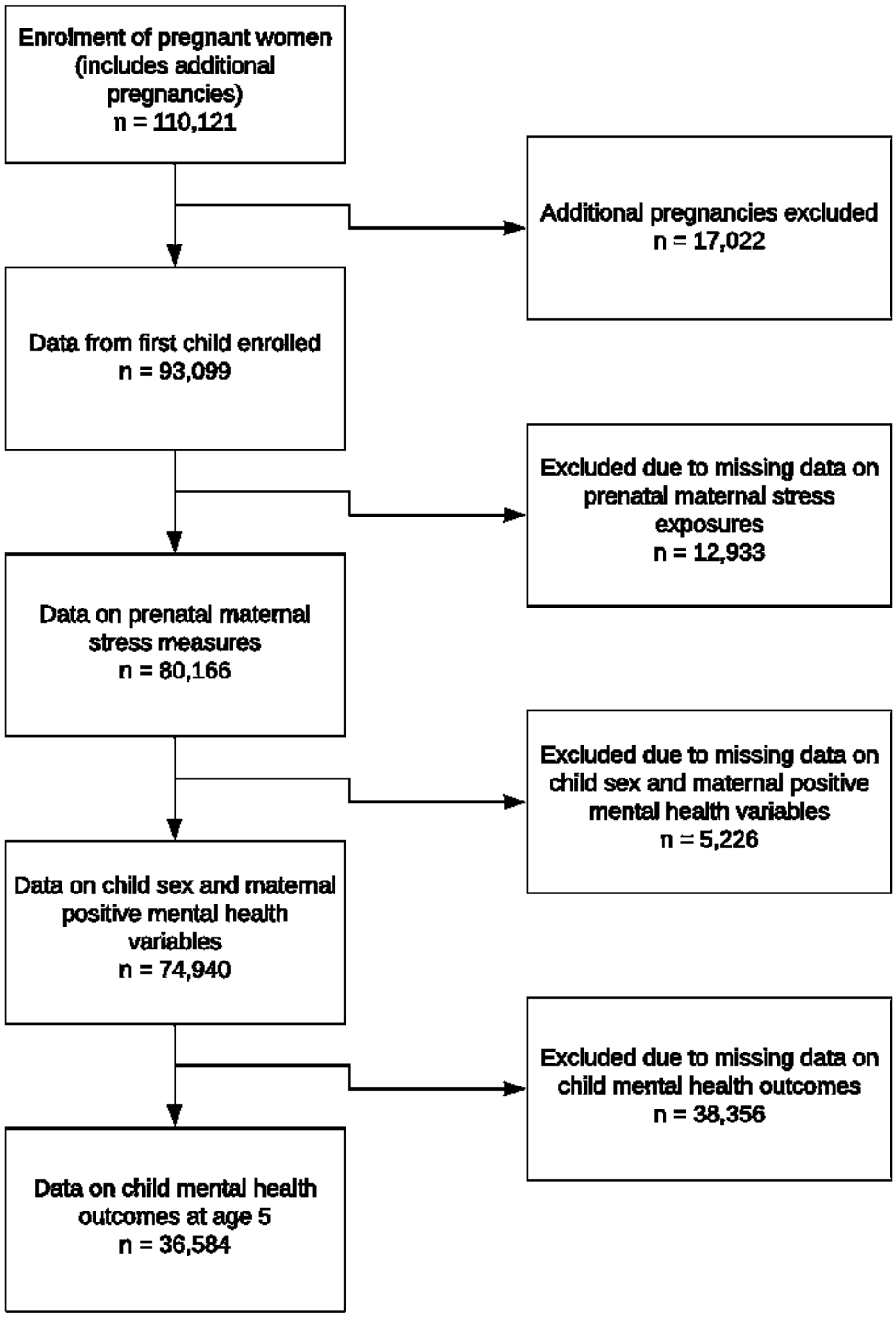

Figure 3.1. Participant selection flow-chart

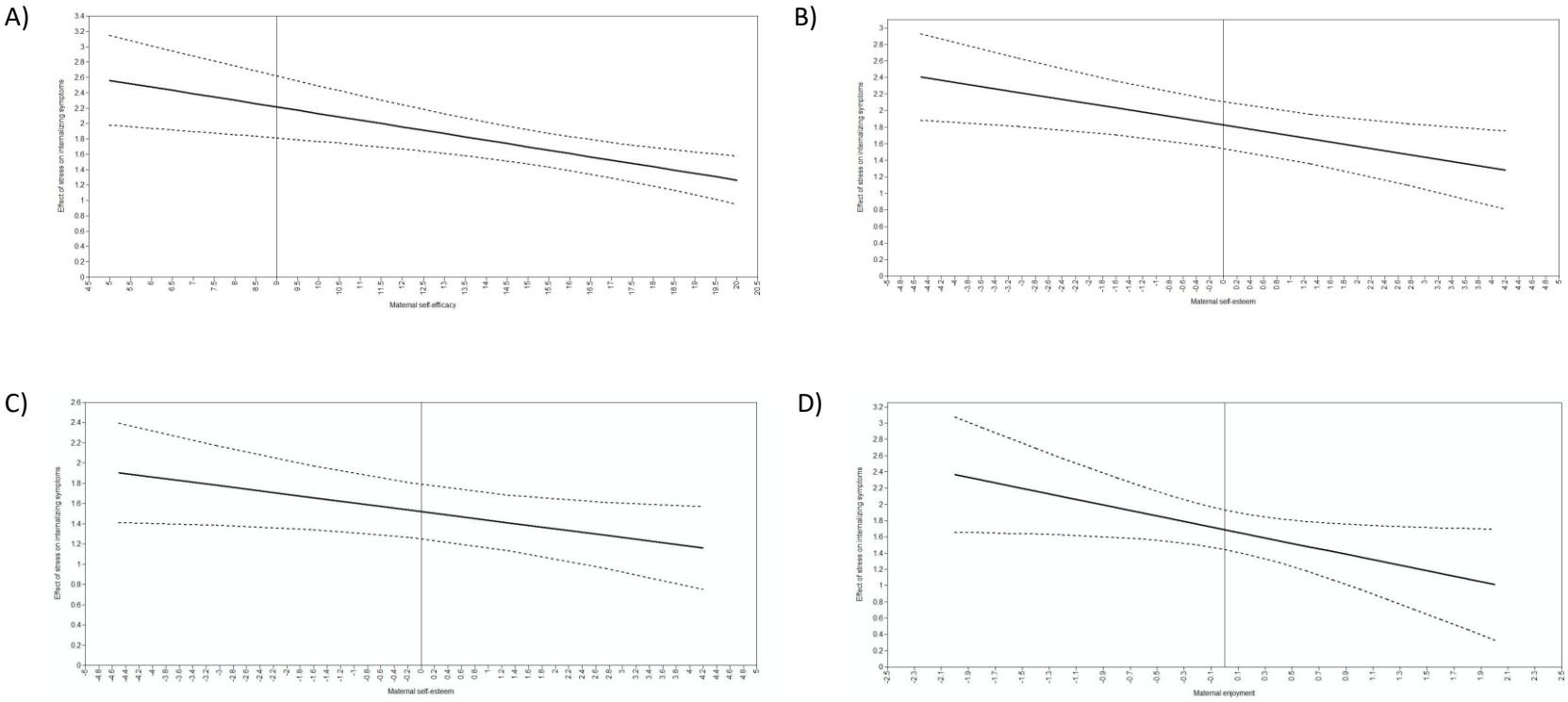

Figure 3.2. Johnson-Neyman plots of moderating role of maternal positive mental health on associations between prenatal maternal stress and internalizing and externalizing symptoms. A) moderating role of maternal self-efficacy at 30 weeks gestation on the relationship between prenatal maternal stress and female internalizing symptoms, B) moderating role of maternal self-esteem on the relationship between prenatal maternal stress and male internalizing symptoms, C) moderating role of maternal self-esteem on the relationship between prenatal maternal stress and female internalizing symptoms, D) moderating role of maternal enjoyment on the relationship between prenatal maternal stress and male internalizing symptoms. Plot lines represent effect (center line) and 95% confidence interval (outer lines

Appendix 3.1: MoBA items included in prenatal maternal stress exposure variable

Life Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Adverse events – Have you lost someone close to you?	30 weeks	Dichotomous (yes/no)	(1,2,3)
Adverse events – Child, partner, or relative was seriously ill	30 weeks	Dichotomous (yes/no)	(1,2,3)
Adverse events – You were ill	30 weeks	Dichotomous (yes/no)	(1,2,3)
Adverse events – Robbery, fire	30 weeks	Dichotomous (yes/no)	(1,2,3)
Unplanned pregnancy	17 weeks	Dichotomous (yes/no)	N/A
Worried about health of baby	30 weeks	Dichotomous (yes/no)	N/A
Dissatisfied with antenatal care	30 weeks	Dichotomous (yes/no)	N/A
Experienced vaginal bleeding during pregnancy	30 weeks	Dichotomous (yes/no)	N/A
Test to see if baby was abnormal (amniocentesis or biopsy)	30 weeks	Dichotomous (yes/no)	N/A

Contextual Stress Domain

Scale/Item	Time of Assessment	Variable Type	References
Adverse events – problems at school or work	30 weeks	Dichotomous (yes/no)	(1,2,3)
Adverse events – major financial problems	30 weeks	Dichotomous (yes/no)	(1,2,3)
Financial difficulties – can your family manage without your income?	17 weeks	Dichotomous (yes/no)	N/A
Employment – lost job since start of pregnancy (fired, laid off)	30 weeks	Dichotomous (yes/no)	N/A
Employment – work stress scale	17 weeks	Dichotomous (median split)	(4,5)
- I have physically heavy work [R]			-
- My work is very stressful [R]			-
- I learn a lot at work			-
- My work is very monotonous [R]			-
- My work demands a lot of me [R]			-
- I am able to decide how my work is to be carried out			-
- There is a good team spirit at my place of work			-
- I enjoy my work			-
Income – low income (< 300,000 NOK per year)	17 weeks	Dichotomous (yes/no)	(6,7)

Note. [R] Item reverse coded

Personal Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Early parenthood (maternal age 18 and under)	17 weeks	Dichotomous (yes/no)	N/A
Feeling fearful	30 weeks	Dichotomous (yes/no)	(8,9)
Nervousness or shakiness inside	30 weeks	Dichotomous (yes/no)	(8,9)
Feeling hopeless about the future	30 weeks	Dichotomous (yes/no)	(8,9)
Feeling blue	30 weeks	Dichotomous (yes/no)	(8,9)
Worrying too much about things	30 weeks	Dichotomous (yes/no)	(8,9)
Feeling everything is an effort	30 weeks	Dichotomous (yes/no)	(8,9)
Feeling tense or keyed up	30 weeks	Dichotomous (yes/no)	(8,9)
Suddenly scared for no reason	30 weeks	Dichotomous (yes/no)	(8,9)
Maternal substance use	17 weeks	Dichotomous (yes/no)	N/A

Interpersonal Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
> 3 children under 18 in household	17 weeks	Dichotomous (yes/no)	N/A
I have a close relationship with my spouse/partner [R]	17 weeks	Dichotomous (yes/no)	(10)
My partner and I have problems in our relationship	17 weeks	Dichotomous (yes/no)	(10)
I am very happy with our relationship [R]	17 weeks	Dichotomous (yes/no)	(10)
My partner is generally understanding [R]	17 weeks	Dichotomous (yes/no)	(10)
I often consider ending our relationship	17 weeks	Dichotomous (yes/no)	(10)
I am satisfied with my relationship with my partner [R]	17 weeks	Dichotomous (yes/no)	(10)
We frequently disagree on important decisions	17 weeks	Dichotomous (yes/no)	(10)
I have been lucky in my choice of a partner [R]	17 weeks	Dichotomous (yes/no)	(10)
We agree on how our child should be raised [R]	17 weeks	Dichotomous (yes/no)	(10)
I believe my partner is satisfied with our relationship [R]	17 weeks	Dichotomous (yes/no)	(10)
Adverse Events – Arguments with family or friends	30 weeks	Dichotomous (yes/no)	(1,2,3)
Adverse Events – Recent separation or divorce	30 weeks	Dichotomous (yes/no)	(1,2,3)
Social Support scale	17 weeks	Dichotomous (median split)	(11)
- Do you have anyone other than your husband/partner you can ask for advice in a difficult situation		Dichotomous (median split)	-
- How often do you meet or talk on the telephone with your family (other than your husband/partner and children) or close friends?			-
- Do you often feel lonely			-

Notes. [R]Item reverse coded

Table S3.1. Correlations between prenatal stress, moderators, outcomes

	Prenatal Maternal Stress	Maternal Self-Esteem	Maternal Self-Efficacy	Maternal Enjoyment	Child Internalizing Symptoms	Child Externalizing Symptoms
Prenatal Maternal Stress	-	-	-	-	-	-
Maternal Self-Esteem	-.430***	-	-	-	-	-
Maternal Self-Efficacy	-.238***	.442***	-	-	-	-
Maternal Enjoyment	-.359***	.580***	.345***	-	-	-
Child Internalizing Symptoms	.191***	-.170***	-.084***	-.145***	-	-
Child Externalizing Symptoms	.186***	-.186***	-.090***	-.166***	.335***	-

Note. $^{***}p < .001$

Table S3.2. Correlations between positive mental health variables

	Self-esteem, 15 weeks	Self-esteem, 6 months	Self-esteem, 18 months	Self-esteem, 36 months	Enjoyment, 30 weeks	Enjoyment, 6 months	Enjoyment, 18 months	Enjoyment, 36 months	Self-efficacy, 30 weeks
Self-esteem, 15 weeks	1.000	-	-	-	-	-	-	-	-
Self-esteem, 6 months	.621***	1.000	-	-	-	-	-	-	-
Self-esteem, 18 months	.598***	.653***	1.000	-	-	-	-	-	-
Self-esteem, 36 months	.572***	.607***	.654***	1.000	-	-	-	-	-
Enjoyment, 30 weeks	.393***	.383***	.367***	.349***	1.000	-	-	-	-
Enjoyment, 6 months	.371***	.505***	.418***	.382***	.600***	1.000	-	-	-
Enjoyment, 18 months	.362***	.416***	.512***	.421***	.568***	.645***	1.000	-	-
Enjoyment, 36 months	.342***	.385***	.412***	.521***	.539***	.580***	.636***	1.000	-
Self-efficacy, 30 weeks	.390***	.379***	.372***	.350***	.353***	.285***	.269***	.265***	1.000

Note. $^{***}p < .001$

Table S3.3. Main effect and moderation models of associations between prenatal maternal stress, combined positive mental health, and internalizing and externalizing symptoms in males and females

		Males (n = 18,596)		Females (n = 17,988)	
		b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Internalizing symptoms	**Main effects model (adjusted)**				
	Prenatal maternal stress	1.855 (.154)***	.257 (.219, .294)	1.399 (.147)***	.204 (.165, .2242)
	Positive mental health	-.001 (.001)	-.007 (-.038, .024)	-.013 (.003)***	-.074 (-.106, -.041)
	Moderation model				
	Prenatal maternal stress	1.754 (.151)***	.243 (.206, .280)	1.347 (.144)***	.197 (.159, .235)
	Positive mental health	-.001 (.003)	-.007 (-.037, .023)	-.013 (.003)***	-.072 (-.104, -.040)
	Prenatal maternal stress x positive mental health	-.144 (.051)**	-.029 (-.049, -.009)	-.101 (.043)*	-.021 (-.038, -.004)
Externalizing symptoms	**Main effects model (adjusted)**				
	Prenatal maternal stress	1.250 (.157)***	.152 (.116, .188)	.921 (.142)***	.128 (.091, .166)
	Positive mental health	-.019 (.003)***	-.094 (-.125, -.064)	-.023 (.003)***	-.125 (-.156, -.094)
	Moderation model				
	Prenatal maternal stress	1.252 (.157)***	.152 (.116, .188)	.896 (.418)***	.125 (.088, .162)
	Positive mental health	-.019 (.003)***	-.094 (-.125, -.064)	-.023 (.003)***	-.124 (-.155, -.093)
	Prenatal maternal stress x positive mental health	-.010 (.048)	-.002 (-.018, .015)	-.053 (.048)	-.010 (-.029, .008)
Model fit statistics		**CFI**	**RMSEA (90% CI)**	**CFI**	**RMSEA (90% CI)**
	Main effects model (adjusted)	.916	.052 (.050, .053)	.915	.051 (.050, .052)

Note. *$p < .05$, **$p < .01$, ***$p < .001$. b = unstandardized regression coefficient, SE = standard error, β = standardized regression coefficient, CI = confidence interval, CFI = comparative fit index, RMSEA = root mean square error of approximation. Models adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, and parity.

Table S3.4. Main effect and moderation models of associations between prenatal maternal stress, maternal self-efficacy, and internalizing and externalizing symptoms in males and females, adjusted for postnatal maternal stressful events

		Males (n = 18,596)		Females (n = 17,988)	
		b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Internalizing symptoms	**Main effects model (adjusted)**				
	Prenatal maternal stress	1.969 (.123)***	.268 (.242, .294)	1.736 (.116)***	.250 (.224, .276)
	Maternal self-efficacy	.001 (.001)	.015 (-.001, .032)	-.002 (.001)**	-.024 (-.041, -.007)
	Moderation model				
	Prenatal maternal stress	2.556 (.377)***	.347 (.250, .445)	2.964 (.411)***	.427 (.317, .537)
	Maternal self-efficacy	.001 (.001)*	.017 (.001, .033)	-.002 (.001)*	-.021 (-.037, -.005)
	Prenatal maternal stress x self-efficacy	-.041 (.025)	-.017 (-.037, .003)	-.086 (.026)**	-.038 (-.060, -.016)
Externalizing symptoms	**Main effects model (adjusted)**				
	Prenatal maternal stress	1.785 (.122)***	.213 (.189, .238)	1.518 (.112)***	.209 (.184, .235)
	Maternal self-efficacy	-.001 (.001)	-.010 (-.028, .003)	-.002 (.001)**	-.028 (-.044, -.011)
	Moderation model				
	Prenatal maternal stress	1.678 (.387)***	.200 (.110, .291)	2.028 (.418)***	.279 (.170, .389)
	Maternal self-efficacy	-.001 (.001)	-.010 (-.026, .006)	-.002 (.001)**	-.027 (-.043, -.010)
	Prenatal maternal stress x self-efficacy	.009 (.026)	.003 (-.015, .022)	-.036 (.027)	-.015 (-.037, .007)
Model fit statistics		**CFI**	**RMSEA (90% CI)**	**CFI**	**RMSEA (90% CI)**
	Main effects model (adjusted)	.886	.043 (.041, .045)	.883	.042 (.040, .044)

Note. *$p < .05$, **$p < .01$, ***$p < .001$. b = unstandardized regression coefficient, SE = standard error, β = standardized regression coefficient, CI = confidence interval, CFI = comparative fit index, RMSEA = root mean square error of approximation. Models also adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, and parity.

Table S3.5. Main effect and moderation models of associations between prenatal maternal stress, maternal self-esteem, and internalizing and externalizing symptoms in males and females, adjusted for postnatal maternal stressful events

		Males (n = 18,596)		Females (n = 17,988)	
		b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Internalizing symptoms	**Main effects model (adjusted)**				
	Prenatal maternal stress	1.885 (.146)***	.255 (.221, .288)	1.522 (.139)***	.215 (.180, .249)
	Maternal self-esteem	-.002 (.002)	-.009 (-.036, .018)	-.018 (.002) ***	-.058 (-.085, -.031)
	Moderation model				
	Prenatal maternal stress	1.809 (.143)***	.245 (.211, .278)	1.493 (.138)***	.211 (.177, .245)
	Maternal self-esteem	-.001 (.002)	-.006 (-.032, .020)	-.010 (.002)***	-.055 (-.082, -.028)
	Prenatal maternal stress x self-esteem	-.127 (.048)***	-.026 (-.045, -.007)	-.083 (.043)*	-.017 (-.034, .000)
Externalizing symptoms	**Main effects model (adjusted)**				
	Prenatal maternal stress	1.398 (.147)***	.165 (.133, .198)	1.108 (.133)***	.150 (.116, .183)
	Maternal self-esteem	-.015 (.003)***	-.078 (-.104, -.052)	-.018 (.002)***	-.098 (-.125, -.072)
	Moderation model				
	Prenatal maternal stress	1.398 (.147)***	.166 (.133, .198)	1.093 (.132)***	.148 (.115, .181)
	Maternal self-esteem	-.015 (.003)***	-.078 (-.104, -.052)	-.018 (.002)***	-.097 (-.123, -.070)
	Prenatal maternal stress x self-esteem	-.004 (.047)	-.001 (-.017, .016)	-.050 (.049)	-.010 (-.029, .009)
Model fit statistics		**CFI**	**RMSEA (90% CI)**	**CFI**	**RMSEA (90% CI)**
	Main effects model (adjusted)	.968	.032 (.031, .034)	.966	.032 (.030, .034)

Note. *$p < .05$, **$p < .01$, ***$p < .001$. b = unstandardized regression coefficient, SE = standard error, β = standardized regression coefficient, CI = confidence interval, CFI = comparative fit index, RMSEA = root mean square error of approximation. Models also adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, and parity.

Table S3.6. Main effect and moderation models of associations between prenatal maternal stress, maternal enjoyment, and internalizing and externalizing symptoms in males and females, adjusted for postnatal maternal stressful events

		Males (n = 18,596)		Females (n = 17,988)	
		b (SE)	**β (95% CI)**	**b (SE)**	**β (95% CI)**
Internalizing symptoms	**Main effects model (adjusted)**				
	Prenatal maternal stress	1.738 (.128)***	.264 (.231, .297)	1.441 (.122)***	.232 (.198, .266)
	Maternal enjoyment	-.001 (.007)	-.001 (-.026, .024)	-.023 (.007)**	-.041 (-.067, -.015)
	Moderation model				
	Prenatal maternal stress	1.678 (.125)***	.254 (.222, .287)	1.408 (.120)***	.227 (.194, .260)
	Maternal enjoyment	-.001 (.007)	-.001 (-.026, .024)	-.022 (.007)**	-.040 (-.065, -.014)
	Prenatal maternal stress x enjoyment	-.337 (.166)*	-.023 (-.045, -.001)	-.215 (.125)	-.016 (-.034, .002)
Externalizing symptoms	**Main effects model (adjusted)**				
	Prenatal maternal stress	1.324 (.129)***	.176 (.145, .208)	1.090 (.117)***	.168 (.135, .201)
	Maternal enjoyment	-.046 (.008)***	-.071 (-.095, -.047)	-.049 (.007)***	-.084 (-.109, -.059)
	Moderation model				
	Prenatal maternal stress	1.334 (.128)***	.177 (.146, .208)	1.083 (.115)***	.167 (.135, .199)
	Maternal enjoyment	-.046 (.008)***	-.071 (-.095, .047)	-.048 (.007)***	-.084 (-.108, -.059)
	Prenatal maternal stress x enjoyment	-.009 (.150)	.001 (-.017, .018)	-.059 (.130)	-.004 (-.022, .014)
Model fit statistics		**CFI**	**RMSEA (90% CI)**	**CFI**	**RMSEA (90% CI)**
	Main effects model (adjusted)	.957	.035 (.034, .037)	.952	.039 (.037, .040)

Note. *$p < .05$, **$p < .01$, ***$p < .001$. b = unstandardized regression coefficient, SE = standard error, β = standardized regression coefficient, CI = confidence interval, CFI = comparative fit index, RMSEA = root mean square error of approximation. Models also adjusted for the following covariates: maternal education, paternal education, maternal alcohol use, maternal smoking, and parity.

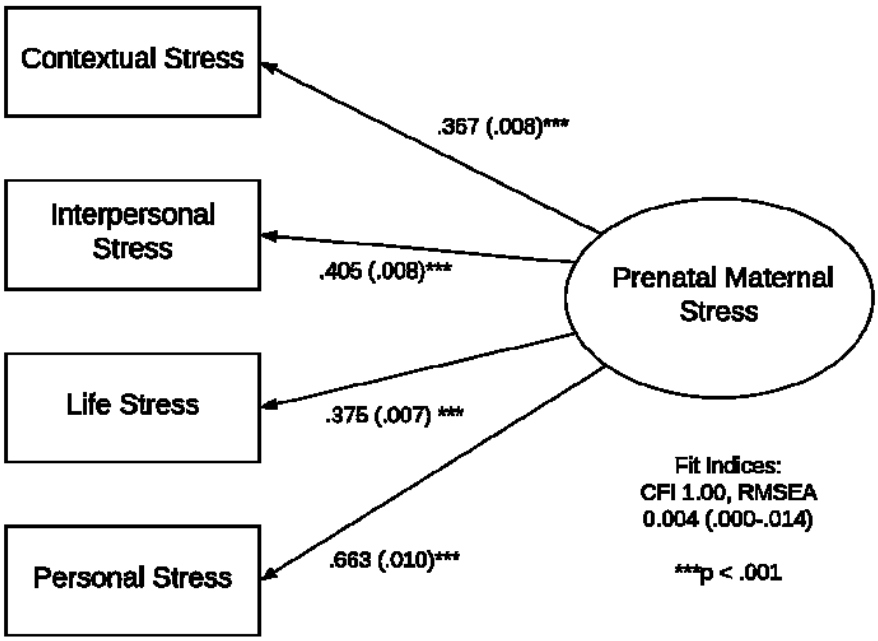

Figure S3.1. Measurement model for latent prenatal maternal stress

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Chapter 4

Associations between prenatal maternal stress, maternal inflammation during pregnancy, and children's internalizing and externalizing symptoms throughout childhood

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The article presented in this chapter has been prepared for submission to *Brain, Behavior and Immunity*. All tables and figures are numbered with two digits (chapter number followed by table or figure number). Supplementary materials are included as appendices at the end of this chapter, with tables and figures denoted with an "S" followed by two digits (chapter number followed by table or figure number).

Article preface: The aims of this study were to examine the associations between prenatal maternal stress, maternal inflammation during pregnancy, and children's internalizing and externalizing symptoms from 36 months to 9 years of age, and to ascertain whether maternal inflammation during pregnancy mediated the associations between prenatal stress and children's internalizing and externalizing symptoms.

Contribution statement: I am the first author on this article. I designed the study and its objectives, with guidance from my co-authors. I conducted study analyses in collaboration with Runyu Zou, prepared the first draft of the manuscript, and prepared the manuscript for submission.

ABSTRACT

Background: Maternal inflammation has been posited as a potential mechanism underlying the associations between prenatal maternal stress and offspring mental health, however, few studies have investigated its role in these associations. The aims of this study were to examine the associations between prenatal maternal stress, maternal inflammation during pregnancy, and children's internalizing and externalizing symptoms from 36 months to 9 years of age, and to ascertain whether maternal inflammation mediated the associations between prenatal maternal stress and children's internalizing and externalizing symptoms.

Methods: This study utilized data from the Generation R cohort, and comprised 4,902 mother-child dyads. Prenatal maternal stress was assessed using 43 items measured during pregnancy. Maternal inflammation during pregnancy was assessed using serum levels of C-reactive protein (CRP) taken at a median of 13.5 weeks' gestation. Child internalizing and externalizing symptoms were assessed by maternal report at ages 36 months, 5 years, and 9 years; paternal-reported data was also available at 36 months and 9 years. Analyses involved structural equation modeling techniques.

Results: Prenatal maternal stress was consistently associated with maternal-reported internalizing and externalizing symptoms at 36 months, 5 years, and 9 years of age, and with paternal-reported internalizing and externalizing symptoms at 36 months and 9 years. Maternal CRP levels during pregnancy were associated with paternal-reported internalizing symptoms at 9 years of age. There was no evidence that maternal levels of CRP mediated the associations between prenatal maternal stress and children's internalizing and externalizing symptoms.

Conclusions: This study provides evidence of associations between prenatal maternal stress and children's internalizing and externalizing symptoms, and adds to the evidence base of studies

examining the role of maternal inflammation in these associations. Findings may inform future research that investigates the role of maternal inflammation in the associations between prenatal maternal stress and offspring psychiatric outcomes.

Keywords: prenatal stress, inflammation, mental health, development, epidemiology

INTRODUCTION

An extensive body of research has established associations between potential sources of stress during pregnancy, including maternal stressful life events, depressive symptoms, and anxiety, and greater risk of outcomes including depression, generalized anxiety disorder, and externalizing behaviours in offspring (1–7). Given these demonstrated relationships, there is emerging interest in understanding the potential biological mechanisms that may underly the associations between prenatal maternal stress and offspring mental health and development.

Dysregulation of the maternal and fetal hypothalamic-pituitary-adrenal (HPA) axes and immune systems have been proposed as likely mechanisms for the transmission of stress reactivity and vulnerability for mental disorders from mother to child (8–14). This is due to clinical, animal, and epidemiological studies which suggest that: 1) prenatal maternal stress is associated with higher levels of cortisol and pro-inflammatory markers including interleukin 6 (IL-6) and C-reactive protein (CRP) in mothers and their children (15–18); 2) cortisol and pro-inflammatory markers including IL-6 and CRP can exhibit maternal-fetal and fetal-maternal transfer via the placenta (19,20); and 3) higher levels of glucocorticoids and pro-inflammatory markers are strongly associated with incident depression and other mental disorders (8–13,21). The mediating role of HPA axis dysregulation in the relationships between prenatal stress and children's mental health has previously been examined (18,22). Emerging research has also examined the mediating role of inflammation during pregnancy on the associations between prenatal maternal stress exposures and offspring development. For example, prior studies suggest that maternal levels of CRP during pregnancy mediate the associations between prenatal environmental adversities and offspring neurodevelopmental delay, and between prenatal

maternal depression and infant negative affect (23,24). Research also suggests that maternal immune activation during pregnancy may mediate the associations between socioeconomic disadvantage and children's neurodevelopment and self-regulation (25,26). However, few studies have examined whether maternal inflammation mediates the associations between prenatal maternal stress and children's risk of internalizing or externalizing behaviours throughout childhood, calling for further inquiry into these associations.

Importantly, most studies that have examined the associations between prenatal maternal stress and maternal inflammation, as well as the mediating role of maternal inflammation in the associations between prenatal maternal stress and children's developmental outcomes have conceptualized stress using single measures of maternal stress, including symptoms of prenatal depression and/or anxiety, or stressful life events (23,24,27,28). Stress is a multidimensional concept, and many stressors are correlated and co-occur (29); thus, it has been suggested that shifting to broader representations of prenatal maternal stress may better address the commonalities across stressors (30). In addition, many of the studies examining these associations have been limited by study design or small sample sizes, constraining opportunities to adjust for a range of confounding variables and to investigate potential sex differences. The latter is particularly important, as sex differences in both the biological and psychological consequences of exposure to prenatal maternal stress are well-documented (31). For example, animal studies report sex-specific alterations to the fetal immune system after prenatal maternal stress exposure, and epidemiological research suggests that there are sex differences in the associations between prenatal maternal stress and internalizing and externalizing symptoms in children (31,32).

Taken together, these gaps in the literature illustrate the need to examine whether maternal inflammation mediates the associations between broad conceptualizations of prenatal maternal stress and children's internalizing and externalizing outcomes throughout childhood; there is also a need to investigate whether these associations differ between males and females. To address these evidence gaps, we conducted a study utilizing data from a population-based cohort study with two objectives. The first objective was to examine the interrelationships between a broad measure of prenatal maternal stress, maternal CRP levels during pregnancy, and children's internalizing and externalizing symptoms at 36 months, 5 years, and 9 years of age; we also sought to examine if these relationships differed by sex. The second objective was to examine the mediating role of maternal inflammation on the associations between prenatal maternal stress and children's internalizing and externalizing symptoms at 36 months, 5 years, and 9 years of age.

METHODS

Data Source and Participants. This study used data from the Generation R study, a population-based prospective cohort study in Rotterdam, the Netherlands; methods for the Generation R study have previously been described in detail (33). Mothers residing in Rotterdam with delivery dates between April 2002 and January 2006 were enrolled into the study; baseline response rates were 61%, with approximately 80% of children followed up to 10 years of age (34). The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, and written informed consent was obtained from all adult participants. The study sample included 4,902 mother-child dyads with available data on prenatal maternal stress (see Figure S4.1); given

later attrition, data on mental health outcomes from ages 36 months to 9 years were imputed to maximize sample size.

Measures

Prenatal maternal stress. A latent measure of prenatal maternal stress, developed by Cecil and colleagues (35), and previously utilized in the current cohort with good model fit (36,37), was constructed for this study. This measure comprises 43 maternal-reported items covering four domains of prenatal stress: life stress (including adverse events), personal stress (including maternal psychopathology), contextual stress (including financial problems), and interpersonal stress (including relationship problems). Mothers were required to have complete data on at least 75% of items in each domain to improve stability of the latent variable; as such, weighted mean scores were generated for each domain, with higher scores representing higher stress levels. Weighted domain scores were then used as indicators to extract a single, latent prenatal maternal stress factor using confirmatory factor analysis; the generated prenatal maternal stress variable had excellent model fit (see Figure S4.2). Maternal education was excluded from the personal stress domain, as prior research suggests that maternal education may impact child development through pathways independent of prenatal stress (36). A list of included items is provided in Appendix 4.1.

Maternal inflammation. Maternal venous blood samples were collected in early pregnancy (median, 13.5 weeks' gestation; range, 5.9–17.9 weeks) and transported to a regional laboratory for processing and storage at −80°C (38). High-sensitivity C-reactive protein (hs-CRP) concentrations were measured in EDTA plasma samples at the Department of Clinical

Chemistry, Erasmus MC, using an immunoturbidimetric assay on the Architect System (Abbot Diagnostics BV, Hoofddorp, the Netherlands). The within-run precision for hs-CRP was 1.3% at 12.9 mg/L and 1.2% at 39.9 mg/L, and the lowest level of detection was 0.2 mg/L (39); participants below the lowest level of detection were assigned a value equal to the minimum detection limit of 0.2 mg/L. CRP values in the study sample ranged from 0.2 to 93.6 mg/L; mean ± SD = 6.43 ± 7.01 mg/L. CRP values were right-skewed and, thus, were log-transformed for analysis.

Child mental health. Children's mental health outcomes comprised maternal-reported internalizing and externalizing symptoms, measured using the Child Behavior Checklist (CBCL) at ages 36 months, 5 years, and 9 years (40). The CBCL is a 99-item questionnaire with items rated on a 3-point scale from 0 (not true) to 2 (very true or often true), which are used to generate sum scores for seven syndromes (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behaviour). Two broadband scales representing internalizing and externalizing symptoms were derived: the internalizing score represents the sum of the first four syndrome scales, and the externalizing score is a sum score of attention problems and aggressive behaviour. Continuous scores for internalizing and externalizing symptoms at each measurement point were utilized for analysis, with higher scores representing greater symptom severity. The CBCL has demonstrated good reliability (mean test–retest $r = 0.85$, interparent agreement $r = 0.61$) and validity (40), and the Dutch translation of the CBCL has also demonstrated good reliability and validity (41). Paternal-reported CBCL internalizing and externalizing scores at age 36 months and 9 years were also examined in order to address potential maternal reporting bias.

Covariates. A number of potential confounding variables related to prenatal maternal stress, inflammation, and children's internalizing and externalizing symptoms were identified a priori based on existing literature and included in analyses; these included maternal ethnicity (Dutch, non-Dutch Western, and non-Western), smoking during pregnancy (never, smoked until pregnancy was known, continued smoking), alcohol use during pregnancy (never, drank until pregnancy was known, continued drinking occasionally, continued drinking frequently), maternal educational level (primary or below, secondary, higher), parity (0, ≥ 1), maternal body mass index (BMI) at intake, gestational age at CRP measurement, and child age at outcome ascertainment. Sex of the child (male or female) was first examined as a moderating variable, and then included as a covariate in later analyses.

Statistical Analyses

All analyses were conducted in R (version 3.6.3). Missing data on covariates and internalizing and externalizing outcomes were imputed using multiple imputation by chained equations via the mice package, generating 20 imputed datasets. Estimation of the associations between prenatal maternal stress, maternal inflammation, and child internalizing and externalizing symptoms were performed using the semTools package with the runMI command, which fits structural equation models and pools point and standard error estimates across imputed datasets. In detail, we first tested for potential sex differences by conducting multiple group analyses, whereby models examining the associations between prenatal maternal stress, maternal inflammation, and child internalizing or externalizing symptoms at 36 months of age were stratified by sex and examined simultaneously. A constrained model, where all factor loadings were held equal, was compared to an unconstrained model where the paths of interest were freely estimated; a likelihood ratio

test was then conducted to ascertain whether or not the unconstrained estimates significantly differed by sex ($p < .05$). The multiple group analysis was not statistically significant ($p > .05$), thus, all subsequent adjusted analyses included sex as a covariate.

We used confirmatory factor analysis to estimate a latent factor of prenatal maternal stress using the previously described prenatal stress domains as indicators, and structural equation models between latent prenatal maternal stress, maternal inflammation, and child internalizing and externalizing symptoms at each measurement point were analyzed simultaneously. We computed unstandardized parameter estimates (*b*) and their standard errors (SEs) and associated *p*-values, where unstandardized estimates represented changes in the outcome variables (i.e., log-transformed maternal CRP or child internalizing or externalizing symptoms) per one unit increase in the exposure variables (i.e., prenatal maternal stress or log-transformed maternal CRP). We also reported standardized parameter estimates, (β) which represent changes in the standard deviations of outcome variables per one standard deviation increase in exposure variables. Unadjusted and adjusted models were estimated, and internalizing and externalizing symptoms were tested in the same models and allowed to correlate. To assess model fit, the comparative fit index (CFI) and the root mean square error of approximation (RMSEA) were examined, with good fit categorized as a value of 0.90 and above on the CFI, or 0.06 and below on the RMSEA (42,43).

To test the indirect effects between prenatal maternal stress and child internalizing and externalizing outcomes through maternal inflammation, the paths constituting the effect were multiplied, with point estimates and standard errors pooled across the imputed datasets.

Secondary analyses included examining the associations between individual prenatal maternal stress domains, maternal inflammation during pregnancy, and children's internalizing and externalizing symptoms between 36 months and 9 years of age. As sensitivity analyses, we examined children's internalizing and externalizing symptoms at 36 months and 9 years of age using paternal-reported data, and also conducted analyses excluding women with CRP values > 10.0 mg/L (n = 834 participants), as CRP levels above this threshold are indicative of acute inflammation or infection (15,44).

RESULTS

The majority of mothers included in the sample were of Dutch ethnicity, had secondary or higher education, were pregnant with their first child, and reported a household income greater than 2000 Euros per month. Remaining descriptive characteristics of the study sample are displayed in Table 4.1. Comparisons between those included and excluded from the study sample are presented in Table S4.1; on average, excluded participants were generally less likely to report higher education, and were more likely to report non-Western ethnicity, lower income, never smoking or drinking alcohol during their pregnancies, higher BMI, and higher levels of all four prenatal stress domains.

The direct and indirect associations between prenatal maternal stress, maternal CRP, and maternal-reported internalizing and externalizing symptoms at 36 months, 5 years, and 9 years of age are presented in Table 4.2. Higher prenatal maternal stress was moderately associated with higher internalizing and externalizing symptoms in children at ages 36 months, 5 years, and 9 years of age in unadjusted and adjusted models (see Table 4.2). Model fit for adjusted models

examining associations between prenatal maternal stress and internalizing and externalizing symptoms at 36 months (CFI = .954, RMSEA = .032, 90% CI: .027, .037), 5 years (CFI = .968, RMSEA = .031, 90% CI: .027, .035), and 9 years of age (CFI = .988, RMSEA = .034, 90% CI: .023, .046) was excellent. Prior to adjustment, there was a small but significant association between higher prenatal maternal stress and higher levels of maternal CRP, however, this association was significantly attenuated after adjustment for covariates; model fit for the adjusted model was very good (CFI = .952, RMSEA = .031, 90% CI: .027, .035). There was a small but significant association between maternal CRP and higher internalizing symptoms at 5 years of age prior to adjustment; this association was no longer significant after adjustment. There was no evidence of associations between CRP and internalizing and externalizing symptoms at 36 months, 5 years, and 9 years of age. No significant indirect effects between prenatal maternal stress and child internalizing and externalizing symptoms from 36 months to 9 years through maternal CRP were observed prior to or after covariate adjustment. Removal of CRP values above 10 mg/L did not significantly alter findings (Table S4.2).

Direct and indirect associations between prenatal maternal stress, maternal CRP, and paternal-reported internalizing and externalizing symptoms at 36 months and 9 years of age are presented in Table 4.3. Consistent with maternal-reported internalizing and externalizing symptoms, higher prenatal maternal stress was moderately associated with higher paternal-reported internalizing and externalizing symptoms at 36 months and 9 years of age. There was a small but significant association between maternal CRP and paternal-reported internalizing symptoms at 9 years of age in both unadjusted and adjusted models; remaining analyses with CRP were not statistically significant. No significant indirect effects between prenatal maternal stress and paternal-reported

internalizing and externalizing symptoms at 36 months and 9 years through maternal CRP were observed.

The associations between individual prenatal maternal stress domains, maternal CRP, and child internalizing and externalizing symptoms at 36 months, 5 years, and 9 years of age are presented in Tables S4.3 through S4.6. Consistent with analyses including the latent prenatal maternal stress variable, all individual stress domains were positively associated with child internalizing and externalizing symptoms at 36 months, 5 years, and 9 years of age prior to and after covariate adjustment. Prior to adjustment, prenatal interpersonal stress and prenatal contextual stress were positively associated with maternal CRP levels; these associations were no longer significant after adjustment. There was no evidence of associations between remaining stress domains and CRP, and of mediation between stress domains and outcomes through maternal CRP prior to or after covariate adjustment.

DISCUSSION

Results from this population-based prospective study of almost 5,000 mothers and their children demonstrate that higher prenatal maternal stress is associated with higher internalizing and externalizing symptoms throughout childhood; results did not significantly differ by sex of the child. Contrary to a number of other studies examining the associations between prenatal maternal stress and maternal inflammation (45–48), we did not find associations between prenatal maternal stress and maternal CRP during pregnancy after adjustment for covariates. As a consequence, we did not find evidence suggesting a mediating role of maternal CRP in the associations between prenatal maternal stress and children's internalizing and externalizing

symptoms. However, our findings suggest that maternal CRP levels during pregnancy may be associated with paternal-reported internalizing symptoms at 9 years of age.

Extensive research supports associations between psychosocial stress and inflammation in healthy adults (49–51). However, analyses of the associations between stress and inflammation during pregnancy are complicated by the important role that the immune system plays in the maintenance of pregnancy and the onset of labour. During pregnancy, immune responses shift, with the first and third trimesters representing pro-inflammatory periods (52), whereas the second trimester is generally considered anti-inflammatory (53); these immune responses also exhibit substantial inter-individual variability (54). For example, a study by Coussons-Read and colleagues reported significant associations between elevated stress and serum levels of CRP and IL-6 in the first and third trimesters, but not during the second trimester (45). Another study by Christian and colleagues did not find an association between perceived stress and IL-6 at 15 weeks of pregnancy, although an association with maternal depression was reported (27). Additional studies have also reported no associations between maternal psychiatric symptoms and IL-6 and tumour necrosis factor alpha (TNF-α) at 18 weeks' gestation (28), and maternal history of child maltreatment and circulating levels of IL-6 in the second and third trimesters (55). Our findings are consistent with these results, given that maternal CRP was measured early in the second trimester for most women in the Generation R cohort. Although we adjusted for gestational age at time of measurement, it is possible that pregnancy-induced variations of CRP may have confounded potential associations between prenatal maternal stress and maternal CRP that would otherwise be observed outside of the second trimester. Nonetheless, these findings highlight the importance of continued research of these associations using maternal inflammation

data from a range of measurement points throughout pregnancy to better ascertain how prenatal maternal stress impacts maternal inflammation and subsequent developmental outcomes in children.

Research examining the associations between maternal inflammation during pregnancy and offspring psychiatric outcomes during childhood is limited. To the best of our knowledge, only one study has examined the associations between maternal inflammation during pregnancy and children's internalizing and externalizing symptoms. This study by Giollabhui and colleagues reported that elevated levels of interleukin 8 (IL-8) and interleukin 1 receptor antagonist (IL-1ra) were associated with higher internalizing and externalizing symptoms in children between the ages of 9 and 11 (56). Although inflammation was not directly measured, another study by Patel and colleagues reported associations between maternal immune activation during pregnancy (defined as the presence of asthma, allergy, atopy, eczema, or infection) and child internalizing and externalizing symptoms up to 17 years of age (57). In the current study, maternal CRP was not associated with maternal-reported internalizing and externalizing symptoms between 36 months and 9 years of age, however, higher maternal CRP was associated with higher paternal-reported internalizing symptoms at 9 years of age. These inconsistent findings may be due to the timing of outcome ascertainment. It is possible that the impacts of maternal inflammation during pregnancy may not be identified in offspring until later in development; for example, research suggests that the mean age of first onset for both depression and anxiety disorders ranges from mid-adolescence to early adulthood (58,59). In line with this, several studies have reported associations between maternal inflammation during pregnancy and risk of a range of mental disorders in adult offspring, including schizophrenia and major depressive disorder (60,61). In

addition, sex differences in these associations were not observed in our study; however, sex differences in risk of mental disorders may also start to emerge later in childhood and into adolescence (62,63). Similar to our findings examining the direct associations between prenatal maternal stress and maternal CRP, it is also possible that pregnancy-induced changes in maternal CRP may have masked the potential associations between maternal CRP and offspring internalizing and externalizing behaviours in childhood. Thus, evaluating the effects of maternal inflammation on offspring mental health outcomes into adolescence and adulthood, in combination with robust measurement of maternal inflammation during pregnancy and examination of potential sex differences among offspring represent important avenues for future research.

Results from the current study should be considered in light of several limitations. First, we only had data for maternal CRP measured during the second trimester of pregnancy. Given our reliance on CRP assessed at a single measurement point, we were not able to examine whether fluctuations or stability in maternal CRP levels during pregnancy may have influenced offspring outcomes, nor could we ascertain whether measurement at different points during pregnancy may have had differential effects on offspring outcomes. In addition, other markers of maternal inflammation that have demonstrated associations with prenatal maternal stress, including interleukin-6 (45), were not assayed in the Generation R cohort. Second, we were not able to adjust for concurrent maternal depression or other markers of stress during measurement of maternal-reported child internalizing and externalizing symptoms, which may bias our findings; however, to address this bias to the best of our ability, we examined paternal-reported internalizing and externalizing symptoms at 36 months and 9 years of age, and findings were

largely similar for maternal- and paternal-reported data. Third, although our measure of prenatal maternal stress included a number of items, we did not have data on important sources of chronic stress, including discrimination, exposure to violence, extended work stress or unstable employment, or a history of child maltreatment, all of which have demonstrated associations with both maternal inflammation and offspring mental health (14,64,65). Thus, future studies may seek to incorporate these measures when assessing the relationships between prenatal maternal stress, maternal inflammation, and offspring development. Finally, although inclusion into the study only required complete data on prenatal stress and maternal CRP, there was substantial missing data on these measures; mothers excluded from the current study tended to report higher levels of prenatal stress, as well as lower socioeconomic status and higher BMI at intake. As a result, we cannot rule out the possibility of biased findings due to selective attrition.

The use of data from a prospective cohort study with extensive maternal- and paternal-reported data and biological sampling allowed us to analyze the associations between a broad and comprehensive measure of prenatal maternal stress with maternal inflammation during pregnancy and with children's internalizing and externalizing outcomes throughout childhood. Furthermore, this study contributes to an emerging but limited evidence base that considers the potential role of maternal inflammation in the associations between prenatal maternal stress and children's mental health outcomes.

CONCLUSIONS

Consistent with several studies, our findings demonstrate moderate associations between prenatal maternal stress and internalizing and externalizing symptoms throughout childhood; these

associations persisted when examining the effects of individual stress domains, as well as when examining paternal-reported data on internalizing and externalizing symptoms. Contrary to existing hypotheses (14), as well as the limited evidence base that has examined the mediating role of maternal inflammation on the associations between prenatal maternal stress and children's developmental outcomes, we did not find any evidence of mediation of these associations through maternal CRP. Findings from our study may serve to inform future research that evaluates the role of inflammation in the associations between prenatal maternal stress and offspring psychiatric outcomes, in order to better understand the biological processes underlying these associations.

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Conflicts of Interest: None

Ethics Approval and Ethical Standards: This study was approved by the Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands, and the University of Ottawa Research Ethics Board (REB #: H-09-19-4923). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and

institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 4.1. Sociodemographic characteristics of the study sample (*n* = 4,902)

Characteristics	Mean (SD) or n (%)
Maternal age at enrollment, years	30.0 (4.9)
Maternal ethnicity	
Dutch	2731 (55.7)
Other western	451 (9.2)
Non-western	1720 (35.1)
Maternal educational level	
Primary or below	414 (8.4)
Secondary	2202 (44.9)
Higher	2286 (46.6)
Maternal BMI[1]	24.4 (4.4)
Parity, ≥1	2012 (41.0)
Maternal smoking during pregnancy	
Never	3545 (72.3)
Smoked until pregnancy was known	458 (9.3)
Continued smoking	899 (18.3)
Maternal alcohol use during pregnancy	
Never	2028 (41.4)
Drank until pregnancy was known	692 (14.1)
Continued drinking occasionally	1749 (35.7)
Continued drinking frequently[2]	433 (8.8)
Maternal infection during pregnancy (yes)	4668 (95.2)
Household income, €/month	
~1200	951 (19.4)
~2000	931 (19.0)
2001~	3020 (61.6)
Maternal stress score	
Total	1.9 (1.6)
Life stress	1.0 (1.3)
Contextual stress	0.2 (0.5)
Personal stress	2.0 (2.6)
Interpersonal stress	2446 (49.9)
Child sex (male)	39.9 (1.7)
Child gestational age at birth, weeks	3461.8 (687.1)
Child birth weight, grams	30.0 (4.9)

Note. Statistics of the first imputed dataset are reported. [1]BMI = Body mass index. [2]Defined as 'one or more glasses of alcohol per week in at least two trimesters'.

Table 4.2. Direct and indirect associations between prenatal maternal stress, maternal inflammation during early pregnancy, and children's internalizing and externalizing symptoms

	Unadjusted			Adjusted		
Direct associations	*b (SE)*	*β*	*p*	*b (SE)*	*β*	*p*
PNMS → CRP	.029 (.009)	.060	.002	-.012 (.011)	-.024	.267
PNMS → Internalizing, 36m	2.389 (.191)	.364	<.001	2.193 (.222)	.324	<.001
PNMS → Externalizing, 36m	2.639 (.241)	.305	<.001	2.655 (.293)	.297	<.001
CRP → Internalizing, 36m	.129 (.216)	.011	.551	-.198 (.231)	-.017	.392
CRP → Externalizing, 36m	.405 (.285)	.026	.155	.036 (.311)	.002	.909
PNMS → Internalizing, 5y	2.658 (.201)	.332	<.001	2.752 (.252)	.332	<.001
PNMS → Externalizing, 5y	2.442 (.215)	.274	<.001	2.593 (.273)	.281	<.001
CRP → Internalizing, 5y	.523 (.245)	.036	.033	.248 (.268)	.017	.354
CRP → Externalizing, 5y	.318 (.272)	.020	.244	.037 (.297)	.002	.900
PNMS → Internalizing, 9y	2.106 (.184)	.311	<.001	2.601 (.238)	.376	<.001
PNMS → Externalizing, 9y	1.709 (.172)	.262	<.001	2.215 (.224)	.333	<.001
CRP → Internalizing, 9y	.415 (.230)	.034	.072	.279 (.253)	.023	.270
CRP → Externalizing, 9y	-.018 (.222)	-.002	.934	-.143 (.242)	-.012	.557
Indirect associations						
PNMS → CRP → Internalizing, 36m	-.002 (.006)	-.000	.701	.001 (.003)	.768	.792
PNMS → CRP → Externalizing, 36m	.005 (.008)	.001	.559	.000 (.002)	.629	.816
PNMS → CRP → Internalizing, 5y	.001 (.003)	.000	.792	-.007 (.008)	-.001	.347
PNMS → CRP → Externalizing, 5y	-.000 (.002)	-.000	.816	-.003 (.006)	.000	.613
PNMS → CRP → Internalizing, 9y	.000 (.003)	.000	.618	-.003 (.006)	-.000	.645
PNMS → CRP → Externalizing, 9y	-.000 (.002)	-.000	.694	.001 (.002)	.000	.757

Note. *b* = unstandardized regression coefficient, *SE* = standard error, *β* = standardized regression coefficient, *p* = p-value, CRP = C-reactive protein. Separate models run for each measurement point. All models converged on 20 imputed data sets. Covariates adjusted for include maternal ethnicity, alcohol use during pregnancy, smoking during pregnancy, maternal education, parity, sex of child, maternal BMI at intake, and gestational age at measurement of CRP.

Table 4.3. Direct and indirect associations between prenatal maternal stress, maternal inflammation during early pregnancy, and paternal-reported children's internalizing and externalizing symptoms

	Unadjusted			Adjusted		
Direct associations	*b (SE)*	*β*	*p*	*b (SE)*	*β*	*p*
PNMS → Internalizing, 36m	1.941 (.235)	.258	<.001	1.877 (.284)	.239	<.001
PNMS → Externalizing, 36m	1.923 (.297)	.192	<.001	2.239 (.377)	.215	<.001
CRP → Internalizing, 36m	-.254 (.246)	-.021	.302	-.169 (.250)	-.014	.499
CRP → Externalizing, 36m	.134 (.327)	.008	.682	.206 (.337)	.013	.541
PNMS → Internalizing, 9y	1.309 (.232)	.182	<.001	1.761 (.293)	.236	<.001
PNMS → Externalizing, 9y	1.209 (.234)	.164	<.001	1.718 (.296)	.225	<.001
CRP → Internalizing, 9y	.527 (.249)	.046	.034	.539 (.257)	.047	.036
CRP → Externalizing, 9y	.363 (.255)	.031	.155	.387 (.261)	.033	.139
Indirect associations						
PNMS → CRP → Internalizing, 36m	-.004 (.007)	-.001	.521	.000 (.004)	.000	.932
PNMS → CRP → Externalizing, 36m	.001 (.005)	.000	.853	-.006 (.002)	-.001	.589
PNMS → CRP → Internalizing, 9y	.015 (.012)	.002	.221	.001 (.008)	.000	.901
PNMS → CRP → Externalizing, 9y	.009 (.011)	.001	.416	.001 (.007)	.000	.907

Note. *b* = unstandardized regression coefficient, *SE* = standard error, *β* = standardized regression coefficient, *p* = p-value, CRP = C-reactive protein. Separate models run for each measurement point. All models converged on 20 imputed data sets. Covariates adjusted for include maternal ethnicity, alcohol use during pregnancy, smoking during pregnancy, maternal education, parity, sex of child, maternal BMI at intake, and gestational age at measurement of CRP.

Appendix 4.1: Generation R items included in prenatal maternal stress exposure variable

Life Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Death of partner or child	20-25 weeks	Dichotomous (yes/no)	(1)
Death of a friend or relative	20-25 weeks	Dichotomous (yes/no)	(1)
Serious illness of child, partner or relative	20-25 weeks	Dichotomous (yes/no)	(1)
Job loss	20-25 weeks	Dichotomous (yes/no)	(1)
Residence change	20-25 weeks	Dichotomous (yes/no)	(1)
Personal illness (moderate or poor health)	20-25 weeks	Dichotomous (yes/no)	(2)
Problems at work or school	20-25 weeks	Dichotomous (yes/no)	(3)
Unplanned pregnancy	12-20 weeks	Dichotomous (yes/no)	(4)
Vaginal bleeding in preceding two months	20-25 weeks	Dichotomous (yes/no)	(4)
Chromosomal abnormalities tests (e.g. Chorionic villus sampling)	30 weeks	Dichotomous (yes/no)	(4)
Dissatisfaction with obstetric care	30 weeks	Dichotomous (yes/no)	(4)
Admission to a hospital for more than 24 hours	30 weeks	Dichotomous (yes/no)	(4)
Victim of robbery, theft, physical abuse or rape	20-25 weeks	Dichotomous (yes/no)	(4)
Worry about the health of the baby	12-20 weeks	Dichotomous (Likert scale dichotomized into worried/not worried)	(5)
Worry about the pregnancy	12-20 weeks	Dichotomous (Likert scale dichotomized into worried/not worried)	(5)

Contextual Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Lack of housing major appliances (heating, washing machine, refrigerator)	30 weeks	Dichotomous (yes/no)	(4)
Housing defects (draughts, windows with condensations or dampness)	30 weeks	Dichotomous (yes/no)	(4)
Financial difficulties (e.g. difficulties in paying rent)	30 weeks	Dichotomous (yes/no)	(4)
House inadequacy (e.g., too small, lack of privacy)	20-25 weeks	Dichotomous (yes/no)	(4)
Major financial problem (e.g. income insufficient)	20-25 weeks	Dichotomous (yes/no)	(4)
Downturn in financial situation	20-25 weeks	Dichotomous (yes/no)	(1)

Personal Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Having a criminal record	17 weeks	Dichotomous (yes/no)	(6)
Violent interpersonal offenses (threats, assault)	30 weeks	Dichotomous (yes/no)	(6)
Public order offenses (drunk driving, theft, vandalism)	30 weeks	Dichotomous (yes/no)	(6)
Early parenthood (age < 19 years)	30 weeks	Dichotomous (yes/no)	(4)
Maternal psychopathology: Global BSI score	30 weeks	Dichotomous (cut-off of 0.72 points)	(7)

Interpersonal Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Arguments with partner	17 weeks	Dichotomous (yes/no)	(3)
Arguments with family or friends	17 weeks	Dichotomous (yes/no)	(3)
Difficulties in contact with others	17 weeks	Dichotomous (yes/no)	(3)
Marital status	17 weeks	Dichotomous (yes/no)	(4)
Large family size	17 weeks	Dichotomous (yes/no)	(4)
Difficulty in making plans	17 weeks	Dichotomous (Likert scale dichotomized)	(8)
Disapproval of others	17 weeks	Dichotomous (Likert scale dichotomized)	(8)
Difficulty in talking about sadness	17 weeks	Dichotomous (Likert scale dichotomized)	(8)
Avoidance of talking about problems	17 weeks	Dichotomous (Likert scale dichotomized)	(8)
Feelings of being unaccepted	17 weeks	Dichotomous (Likert scale dichotomized)	(8)
Unpleasant and painful feelings	30 weeks	Dichotomous (Likert scale dichotomized)	(8)
Inability to solve problems	30 weeks	Dichotomous (Likert scale dichotomized)	(8)
Decision-making is a problem	17 weeks	Dichotomous (Likert scale dichotomized)	(8)
Distrust of each other	17 weeks	Dichotomous (Likert scale dichotomized)	(8)
Conflicts with each other	17 weeks	Dichotomous (Likert scale dichotomized)	(8)
Family support problems	17 weeks	Dichotomous (Likert scale dichotomized)	(8)
Divorce in the preceding year	17 weeks	Dichotomous (yes/no)	(1)

Table S4.1. Comparison between included and excluded respondents on participant characteristics

Characteristics	Statistics	
	Respondents (n=4,902)	Non-respondents (n=4,992)
Maternal age at enrollment, years	30.0 (4.9)	29.8 (5.8)
Maternal ethnicity		
Dutch	2731 (55.7)	1914 (43.6)
Other western	451 (9.2)	349 (8.0)
Non-western	1720 (35.1)	2125 (48.4)
Maternal educational level		
Primary or below	414 (8.4)	590 (14.9)
Secondary	2202 (44.9)	1900 (48.0)
Higher	2286 (46.6)	1472 (37.2)
Maternal BMI[1]	24.4 (4.4)	25.5 (4.7)
Parity, ≥1	2012 (41.0)	2282 (49.1)
Maternal smoking during pregnancy		
Never	3545 (72.3)	2806 (74.9)
Smoked until pregnancy was known	458 (9.3)	287 (7.7)
Continued smoking	899 (18.3)	651 (17.4)
Maternal alcohol use during pregnancy		
Never	2028 (41.4)	1907 (57.9)
Drank until pregnancy was known	692 (14.1)	392 (11.9)
Continued drinking occasionally	1749 (35.7)	830 (25.2)
Continued drinking frequently[2]	433 (8.8)	162 (4.9)
Maternal infection during pregnancy (yes)	4668 (95.2)	723 (99.7)
Household income, €/month		
~1200	951 (19.4)	685 (26.8)
~2000	931 (19.0)	487 (19.0)
2001~	3020 (61.6)	1387 (54.2)
Maternal stress score		
Life stress	1.9 (1.6)	2.1 (1.7)
Contextual stress	1.0 (1.3)	1.1 (1.3)
Personal stress	0.2 (0.5)	0.3 (0.6)
Interpersonal stress	2.0 (2.6)	2.4 (2.9)
Child sex (male)	2446 (49.9)	2492 (51.4)
Child gestational age at birth, weeks	39.9 (1.7)	39.5 (2.3)
Child birth weight, grams	3461.8 (687.1)	3623.5 (1488.0)

Note. Mean (SD) is reported for continuous variables, and frequency (%) is reported for categorical variables. Statistics of the first imputed dataset are reported for respondents. [1]BMI-Body mass index. [2]Defined as 'one or more glasses of alcohol per week in at least two trimesters'

Table S4.2. Direct and indirect associations between prenatal maternal stress, maternal inflammation during early pregnancy, and children's internalizing and externalizing symptoms, excluding CRP values > 10 mg/L

	Unadjusted			Adjusted		
Direct associations	*b (SE)*	*β*	*p*	*b (SE)*	*β*	*p*
PNMS → CRP	.012 (.009)	.031	.193	.003 (.011)	.008	.767
CRP → Internalizing, 36m	187. (.299)	.011	.621	-.034 (.308)	-.002	.912
CRP → Externalizing, 36m	.385 (.315)	.026	.417	.072 (.409)	.004	.861
CRP → Internalizing, 5y	.413 (.377)	.017	.337	.183 (.361)	.010	.612
CRP → Externalizing, 5y	.318 (.471)	.009	.644	.049 (.403)	.002	.904
CRP → Internalizing, 9y	.221 (.292)	.018	.318	-.018 (.331)	-.001	.956
CRP → Externalizing, 9y	-.027 (.295)	-.003	.615	-.418 (.321)	-.029	.193
Indirect associations						
PNMS → CRP → Internalizing, 36m	-.001 (.005)	-.000	.781	-.001 (.004)	-.000	.732
PNMS → CRP → Externalizing, 36m	.003 (.007)	.001	.717	-.001 (.005)	-.000	.920
PNMS → CRP → Internalizing, 5y	.001 (.004)	.000	.778	-.000 (.003)	-.000	.967
PNMS → CRP → Externalizing, 5y	-.001 (.003)	-.000	.891	-.000 (.001)	-.000	.938
PNMS → CRP → Internalizing, 9y	.000 (.004)	.000	.656	-.002 (.005)	-.000	.721
PNMS → CRP → Externalizing, 9y	-.002 (.007)	-.001	.714	-.007 (.010)	-.001	.486

Note. *b* = unstandardized regression coefficient, *SE* = standard error, *β* = standardized regression coefficient, *p* = p-value, CRP = C-reactive protein. Separate models run for each measurement point. All models converged on 20 imputed data sets. Covariates adjusted for include maternal ethnicity, alcohol use during pregnancy, smoking during pregnancy, maternal education, parity, sex of child, maternal BMI at intake, and gestational age at measurement of CRP.

Table S4.3. Direct and indirect associations between prenatal life stress, maternal inflammation during early pregnancy, and children's internalizing and externalizing symptoms

	Unadjusted			Adjusted		
Direct associations	*b (SE)*	*β*	*p*	*b (SE)*	*β*	*p*
LS → CRP	.006 (.004)	.022	.137	-.002 (.004)	-.008	.557
LS → Internalizing, 36m	.691 (.059)	.211	<.001	.525 (.061)	.161	<.001
LS → Externalizing, 36m	.684 (.079)	.160	<.001	.545 (.083)	.126	<.001
LS → Internalizing, 5y	.756 (.067)	.187	<.001	.591 (.071)	.147	<.001
LS → Externalizing, 5y	.643 (.075)	.143	<.001	.487 (.079)	.109	<.001
LS → Internalizing, 9y	.693 (.062)	.204	<.001	.657 (.065)	.194	<.001
LS → Externalizing, 9y	.445 (.061)	.136	<.001	.421 (.063)	.129	<.001
Indirect associations						
LS → CRP → Internalizing, 36m	.000 (.001)	.000	.736	.000 (.001)	.000	.739
LS → CRP → Externalizing, 36m	.001 (.002)	.000	.552	-.000 (.001)	-.000	.865
LS → CRP → Internalizing, 5y	.001 (.002)	.000	.564	-.001 (.002)	-.000	.405
LS → CRP → Externalizing, 5y	.001 (.002)	.000	.610	-.000 (.001)	-.000	.794
LS → CRP → Internalizing, 9y	.000 (.002)	.000	.822	-.001 (.002)	-.000	.405
LS → CRP → Externalizing, 9y	-.000 (.000)	-.000	.943	-.001 (.002)	.000	.641

Note. *b* = unstandardized regression coefficient, *SE* = standard error, *β* = standardized regression coefficient, *p* = p-value, CRP = C-reactive protein. Separate models run for each measurement point. All models converged on 20 imputed data sets. Covariates adjusted for include maternal ethnicity, alcohol use during pregnancy, smoking during pregnancy, maternal education, parity, sex of child, maternal BMI at intake, and gestational age at measurement of CRP.

Table S4.4. Direct and indirect associations between prenatal contextual stress, maternal inflammation during early pregnancy, and children's internalizing and externalizing symptoms

	Unadjusted			Adjusted		
Direct associations	*b (SE)*	*β*	*p*	*b (SE)*	*β*	*p*
CS → CRP	.016 (.005)	.048	.001	-.006 (.005)	-.019	.211
CS → Internalizing, 36m	.848 (.079)	.198	<.001	.539 (.084)	.126	<.001
CS → Externalizing, 36m	.925 (.105)	.164	<.001	.668 (.114)	.118	<.001
CS → Internalizing, 5y	.999 (.085)	.200	<.001	.736 (.094)	.145	<.001
CS → Externalizing, 5y	.858 (.096)	.155	<.001	.643 (.105)	.114	<.001
CS → Internalizing, 9y	.901 (.081)	.209	<.001	.877 (.089)	.201	<.001
CS → Externalizing, 9y	.626 (.079)	.151	<.001	.629 (.086)	.150	<.001
Indirect associations						
CS → CRP → Internalizing, 36m	.001 (.002)	.000	.749	.001 (.002)	.000	.524
CS → CRP → Externalizing, 36m	.003 (.004)	.001	.337	-.000 (.002)	-.000	.793
CS → CRP → Internalizing, 5y	.005 (.004)	.001	.164	-.002 (.003)	-.000	.369
CS → CRP → Externalizing, 5y	.003 (.003)	.001	.409	-.001 (.002)	-.000	.777
CS → CRP → Internalizing, 9y	.005 (.004)	.001	.240	-.001 (.002)	-.000	.628
CS → CRP → Externalizing, 9y	-.002 (.003)	-.000	.635	.000 (.001)	.000	.750

Note. *b* = unstandardized regression coefficient, *SE* = standard error, *β* = standardized regression coefficient, *p* = p-value, CRP = C-reactive protein. Separate models run for each measurement point. All models converged on 20 imputed data sets. Covariates adjusted for include maternal ethnicity, alcohol use during pregnancy, smoking during pregnancy, maternal education, parity, sex of child, maternal BMI at intake, and gestational age at measurement of CRP.

Table S4.5. Direct and indirect associations between prenatal personal stress, maternal inflammation during early pregnancy, and children's internalizing and externalizing symptoms

	Unadjusted			Adjusted		
Direct associations	*b (SE)*	*β*	*p*	*b (SE)*	*β*	*p*
PS → CRP	.012 (.012)	.015	.290	.001 (.011)	.001	.920
PS → Internalizing, 36m	1.628 (.205)	.147	<.001	1.245 (.212)	.112	<.001
PS → Externalizing, 36m	1.997 (.271)	.136	<.001	1.564 (.285)	.106	<.001
PS → Internalizing, 5y	2.001 (.215)	.156	<.001	1.562 (.227)	.121	<.001
PS → Externalizing, 5y	2.134 (.239)	.149	<.001	1.696 (.251)	.118	<.001
PS → Internalizing, 9y	1.101 (.207)	.099	<.001	.923 (.219)	.083	<.001
PS → Externalizing, 9y	1.477 (.198)	.138	<.001	1.398 (.209)	.131	<.001
Indirect associations						
PS → CRP → Internalizing, 36m	.002 (.008)	.000	.776	-.006 (.007)	-.001	.411
PS → CRP → Externalizing, 36m	.012 (.012)	.001	.341	-.000 (.008)	-.000	.973
PS → CRP → Internalizing, 5y	.008 (.008)	.001	.339	.001 (.004)	.000	.710
PS → CRP → Externalizing, 5y	.005 (.006)	.000	.476	.000 (.003)	.000	.957
PS → CRP → Internalizing, 9y	.012 (.010)	.001	.243	.004 (.006)	.000	.525
PS → CRP → Externalizing, 9y	-.002 (.008)	-.000	.756	-.002 (.005)	-.000	.627

Note. *b* = unstandardized regression coefficient, *SE* = standard error, *β* = standardized regression coefficient, *p* = p-value, CRP = C-reactive protein. Separate models run for each measurement point. All models converged on 20 imputed data sets. Covariates adjusted for include maternal ethnicity, alcohol use during pregnancy, smoking during pregnancy, maternal education, parity, sex of child, maternal BMI at intake, and gestational age at measurement of CRP.

Table S4.6. Direct and indirect associations between prenatal interpersonal stress, maternal inflammation during early pregnancy, and children's internalizing and externalizing symptoms

	Unadjusted			Adjusted		
Direct associations	*b (SE)*	*β*	*p*	*b (SE)*	*β*	*p*
IS → CRP	.007 (.002)	.045	.002	-.002 (.002)	-.012	.415
IS → Internalizing, 36m	.446 (.037)	.219	<.001	.323 (.039)	.159	<.001
IS → Externalizing, 36m	.509 (.050)	.189	<.001	.411 (.053)	.153	<.001
IS → Internalizing, 5y	.499 (.041)	.204	<.001	.385 (.045)	.157	<.001
IS → Externalizing, 5y	.475 (.045)	.175	<.001	.389 (.050)	.143	<.001
IS → Internalizing, 9y	.342 (.038)	.167	<.001	.324 (.041)	.157	<.001
IS → Externalizing, 9y	.322 (.037)	.163	<.001	.329 (.039)	.166	<.001
Indirect associations						
IS → CRP → Internalizing, 36m	.000 (.001)	.000	.809	.000 (.001)	.000	.734
IS → CRP → Externalizing, 36m	.002 (.002)	.001	.353	-.000 (.001)	-.000	.892
IS → CRP → Internalizing, 5y	.002 (.002)	.001	.190	-.001 (.001)	-.000	.465
IS → CRP → Externalizing, 5y	.001 (.002)	.000	.463	-.000 (.001)	-.000	.805
IS → CRP → Internalizing, 9y	.002 (.002)	.001	.243	-.000 (.001)	-.000	.690
IS → CRP → Externalizing, 9y	-.001 (.001)	-.000	.697	.000 (.001)	.000	.770

Note. *b* = unstandardized regression coefficient, *SE* = standard error, *β* = standardized regression coefficient, *p* = p-value, CRP = C-reactive protein. Separate models run for each measurement point. All models converged on 20 imputed data sets. Covariates adjusted for include maternal ethnicity, alcohol use during pregnancy, smoking during pregnancy, maternal education, parity, sex of child, maternal BMI at intake, and gestational age at measurement of CRP.

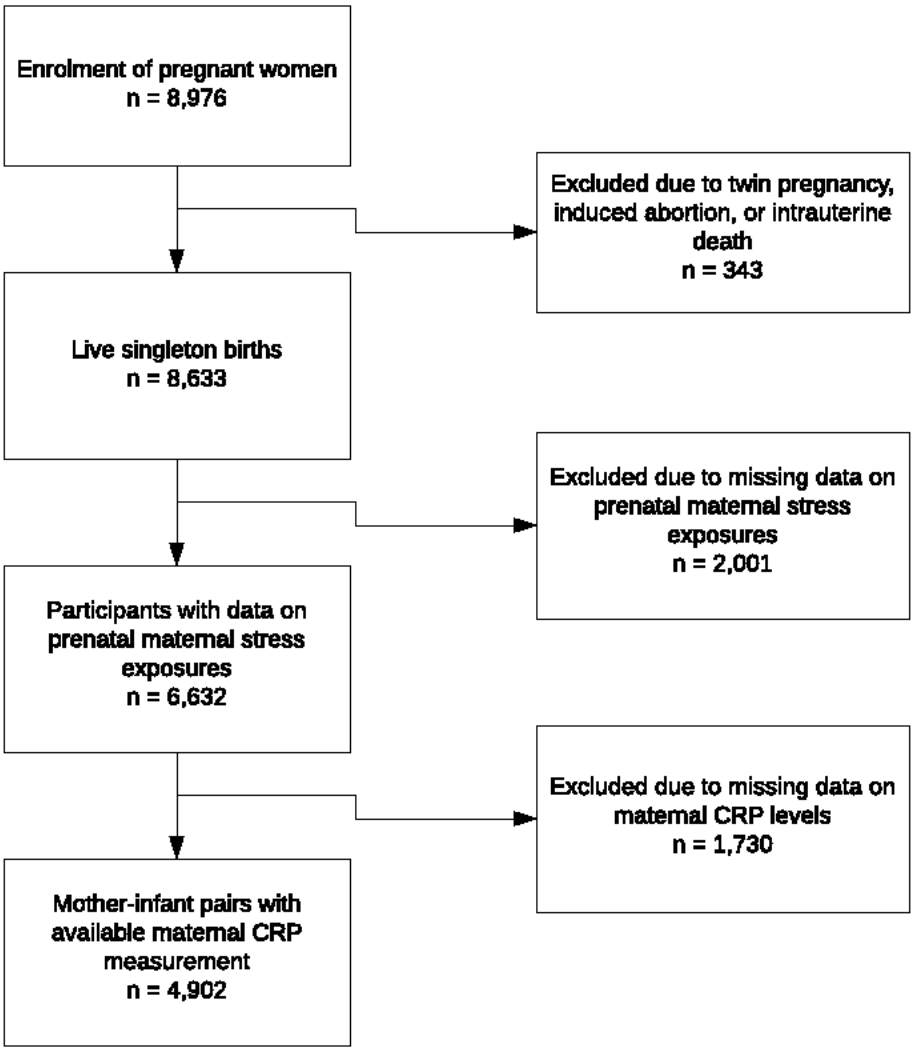

Figure S4.1. Participant inclusion flow chart

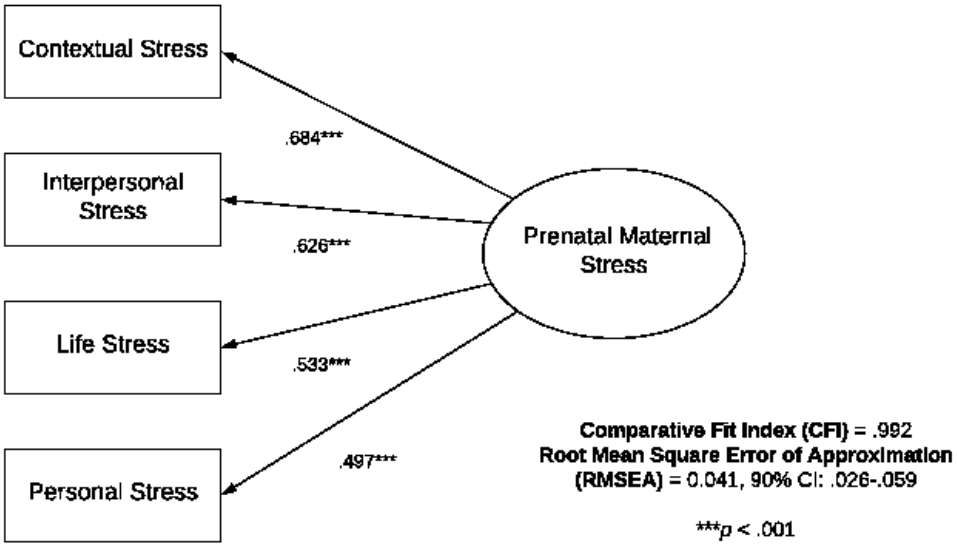

Figure S4.2. Path diagram of latent prenatal maternal stress variable, including standardized factor loadings and indices of model fit

References (Appendix)

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Chapter 5

The mediating role of childhood inflammation in the associations between prenatal maternal stress and adolescent mental health disorders

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number). Supplementary materials are included as appendices at the end of this chapter, with tables and figures denoted with an "S" followed by two digits (chapter number followed by table or figure number).

Article preface: The primary aim of this study was to examine the associations between prenatal maternal stress, children's pro-inflammatory marker levels at age 9, and diagnoses of generalized anxiety disorder and depression during adolescence, and to ascertain whether childhood inflammation mediated the associations between prenatal maternal stress and diagnoses of generalized anxiety disorder and depression in adolescence.

Contribution statement: I am the first author on this article. I designed the study and its objectives, with guidance from my co-authors. I conducted all study analyses, prepared the first draft of the manuscript, and prepared the manuscript for submission.

ABSTRACT

Background: Inflammation has been proposed as a potential mediator of the associations between prenatal maternal stress and offspring mental disorders, however, few studies have investigated the role of offspring inflammation in these associations. The objective of this study was to examine the associations between prenatal maternal stress, children's pro-inflammatory marker concentrations at age 9, and diagnoses of generalized anxiety disorder and depression during adolescence, and to examine whether inflammation mediated the associations between prenatal maternal stress and diagnoses of generalized anxiety disorder and depression.

Methods: This study included 3,019 mother-child pairs from the Avon Longitudinal Study of Parents and Children. Prenatal maternal stress was examined using 55 items measured during pregnancy. Inflammation was assessed using serum concentrations of C-reactive protein (CRP) and interleukin-6 (IL-6) when children were 9 years old. Generalized anxiety disorder and depression was assessed when children were 16 and 18 years old, respectively. Analyses comprised of linear and logistic regression-based structural equation models.

Results: Prenatal maternal stress was associated with higher concentrations of IL-6 in childhood, and with diagnoses of depression and generalized anxiety disorder in adolescence; IL-6 was also associated with generalized anxiety disorder. The association between prenatal maternal stress and generalized anxiety disorder was partially mediated by IL-6.

Conclusions: The association between prenatal maternal stress and generalized anxiety disorder may be mediated by inflammation during childhood. This finding adds to a growing body of research examining the role of inflammation in the associations between prenatal maternal stress and children's risk towards mental health disorders.

Keywords: prenatal stress, inflammation, depression, anxiety, development, ALSPAC

INTRODUCTION

Exposure to stress in-utero can lead to physiological alterations in the fetus, which can have long-lasting effects on children's health and development (1,2). Several studies have demonstrated associations between prenatal maternal stress exposures, including stressful life events and maternal psychopathology, and children's mental health from early childhood into adulthood, including depression and externalizing behaviours (3–5). Experiencing mental disorders early in development can lead to a range of adverse outcomes, including recurrence and/or comorbidity with other disorders (6,7), lower socioeconomic attainment (8), and earlier parenthood (8). Considering this evidence, the effects of both prenatal stress exposure and of experiencing mental disorders on children have the potential to span generations (9,10).

It has been suggested that the associations between prenatal maternal stress and children's risk of mental health disorders may be partially mediated by dysregulation of the maternal and fetal immune systems (11,12). The potential role of inflammation as a mechanism underlying these associations is supported by animal and epidemiological research which has demonstrated associations between prenatal maternal stress and higher concentrations of pro-inflammatory markers including interleukin 6 (IL-6) and C-reactive protein (CRP) in mothers and their children (11,13,14). The role of inflammation is further reinforced by extensive research demonstrating robust associations between concentrations of pro-inflammatory markers and risk of incident depression and other mental health disorders (15–21), as well as laboratory studies which suggest that IL-6 and CRP may cross the placental barrier from mother and child and vice versa (22,23). To date, emerging research has examined mediation of the associations between prenatal maternal stress and children's developmental outcomes through maternal and placental

levels of inflammatory markers (24,25). However, few studies have examined mediation of these associations through children's inflammation. One recent study by Flouri and colleagues suggested that higher IL-6 levels in children mediated the association between postnatal, but not prenatal, stressful life events and children's depression (26); thus, limited research to date calls for further inquiry into the role of children's inflammation in these associations.

Given that stress is a broad concept, there is also need for research that considers how comprehensive prenatal stress measures (i.e., measures including stressful experiences, psychopathology, and other potential sources of stress) may be associated with children's inflammation and mental health (27). Examining the effects of comprehensive measures of prenatal stress on inflammation and later mental health outcomes can address the overlap that exists between many of these stressors (27). Furthermore, few studies have demonstrated direct associations between comprehensive prenatal maternal stress measures and children's inflammation, necessitating the need for further research into these associations.

Using data from a prospective birth cohort of over 3,000 mothers and their children, we conducted a study to address the above-highlighted evidence gaps, including the need for comprehensive stress measurement as well as the need for further inquiry into the potential mediating role of offspring inflammation in the associations between prenatal maternal stress and offspring mental health. The objective of this study was to examine the associations between prenatal maternal stress, children's pro-inflammatory marker levels at age 9, and diagnoses of generalized anxiety disorder and depression during adolescence, and to ascertain whether children's inflammation mediated the longitudinal associations between prenatal maternal stress

and generalized anxiety disorder and depression during adolescence. We hypothesized that higher prenatal maternal stress would be associated with greater inflammation during childhood, measured via serum levels of IL-6 and CRP at age 9, and greater risk towards generalized anxiety disorder and depression in adolescence, and that that the associations between prenatal maternal stress and children's risk towards generalized anxiety disorder and depression would be mediated by higher levels of IL-6 or CRP.

METHODS

Data and participants

This study used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based, prospective pregnancy cohort based in Avon County, in southwest England. Pregnant women residing in the region with delivery dates between April 1, 1991 and December 31, 1992 were enrolled; the cohort comprises 14,062 live births from 14,541 pregnancies. ALSPAC includes several components, such as questionnaires, which are completed by carers (typically the mother), partners and/or fathers, children, and schools; and detailed cognitive and physical examinations, biological sampling, and genome-wide screens (28,29). The current study sample includes 3,019 mother-child pairs with available data on main study variables (Figure 5.1). This study received ethical approval from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees, and the University of Ottawa Research Ethics Board (REB # H-09-19-4923).

Measures

Prenatal maternal stress. A broad measure of prenatal maternal stress was constructed based on an existing measure developed in ALSPAC by Cecil and colleagues (30), which has been adapted for further use in Dutch and Norwegian birth cohort studies (31,32). The prenatal stress measure comprised of 55 items collected through maternal questionnaires delivered to mothers between 8 and 32 weeks of pregnancy. Items fell under four stress domains: life stress, contextual stress, personal stress, and interpersonal stress (see Appendix 5.1 for detailed information on included items). Mean scores were generated from each domain by summing included items and dividing by the number of items in each domain, and scores were then used as indicators in a confirmatory factor analysis to extract a latent prenatal maternal stress factor with good model fit (see Figure S5.1). Consistent with prior studies utilizing this method to examine prenatal maternal stress (33), inclusion into the study required complete data for at least two out of four stress domains. Maternal education was excluded from the measure and analyzed as a covariate, as maternal education may impact children's development through pathways independent of prenatal maternal stress (32).

Child inflammation. Serum concentrations of IL-6 and CRP were examined in children at approximately 9 years of age (mean ± SD = 9.83 ± 0.29 years). Blood samples were drawn from non-fasting participants, centrifuged, frozen at −80 °C in 1 mL aliquots, and IL-6 and CRP levels were assayed in 2008 after a median storage period of 7.5 years. High sensitivity CRP levels were measured via automated particle-enhanced immunoturbidimetric assay (Roche), with a minimum detection limit of 0.03 mg/L. CRP values in the study sample ranged from 0.01 to 67.44 mg/L; mean ± SD = 0.75 ± 2.72 mg/L (31 participants > 10 mg/L). IL-6 levels were

measured using enzyme-linked immunosorbent assay (ELISA; R&D Systems) with a minimum detection limit of 0.007 pg/mL. IL-6 values for the study sample ranged from 0.007 to 13.90 pg/mL; mean ± SD = 1.26 ± 1.52 pg/mL. Interassay coefficients of variation for both CRP and IL-6 were below 5%. Analyses were carried out using continuous values of IL-6 and CRP, and given right-skewed distributions, both measures were log-transformed. Furthermore, we carried out sensitivity analyses excluding those with CRP levels > 10.0mg/L, as CRP levels above this threshold are typically indicative of acute infection/inflammation (11,34).

Adolescent mental health. Presence of generalized anxiety disorder according to criteria from the fourth revision of the Diagnostic and Statistical Manual (DSM-IV)(35) and the tenth version of the International Classification of Diseases (ICD-10)(36) was assessed using the Development and Well-being Assessment (DAWBA) at 16 years of age (37). The DAWBA was delivered using structured interviews by non-clinicians with study participants; its diagnostic algorithm provided a likely diagnosis (yes or no) of current generalized anxiety disorder. The DAWBA is considered a valid and reliable measure of psychopathology in general population and clinical contexts (38).

Depression was assessed at age 18 using a self-administered, computerized version of the Clinical Interview Schedule–Revised (CIS-R). The CIS-R is a commonly used tool for measuring depression, and the computerized version is considered as reliable as clinician interview (39). The CIS-R includes core symptoms of depression based on ICD-10 criteria and provides a total depression score of 0 to 21 comprising symptom scores for depressive thoughts, fatigue, concentration, and sleep problems. Total scores reflect severity of depressive symptoms

in the past week, with higher scores indicating greater severity. A dichotomous variable indicating possible cases of depression was constructed using a cut-score of 7 or more to represent cases of depression (16). A variable indicating probable ICD-10 diagnosis of depression using the CIS-R was also investigated in sensitivity analyses.

Covariates. A number of potential confounding measures related to exposure and outcome variables were identified and included in analyses, including maternal education (below O-level, O-level, A-level, postsecondary degree); paternal social class (defined as classes I-VI and manual or non-manual); offspring ethnicity (White or non-White); offspring age in months during measurement of inflammatory marker levels; body mass index (BMI) during measurement of inflammatory marker levels; and presence of a recent acute infection (i.e., within the past week) during measurement of inflammatory marker levels. Given that sex differences in the consequences to prenatal maternal stress exposure are well-documented (40), sex of the child (male or female) was first examined as a moderating variable to assess for potential sex differences, and later adjusted for in analyses. Child mental health prior to inflammation was measured using the Strengths and Difficulties Questionnaire (SDQ) at age 7 years, assessed by maternal report. The SDQ measures difficulties in 4 domains (emotional problems, conduct problems, hyperactivity, and peer problems), and is a valid and reliable tool for assessing children's mental health and behaviour (41). Postnatal maternal stressful events were assessed at child age 6 years, using a checklist of 43 events (42,43). A total score indicating number of events experienced by the mother was generated for analysis.

Statistical analyses

Stata version 15 (StataCorp, College Station, TX) was used to examine respondent characteristics, and to examine interactions between prenatal maternal stress and sex of the child on inflammation and mental health variables to determine if subsequent analyses should be sex-stratified. All remaining analyses were performed using MPlus version 8 (Muthén & Muthén, Los Angeles, CA). Confirmatory factor analysis was conducted to estimate a latent factor of prenatal maternal stress, with mean scores from the four prenatal stress domains used as indicators (Figure S5.1). Next, estimation of the associations between prenatal maternal stress, concentrations of IL-6 and CRP, and generalized anxiety disorder and depression was performed using linear and logistic regression-based structural equation models. Unadjusted and adjusted models were run; variables adjusted for included maternal education, paternal social class, offspring ethnicity, and sex. In addition, analyses involving CRP or IL-6 included additional adjustments for offspring BMI at inflammation assessment, offspring age in months at inflammation assessment, and presence of a recent infection at inflammation assessment. Given the use of a latent exposure variable, we did not estimate odds ratios (ORs) for logistic regression-based analyses; unstandardized and standardized parameter estimates were reported for all analyses. Unstandardized parameter estimates (*b*) represent changes in the log-odds of the outcome variable per one unit increase in the latent prenatal maternal stress variable; we reported unstandardized estimates with their standard errors (SEs). The latent prenatal maternal stress variable was standardized by scaling its variance to 1, thus the standardized parameter estimates (β) reported represent changes in the standard deviations of the log-odds of outcome variable per one standard deviation increase in latent prenatal maternal stress; we reported unstandardized

estimates with their 95% confidence intervals (CIs). The standardized estimates were primarily used to ascertain effect size.

Mediation analyses were conducted using the MODEL INDIRECT command in MPlus with bootstrapping (n = 5000) conducted to generate bias-corrected bootstrapped confidence intervals, in line with recommendations by Hayes (44). A conceptual path diagram highlighting these analyses is presented in Figure S5.2. To account for potential non-normality of data and missing values on prenatal stress items and covariates, direct associations were analyzed using full information maximum likelihood estimation with robust standard errors (MLR) to account for potential non-normality of data and to impute for missing values on study measures; this method is valid under the assumption that missing data are missing at random (45). For mediation analyses, MLR estimation is not available, thus a maximum likelihood (ML) estimator coupled with Monte Carlo integration was used to ascertain statistical significance of the indirect effects for the full study sample. Parameter estimates generated using bootstrapping for complete cases and significance levels using ML estimation were not appreciably different, thus parameter estimates are reported with their bootstrapped confidence intervals. Sensitivity analyses comprised the adjustment of children's mental health measured at the assessment point closest to inflammation measurement (age 7 years) to account for potential reverse causality, maternal stressful life events measured prior to inflammation to account for postnatal effects, probable ICD-10 diagnoses of depression, and the exclusion of respondents reporting CRP values greater than 10 mg/L.

RESULTS

The majority of mothers included in the sample completed secondary school (O-level or higher), and the majority of fathers were employed in non-manual labour (classes I-III). Most children were White (94.24%), 15 children (0.50%) reported a diagnosis of generalized anxiety disorder at age 15, and 374 children (12.39%) represented possible cases of depression at age 17. Descriptive characteristics of the sample, including information on missing data, are summarized in Table 5.1. A comparison between included and excluded respondents on study measures is highlighted in Table S5.1; excluded respondents generally appeared to report lower socioeconomic status (i.e., lower maternal education, lower paternal social class).

The measurement model for latent prenatal maternal stress (Figure S5.1) had good fit (RMSEA = .074, 90% CI = .054, .096; CFI = .903). Tests for interactions between prenatal maternal stress and sex were not statistically significant for IL-6 (p = .43), CRP (p = .60), generalized anxiety disorder (p = .12), and depression (p = .97); thus, all subsequent models were adjusted for sex instead of stratified. Prior to and after adjustment for covariates, higher prenatal maternal stress was associated with higher concentrations of children's IL-6 (adjusted β =.071, 95% CI: .015, .126), and greater likelihood of generalized anxiety disorder (adjusted β =.110, 95% CI: .006, .215), and depression (adjusted β =.214, 95% CI: .123, .304; see Table 5.2). Higher IL-6 was associated with greater likelihood of generalized anxiety disorder prior to and after adjustment (adjusted β =.276, 95% CI: .131, .420); higher IL-6 was also associated with depression, but this association was attenuated after adjustment for covariates (adjusted β =.042, 95% CI: -.022, .107). The associations between prenatal maternal stress and CRP, and CRP and generalized anxiety disorder and depression were not statistically significant prior to or after covariate

adjustment (Table 5.2). A small but statistically significant indirect effect was found prior to and after adjustment for covariates for the association between prenatal maternal stress and generalized anxiety disorder through IL-6 (adjusted β = .014, 95% CI: 001, .027). The proportion of the total effect mediated through IL-6 was 6.14%. Indirect effects for the association between prenatal maternal stress and generalized anxiety disorder through CRP, and for the association between prenatal maternal stress and depression through CRP and IL-6 were not statistically significant.

After additional adjustment for child mental health at age 7 for all analyses involving IL-6 and CRP, the associations between prenatal maternal stress and IL-6, and IL-6 and generalized anxiety disorder, and the indirect effect between prenatal maternal stress and generalized anxiety disorder through IL-6 remained statistically significant (see Table 5.3). Adjustment for postnatal maternal stressful events for all associations involving prenatal maternal stress slightly strengthened the association between prenatal maternal stress and IL-6 (adjusted β = .090, 95% CI: .025, .155). The association between prenatal maternal stress and depression, and the indirect effect between prenatal maternal stress and generalized anxiety disorder through IL-6 (adjusted β = .015, 95% CI: .000, .029) remained statistically significant. However, the direct association between prenatal maternal stress and generalized anxiety disorder (adjusted β = .088, 95% CI: -.056, .232) was attenuated. Examining depression using probable ICD-10 diagnoses, and excluding CRP values above 10 mg/L did not significantly change findings for analyses involving depression and/or CRP (see Tables S5.2-S5.3).

DISCUSSION

Findings from this large population-based prospective study suggest that higher prenatal maternal stress is associated with higher concentrations of IL-6 in children at 9 years of age, with higher likelihood of experiencing depression and generalized anxiety disorder in adolescence, and that higher concentrations of IL-6 during childhood are associated with diagnoses of generalized anxiety disorder in adolescence. Our results further suggest that the associations between prenatal maternal stress and diagnoses of generalized anxiety disorder in adolescence are partially mediated by higher levels of IL-6 in childhood. These associations persisted after adjustment for children's mental health and by maternal stressful life events experienced prior to measurement of pro-inflammatory marker levels. To the best of our knowledge, this study represents one of the first to demonstrate mediation of the associations between prenatal maternal stress and children's mental health outcomes through inflammation in childhood.

These results are consistent with studies that have demonstrated associations between higher prenatal maternal anxiety and reduced adaptive immunity in infants (14), prenatal maternal depression and levels of inflammation in adulthood (11), and prenatal stressful life events and elevated levels of pro-inflammatory cytokines including IL-6 in adult women (13). In addition, in a study by Slopen and colleagues, a composite measure of prenatal adversity was associated with higher levels of CRP in adults, independent of childhood adversity (46). However, some studies have also presented null findings; for example, another study using data from the ALSPAC cohort did not report an association between prenatal stressful life events and children's levels of IL-6 or CRP at age 9 (47). The mixed findings across studies may be due to different measurements of prenatal maternal stress – in line with recommendations from the

broader literature (27), the measure of prenatal maternal stress included in the current study encompassed a range of potential stressors, including stressful life events, depression, substance abuse, housing and financial stress, and interpersonal problems. Thus, future studies that examine these associations may seek to utilize comprehensive measures of stress, in line with the current analysis.

There is robust evidence suggesting a link between inflammation and mental disorders. For example, meta-analyses confirm associations between pro-inflammatory markers including interleukin 1 beta (IL-1ß), IL-6, and CRP, and major depression (18–20), and Mendelian randomization studies have proposed that IL-6 and CRP may represent causal risk factors for depression (48). Although longitudinal studies examining the associations between inflammation and generalized anxiety disorder are scarce, research has reported elevated levels of pro-inflammatory markers including CRP, IL-6, and tumor necrosis factor alpha (TNF-α) (49–51), as well as lower circulating levels of anti-inflammatory markers including interleukin 2 (IL-2) and interleukin 4 (IL-4) among patients with generalized anxiety disorder compared to controls (49). Recent population-based studies have also demonstrated associations between higher levels of CRP and anxiety symptoms including irritability and worrying control (52), and in ALSPAC, concurrent CRP levels at age 15 were associated with cases of generalized anxiety disorder (17). Although we did not observe associations between CRP at age 9 and generalized anxiety disorder at age 15, we did find associations between IL-6 at age 9 and generalized anxiety disorder, which when contrasted with the broader evidence base, is one of the few population-based studies to have reported a longitudinal association between inflammation and generalized anxiety disorder in children. In addition, research using ALSPAC data has demonstrated

associations between IL-6 at age 9 and depression using the CIS-R at age 18 (16). Although we did not report the same finding, the study by Khandaker and colleagues examined IL-6 using tertiles in a larger sample of 4,500 participants, whereas we utilized a log-transformed continuous measure of IL-6 as well as ICD-10 diagnoses of depression (compared to total depression scores), which may account for this difference in results.

Our findings should be considered in the context of several limitations. First, our measure of prenatal maternal stress contained no markers of long-term maternal adversity (e.g., socioeconomic deprivation, prior emotional, physical or sexual abuse, or child maltreatment), which have demonstrated associations with inflammation and children's mental health (46,53–55). Future studies may seek to incorporate measures of long-term maternal adversity when examining the effects of prenatal maternal stress on children's developmental outcomes. Second, there was substantial attrition in the study cohort from birth to 18 years of age, which may bias our findings. From our comparison between included and excluded participants, those excluded due to attrition or incomplete data tended to report lower socioeconomic status; this is in line with other attrition analyses in ALSPAC, which suggest that attrition is greater for those experiencing greater socioeconomic adversity (28,56). Explorations of this bias in ALSPAC have suggested that this attrition may result in the underestimation of perinatal effects on offspring health (56), thus it is possible that biases arising from sample attrition in the current study may have led to an underestimation of the true associations between prenatal maternal stress, inflammation, and mental health. Finally, IL-6 generally stimulates production of CRP (57) – although we observed associations with IL-6, we did not observe any significant findings with CRP at age 9, in line with other ALSPAC studies (16,47,58). Measurement error may

potentially explain why associations with CRP were not observed in the current study. We were also unable to assess other markers of inflammation that have demonstrated associations with both early adversity and onset of mental disorders, such as IL-1ß and TNF-α, since these markers were not assayed in ALSPAC.

The current study also has several strengths. The use of a prospective cohort study with extensive maternal-child data available from questionnaires, clinics, and biological sampling allowed us to examine the associations of a comprehensive stress measure with inflammation and with probable cases of generalized anxiety disorder and depression. This also serves to add to the evidence base that has examined associations between prenatal maternal stress exposures and offspring inflammation, as some studies have utilized small samples or cross-sectional and retrospective study designs (13), which may limit their power to appropriately adjust for confounding and assess for mediation. Importantly, although the role of inflammation as a mechanism underlying the associations between prenatal maternal stress and offspring mental health has been hypothesized (12), this finding is one of the first to report significant mediation. This can encourage future population-based studies that consider the effects of other maternal stress exposures in these mediation analyses, that examine synergistic effects between the prenatal and postnatal environments on offspring inflammation and mental health, and which utilize a range of psychiatric outcomes throughout development.

CONCLUSIONS

Our findings suggest that the association between prenatal maternal stress and diagnoses of generalized anxiety disorder in adolescence may be partially mediated by childhood levels of IL-

6. Findings from the current study contribute to an emerging evidence base of studies investigating the role of inflammation on the associations between prenatal maternal stress and mental health outcomes in offspring. Study findings may further serve to highlight the importance of early-life prevention and intervention strategies to minimize children's risk towards mental disorders. For example, the prenatal and postnatal periods may present as opportune times to assess for and reduce the potential impacts of chronic stress on mothers and children, given that pregnant individuals and new parents may experience more contacts with health care systems. Broadly, these results can aid towards better understanding the biological mechanisms that underpin the associations between prenatal maternal stress and children's risk towards mental health disorders.

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Conflicts of Interest: None

Ethics Approval and Ethical Standards: All participants provided informed consent, and ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees and by the University of Ottawa Research Ethics Board (REB #: H-09-19-4923). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 5.1. Descriptive characteristics of study sample (*n* = 3,019)

Parental characteristics	**N**	**Mean (SD) or %**
Maternal education		
Below O-level	514	17.03
O-level only	1,039	34.42
A-level	868	28.75
University degree	571	18.91
Missing	27	0.89
Paternal social class		
I (non-manual)	398	13.18
II (non-manual)	1,068	35.38
III (non-manual)	362	11.99
III (manual)	732	24.25
IV (manual)	215	7.12
V (manual)	54	1.79
Missing	190	6.29
Stressful life events, 73 months	2,448	4.23 (2.93)
Child characteristics		
Ethnicity		
White	2,845	94.24
Non-white	114	3.78
Missing	60	1.99
Sex		
Male	1,463	48.46
Female	1,556	51.54
SDQ score, age 7	2,715	7.06 (4.50)
IL-6, age 9 (pg/ml)	3,019	1.26 (1.52)
CRP, age 9 (mg/L)	3,019	0.75 (2.49)
BMI, age 9	2,981	17.51 (2.67)
Recent infection, age 9		
No	2,730	90.43
Yes	283	9.37
Missing	6	0.20
Generalized anxiety disorder, age 15		
No	2,754	91.22
Yes	15	0.50
Missing	250	8.28
Depression, age 17		
No	1,895	62.77
Yes	374	12.39
Missing	750	24.84

Note. SDQ = Strengths and Difficulties Questionnaire (mental health assessment at age 7), IL-6 = interleukin-6, CRP = C-reactive protein, SD = standard deviation

Table 5.2. Direct and indirect associations between prenatal maternal stress, children's inflammation at age 9, and mental health in adolescence

	Unadjusted		Adjusted	
Direct associations	**b (SE)**	**β (95% CI)**	**b (SE)**	**β (95% CI)**
PNMS → IL-6	1.955 (.609)**	.090 (.039, .141)	1.715 (.736)*	.071 (.015, .126)
PNMS → CRP	.534 (.802)	.018 (-.035, .071)	.390 (.837)	.012 (-.038, .062)
PNMS → GAD	13.737 (5.642)*	.295 (.081, .509)	13.822 (6.621)*	.110 (.006, .215)
PNMS → Depression	9.501 (2.150)***	.207 (.126, .287)	11.182 (2.833)***	.214 (.123, .304)
IL-6 → GAD	.839 (.198)***	.376 (.226, .525)	.724 (.196)***	.276 (.131, .420)
IL-6 → Depression	.169 (.064)**	.169 (.043, .295)	.091 (.070)	.042 (-.022, .107)
CRP → GAD	.299 (.227)	.192 (-.084, .469)	.094 (.285)	.051 (-.249, .350)
CRP → Depression	.062 (.046)	.041 (-.018, .100)	-.044 (.056)	-.028 (-.098, .041)
Indirect associations				
PNMS → IL-6 → GAD	.583 (.228)**	.023 (.006, .040)	.337 (.164)*	.014 (.001, .027)
PNMS → IL-6 → Depression	.145 (.085)	.006 (-.001, .012)	.035 (.059)	.001 (-.003, .006)
PNMS → CRP → GAD	.050 (.102)	.002 (-.006, .010)	.000 (.054)	.000 (-.004, .004)
PNMS → CRP → Depression	.017 (.036)	.001 (-.002, .003)	-.001 (.026)	.000 (-.002, .002)

Note. *$p < .05$, **$p < .01$, ***$p<.001$. PNMS = prenatal maternal stress, IL-6 = interleukin-6 (log-transformed), CRP = C-reactive protein (log-transformed), GAD = generalized anxiety disorder. Direct and indirect associations were assessed in individual models. Covariates adjusted for include maternal education, paternal social class, offspring ethnicity, and sex. Models including either CRP or IL-6 further included adjustments for BMI at age 9, age at inflammation assessment, and presence of recent infection at inflammation assessment (inflammation only).

Table 5.3. Direct and indirect associations between prenatal maternal stress, children's inflammation at age 9, and mental health in adolescence after additional adjustment for children's mental health and postnatal maternal stressful events

	Adjusted for child mental health at age 7		Adjusted for postnatal maternal stress	
Direct associations	**b (SE)**	**β (95% CI)**	**b (SE)**	**β (95% CI)**
PNMS → IL-6	1.783 (.782)*	.074 (.014, .133)	2.344 (.953)**	.090 (.025, .155)
PNMS → CRP	.160 (.896)	.004 (-.061, .069)	.138 (1.236)	.004 (-.061, .069)
PNMS -> GAD	-	-	11.239 (9.371)	.088 (-.056, .232)
PNMS -> Depression	-	-	13.393 (3.911)**	.229 (.114, .345)
IL-6 → GAD	.700 (.203)**	.261 (.113, .409)	-	-
IL-6 → Depression	.070 (.072)	.032 (-.032, .097)	-	-
CRP → GAD	.084 (.282)	.044 (-.246, .333)	-	-
CRP → Depression	-.057 (.056)	-.036 (-.105, .033)	-	-
Indirect associations				
PNMS → IL-6 → GAD	.343 (.151)*	.013 (.002, .025)	.366 (.191)*	.015 (.000, .029)
PNMS → IL-6 → Depression	.035 (.052)	.001 (-.003, .005)	.037 (.061)	.001 (-.003, .006)
PNMS → CRP → GAD	-.003 (.075)	.000 (-.006, .005)	-.004 (.097)	.000 (-.008, .007)
PNMS → CRP → Depression	.004 (.025)	.004 (-.044, .053)	.014 (.030)	.001 (-.002, .003)

Note. *$p < .05$, **$p < .01$, ***$p < .001$. PNMS = prenatal maternal stress, IL-6 = interleukin-6 (log-transformed), CRP = C-reactive protein (log-transformed), GAD = generalized anxiety disorder. IL-6 = interleukin-6 (log-transformed), CRP = C-reactive protein (log-transformed), GAD = generalized anxiety disorder. Direct and indirect associations were assessed in individual models. Covariates adjusted for include maternal education, paternal social class, offspring ethnicity, sex, child mental health at age 7, and postnatal maternal stressful life events. Models including either CRP or IL-6 further included adjustments for BMI at age 9, age at inflammation assessment, and presence of recent infection at inflammation assessment (inflammation only).

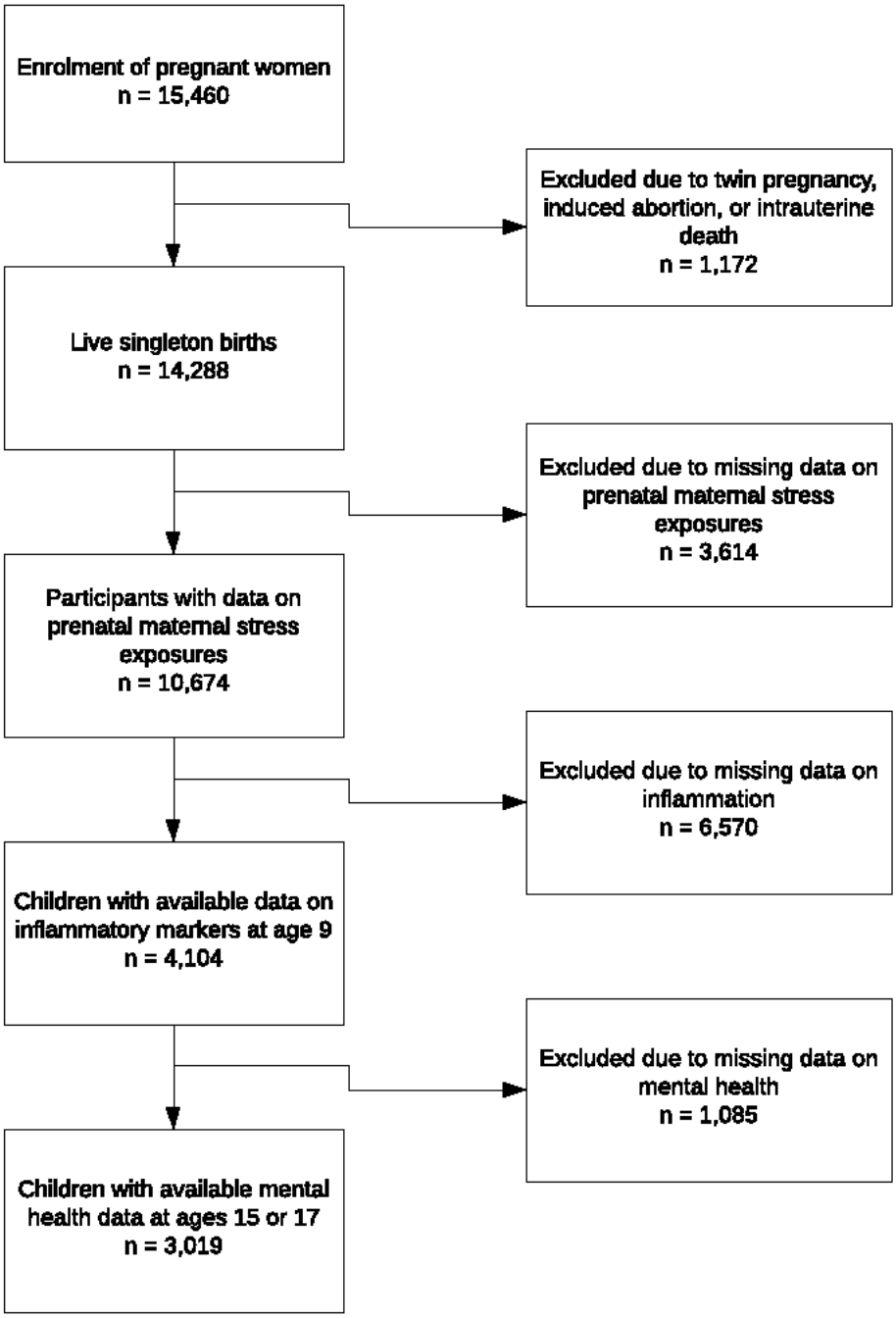

Figure 5.1. Participant selection flow-chart

Appendix 5.1: ALSPAC items included in prenatal maternal stress exposure variable

Life Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Your partner died	18 weeks	Dichotomous (yes/no)	(1)
One of your children died	18 weeks	Dichotomous (yes/no)	(1)
A friend or relative died	18 weeks	Dichotomous (yes/no)	(1)
One of your children was ill	18 weeks	Dichotomous (yes/no)	(1)
Your partner was ill	18 weeks	Dichotomous (yes/no)	(1)
A friend or relative was ill	18 weeks	Dichotomous (yes/no)	(1)
You were admitted to hospital	18 weeks	Dichotomous (yes/no)	(1)
You were very ill	18 weeks	Dichotomous (yes/no)	(1)
Your partner lost his job	18 weeks	Dichotomous (yes/no)	(1)
Your partner had problems at work	18 weeks	Dichotomous (yes/no)	(1)
You had problems at work	18 weeks	Dichotomous (yes/no)	(1)
You lost your job	18 weeks	Dichotomous (yes/no)	(1)
You moved house	18 weeks	Dichotomous (yes/no)	(1)
You were bleeding and thought you might miscarry	18 weeks	Dichotomous (yes/no)	(1)
You started a new job	18 weeks	Dichotomous (yes/no)	(1)
You had a test to see if your baby was abnormal	18 weeks	Dichotomous (yes/no)	(1)
Result on a test that suggested your baby might not be normal	18 weeks	Dichotomous (yes/no)	(1)
You were told that you were going to have twins	18 weeks	Dichotomous (yes/no)	(1)
You heard something that happened might be harmful to the baby	18 weeks	Dichotomous (yes/no)	(1)
You took an examination	18 weeks	Dichotomous (yes/no)	(1)
Your house or car was burgled	18 weeks	Dichotomous (yes/no)	(1)
You had an accident	18 weeks	Dichotomous (yes/no)	(1)

Contextual Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Housing inadequacy (crowding index - people per room >1)	8 weeks	Dichotomous (yes/no)	(2)
Housing Basic Living (no hot water, no toilet, bath or shower, no kitchen)	8 weeks	Dichotomous (yes/no)	(2)
Housing Defects (mould, leaking roof, rodents or cockroaches)	8 weeks	Dichotomous (yes/no)	(2)
You had a major financial problem	18 weeks	Dichotomous (yes/no)	(1)
You became homeless	18 weeks	Dichotomous (yes/no)	(1)
Your income was reduced	18 weeks	Dichotomous (yes/no)	(1)
Financial difficulties (food, clothing, heating, housing, items for baby)	32 weeks	Dichotomous (yes/no)	(2)

Personal Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Early parenthood - maternal age < 20	18 weeks	Dichotomous (yes/no)	(2)
You were in trouble with the law	18 weeks	Dichotomous (yes/no)	(1)
Your partner was in trouble with the law	18 weeks	Dichotomous (yes/no)	(1)
You were convicted of an offence	18 weeks	Dichotomous (yes/no)	(1)
Maternal substance abuse (hard drugs)	18 weeks	Dichotomous (yes/no)	(2)
Maternal suicidality	32 weeks	Dichotomous (yes/no)	(2)
Maternal affective disorder	18 weeks	Dichotomous (yes/no)	(2)

Interpersonal Stress Domain:

Scale/Item	Time of Assessment	Variable Type	References
Family Size (>3 children 15 and under)	8 weeks	Dichotomous (yes/no)	(2)
Partner Status (single)	8 weeks	Dichotomous (yes/no)	(2)
Family major problems (major caregiving problems - child in care/not with mother, or on social services/risk register)	8 weeks	Dichotomous (yes/no)	(2)
You found that your partner didn't want your child	18 weeks	Dichotomous (yes/no)	(1)
You argued with your partner	18 weeks	Dichotomous (yes/no)	(1)
You had arguments with your family or friends	18 weeks	Dichotomous (yes/no)	(1)
Your partner hurt you physically	18 weeks	Dichotomous (yes/no)	(1)
Your partner hurt your children physically	18 weeks	Dichotomous (yes/no)	(1)
Your partner was emotionally cruel to you	18 weeks	Dichotomous (yes/no)	(1)
Your partner was emotionally cruel to your children	18 weeks	Dichotomous (yes/no)	(1)
You were divorced	18 weeks	Dichotomous (yes/no)	(1)
Your partner went away	18 weeks	Dichotomous (yes/no)	(1)
You and your partner separated	18 weeks	Dichotomous (yes/no)	(1)
Your partner hurt you physically	18 weeks	Dichotomous (yes/no)	(1)
Your partner hurt your children physically	18 weeks	Dichotomous (yes/no)	(1)
Partner Affection	12 weeks	Dichotomous (yes/no)	(2)
Partner Support (no support)	12 weeks	Dichotomous (yes/no)	(2)
Social Network - No Emotional Support	12 weeks	Dichotomous (yes/no)	(2)
Social Network - No Practical Support	12 weeks	Dichotomous (yes/no)	(2)

Table S5.1. Comparison between included and excluded participants on sociodemographic and key study variables

	Included (n = 3,019)		Excluded (n = 12,441)	
Parental characteristics	**N**	**Mean (SD) or %**	**N**	**Mean (SD) or %**
Maternal education				
Below O-level	514	17.03	3,161	25.41
O-level only	1,039	34.42	3,238	26,03
A-level	868	28.75	1,894	15.22
University degree	571	18.91	1,021	8.21
Missing	27	0.89	3,127	25.13
Paternal social class				
I (non-manual)	398	13.18	779	6.26
II (non-manual)	1,068	35.38	2,633	21.16
III (non-manual)	362	11.99	822	6.61
III (manual)	732	24.25	2,696	21.67
IV (manual)	215	7.12	845	6.79
V (manual)	54	1.79	253	2.03
Missing	190	6.29	4,413	35.47
PNMS domains				
Life stress	2,917	.11 (.08)	8,422	.10 (.08)
Contextual stress	1,597	.16 (.07)	4,699	.16 (.08)
Personal stress	2,900	.16 (.08)	7,398	.18 (.10)
Interpersonal stress	2,853	.11 (.07)	7,256	.13 (.08)
Stressful life events, 73 months	2,448	4.23 (2.93)	5,113	4.22 (3.25)
Child characteristics				
Ethnicity				
White	2,845	94.24	8,524	68.52
Non-white	114	3.78	489	3.93
Missing	60	1.99	3,428	27.55
Sex				
Male	1,463	48.46	6,128	49.26
Female	1,556	51.54	5,707	45.87
Missing	0	0.00	606	4.87
SDQ score, age 7	2,715	7.06 (4.50)	5,576	7.67 (4.88)
IL-6, age 9 (pg/ml)	3,019	1.26 (1.52)	1,999	1.34 (1.70)

CRP, age 9 (mg/L)	3,019	0.75 (2.49)	2,009	1.88 (3.06)
BMI, age 9	2,981	17.51 (2.67)	4,571	17.84 (3.05)
Recent infection, age 9				
No	2,730	90.43	4,076	32.76
Yes	283	9.37	477	3.83
Missing	6	0.20	7,888	63.40
Generalized anxiety disorder, age 15				
No	2,754	91.22	2,513	20.20
Yes	15	0.50	22	0.18
Missing	250	8.28	9,906	79.62
Depression, age 17				
No	1,895	62.77	1,821	14.64
Yes	374	12.39	429	3.45
Missing	750	24.84	10,191	81.91

Note. PNMS = prenatal maternal stress, SDQ = Strengths and Difficulties Questionnaire (mental health assessment at age 7), IL-6 = interleukin-6 (log-transformed), CRP = C-reactive protein (log-transformed).

Table S5.2. Direct and indirect associations between prenatal maternal stress, children's inflammation at age 9, and depression in adolescence using ICD-10 probable cases of depression at age 17

	Unadjusted		Adjusted	
Direct associations	**b (SE)**	**β (95% CI)**	**b (SE)**	**β (95% CI)**
PNMS -> Depression	7.461 (2.995)*	.165 (.040, .289)	6.829 (2.927)*	.157 (.030, .284)
IL-6 → Depression	.013 (.097)	.007 (-.086, .099)	-.123 (.088)	-.062 (-.156, .033)
CRP → Depression	.050 (.069)	.033 (-.055, .121)	-.070 (.059)	-.042 (-.112, .027)
Indirect associations				
PNMS → IL-6 → Depression	-.021 (.101)	-.001 (-.009, .007)	-.146 (.104)	-.006 (-.014, .002)
PNMS → CRP → Depression	.011 (.035)	.000 (-.002, .003)	-.032 (.054)	-.001 (-.006, .003)

Note. *$p < .05$, **$p < .01$, ***$p < .001$. PNMS = prenatal maternal stress, IL-6 = interleukin-6 (log-transformed), CRP = C-reactive protein (log-transformed). Direct and indirect associations were assessed in individual models. Covariates adjusted for include maternal education, paternal social class, offspring ethnicity, and sex. Models including either CRP or IL-6 further included adjustments for BMI at age 9, age at inflammation assessment, and presence of recent infection at inflammation assessment (inflammation only).

Table S5.3. Associations between prenatal maternal stress, children's inflammation at age 9, and mental health in adolescence after excluding C-reactive protein values > 10.0 mg/L

	Unadjusted		Adjusted	
Direct associations	**b (SE)**	**β (95% CI)**	**b (SE)**	**β (95% CI)**
PNMS → CRP	-.026 (.755)	-.001 (-.054, .052)	-.300 (.751)	-.010 (-.057, .038)
CRP → GAD	.133 (.216)	.082 (-.176, .340)	-.146 (.252)	-.074 (-.327, .179)
CRP → Depression	.050 (.049)	.031 (-.028, .090)	-.070 (.059)	-.042 (-.112, .027)
Indirect associations				
PNMS → CRP → GAD	-.001 (.072)	.000 (-.006, .006)	.031 (.084)	.001 (-.006, .008)
PNMS → CRP → Depression	-.001 (.031)	.000 (-.002, .002)	.016 (.028)	.001 (-.002, .003)

Note. *p < .05, **p < .01, ***p<.001. PNMS = prenatal maternal stress, CRP = C-reactive protein (log-transformed), GAD = generalized anxiety disorder. Direct and indirect associations were assessed in individual models. Covariates adjusted for include maternal education, paternal social class, offspring ethnicityand sex. Models including either CRP or IL-6 further included adjustments for BMI at age 9, age at inflammation assessment, and presence of recent infection at inflammation assessment (inflammation only).

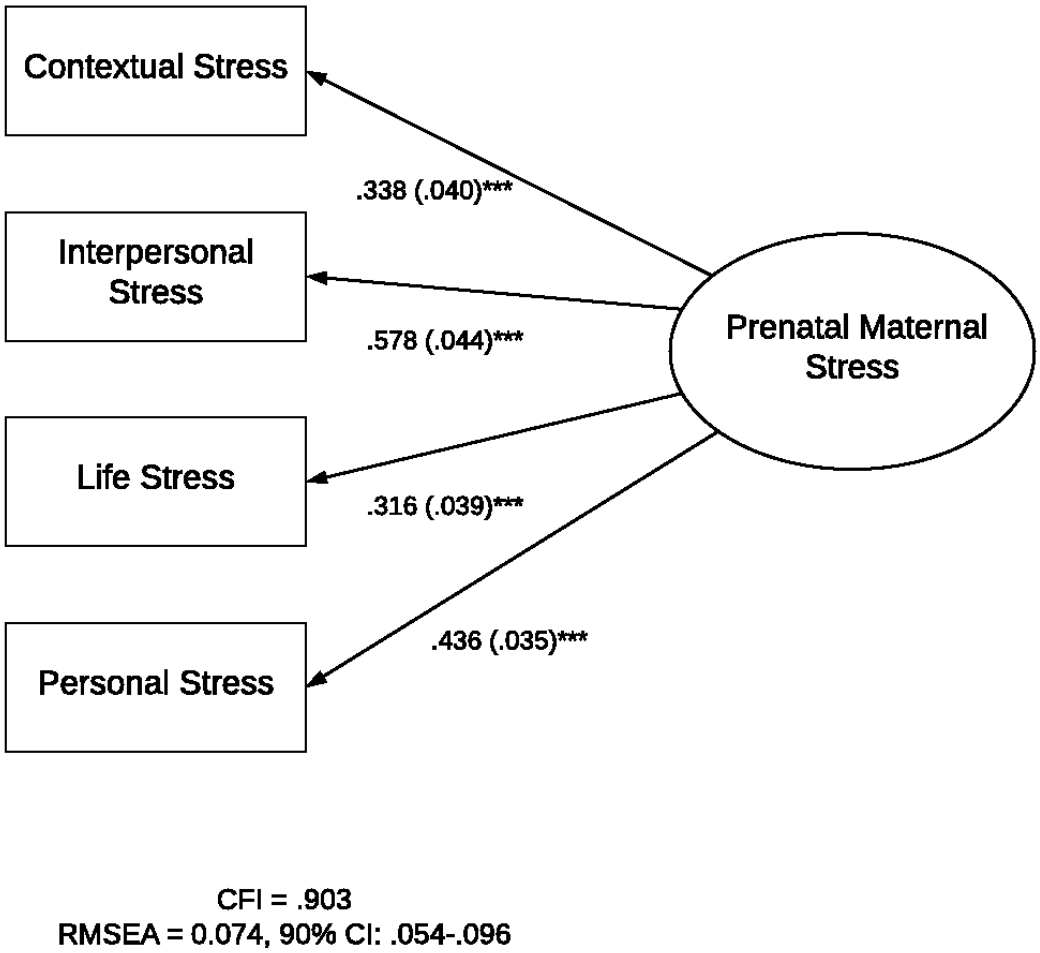

Figure S5.1. Path diagram of prenatal maternal stress latent variable and indicator variables with associated factor loadings (presented as standardized estimates) and fit indices. $^{***}p < .001$. CFI = comparative fit index. RMSEA = root mean square error of approximation.

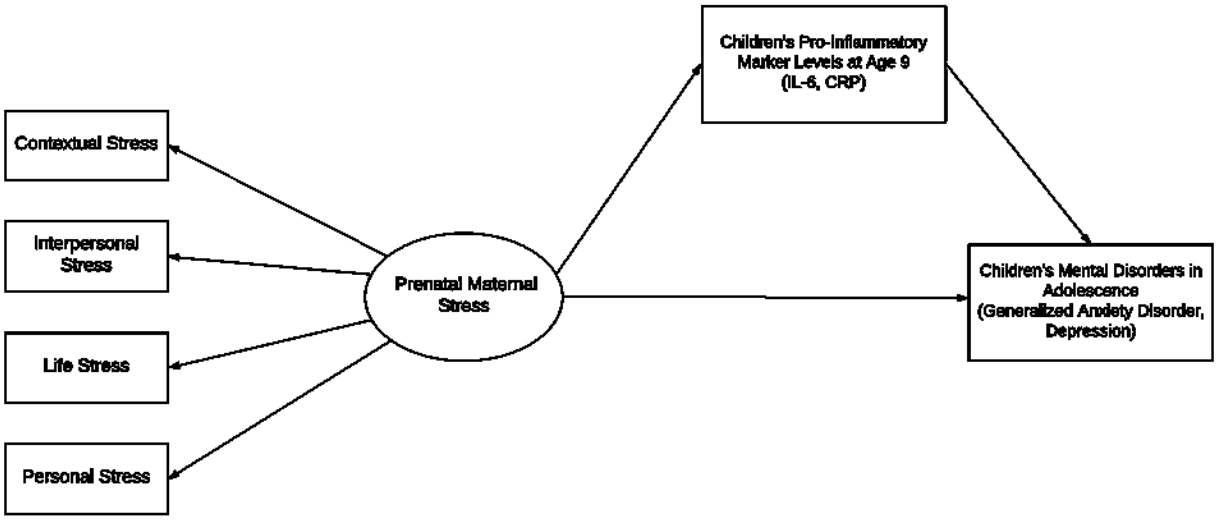

Figure S5.2. Conceptual path diagram of structural equation models examining direct and indirect effects of prenatal maternal stress on children's depression and generalized anxiety disorder through inflammation (covariates not included)

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Chapter 6

DISCUSSION

Chapter 1 of this doctoral thesis presented a conceptual model (Figure 1.2) and five associated research questions, which were assessed in four studies (Chapters 2-5). This final chapter will summarize the findings of these studies, compare these findings to the broader literature, and review the implications of this work for research and practice. The strengths and limitations of these studies will be discussed, as well as future research directions based on findings from this thesis.

6.1 Summary of key findings

6.1.1 Impacts of prenatal maternal stress on children's mental health outcomes. Intrauterine exposure to environmental stressors can potentially "program" offspring in a manner that promotes vulnerability towards experiencing specific mental and physical health outcomes (1,2). Extensive research supports the associations between prenatal maternal stress and children's risk towards poor mental health in childhood and later in life. In line with this body of evidence, all four studies comprising this thesis demonstrated associations between exposure to prenatal maternal stress and children's mental health outcomes.

In Chapters 2 and 3, higher prenatal maternal stress was associated with higher internalizing and externalizing symptoms at 8 and 5 years of age, respectively, in a large cohort of Norwegian mothers and their children (MoBa). In Chapter 4, higher prenatal maternal stress was associated with higher internalizing symptoms at ages 36 months, 5 years, and 9 years of age in a cohort of

Dutch mothers and children (Generation R); strength of these associations were largely unchanged after considering paternal-reported outcomes at 36 months and 9 years. Furthermore, when examining individual stress domains, each domain of stress remained consistently associated with internalizing and externalizing symptoms throughout childhood. Finally, in Chapter 5, higher prenatal maternal stress was associated with cases of generalized anxiety disorder at 15 years of age, and with probable cases of depression at 17 years of age in a cohort of British mothers and their children (ALSPAC). Across studies, investigation into potential sex differences yielded mixed findings. Chapter 2 reported sex differences for the associations between prenatal maternal stress and externalizing symptoms at 8 years of age, whereas Chapter 3 reported sex differences for associations between prenatal maternal stress and both internalizing and externalizing symptoms at 5 years of age; both studies used data from MoBa. In detail, at 5 years of age (Chapter 3), the associations between prenatal maternal stress and internalizing and externalizing symptoms appeared slightly stronger for boys compared to girls. At 8 years of age (Chapter 2), the associations between symptoms of conduct disorder and oppositional defiant disorder appeared slightly stronger for boys, whereas associations with symptoms of attention deficit hyperactivity disorder appeared stronger for girls. Significant sex differences were not found in Chapters 4 (Generation R) and 5 (ALSPAC).

All four studies utilized a comprehensive measure of prenatal maternal stress which included exposure to stressful life events, pregnancy complications, maternal psychopathology, substance use, financial problems, and interpersonal problems; this comprehensive measure was used to address the inconsistent measurement of stress in the broader literature. Considered together, all

four studies comprising this thesis suggest that exposure to prenatal maternal stress is associated with offspring risk towards mental disorders throughout childhood and adolescence.

6.1.2 Modifying role of positive and negative postnatal influences on the associations between prenatal maternal stress on children's mental health outcomes. The differential susceptibility hypothesis suggests that exposure to prenatal stress can promote offspring sensitivity to both positive and negative postnatal influences, which can then reduce or amplify risk towards adverse developmental outcomes (3,4). In Chapter 2, moderation of the associations between prenatal maternal stress and children's internalizing and externalizing symptoms by parenting behaviours was investigated. Findings suggested that exposure to positive parental involvement attenuated the association between prenatal maternal stress and symptoms of attention-deficit hyperactivity disorder in girls. By comparison, exposure to inconsistent discipline strengthened the associations between prenatal maternal stress and symptoms of depression in boys and girls, and conduct disorder and oppositional defiant disorder in boys. In Chapter 3, the moderating role of maternal positive mental health on these associations was examined. Overall, the association between prenatal stress and internalizing symptoms in boys was stronger at low compared to high levels of maternal self-esteem and enjoyment, whereas for girls, the association between prenatal stress and internalizing symptoms was stronger at low compared to high levels of maternal self-esteem and self-efficacy. Maternal positive mental health indicators were also consistently associated with lower internalizing and externalizing symptoms in boys and girls, independent of prenatal maternal stress. In partial support of differential susceptibility, both studies suggest that exposure to positive influences (i.e., positive parenting behaviours, higher positive mental health) may buffer the negative impacts of prenatal maternal stress, whereas

exposure to negative influences (i.e., negative parenting behaviours, lower positive mental health) may amplify the impacts of prenatal maternal stress on children's mental health outcomes.

6.1.3 Role of inflammation as a potential mechanism underlying the associations between prenatal maternal stress and mental disorders in offspring. Dysregulation of the maternal and offspring immune systems have been proposed as potential biological mechanisms underlying the associations between prenatal maternal stress and offspring risk towards mental disorders. Chapters 4 and 5 explored mediation of these associations through maternal and offspring inflammation, respectively. In Chapter 4, no evidence of mediation of the associations between prenatal maternal stress and children's internalizing and externalizing symptoms through maternal CRP levels during pregnancy was reported. After adjustment, prenatal maternal stress was not associated with maternal CRP levels during pregnancy, and maternal CRP levels during pregnancy were not associated with children's internalizing and externalizing symptoms. However, higher maternal CRP during pregnancy was associated with higher paternal-reported internalizing symptoms in children at age 9. In Chapter 5, the association between prenatal maternal stress and diagnosis of generalized anxiety disorder in adolescence was mediated by levels of IL-6 measured in childhood; there was no evidence of mediation by IL-6 or CRP for the association between prenatal maternal stress and depression in adolescence. Prenatal maternal stress was associated with higher levels of IL-6, but not CRP. In addition, IL-6 was associated with higher likelihood of generalized anxiety disorder.

6.1.4 Summary. Findings from this doctoral thesis represent important contributions to the epidemiological and psychiatric literature. To date, analyses utilizing comprehensive measures of prenatal maternal stress has been limited. Furthermore, few studies have investigated the impacts of social and environmental influences on the associations between prenatal maternal stress and children's mental health outcomes, including the effects of parenting behaviours and maternal wellbeing. Finally, few studies have investigated mediation of these associations through maternal and offspring inflammation.

Table 6.1: Overview of research findings from Chapters 2 to 5

Chapter	Research findings
2	- Higher prenatal maternal stress was associated with higher internalizing and externalizing symptoms in children at age 8 - Associations with externalizing symptoms differed by sex; the associations between prenatal maternal stress and conduct disorder and oppositional defiant disorder appeared stronger in boys, whereas associations with attention deficit hyperactivity disorder appeared stronger in girls - Associations between prenatal maternal stress and child depression, and conduct disorder and oppositional defiant disorder in boys, became stronger with increasing levels of inconsistent discipline - Associations between prenatal maternal stress and symptoms of attention-deficit hyperactivity disorder in girls became weaker with increasing levels of positive parental involvement
3	- Higher prenatal maternal stress was associated with higher internalizing and externalizing symptoms in boys and girls at age 5 - Higher maternal self-efficacy, self-esteem, and enjoyment were associated with lower internalizing and externalizing symptoms in boys and girls, independent of prenatal maternal stress - Higher levels of maternal self-esteem and enjoyment buffered the associations between prenatal maternal stress and internalizing symptoms in boys

	- Higher levels of maternal self-esteem and self-efficacy buffered the associations between prenatal maternal stress and internalizing symptoms in girls
4	- Higher prenatal maternal stress was associated with higher internalizing and externalizing symptoms at 36 months, 5 years, and 9 years of age - Associations did not differ with paternal-reported outcomes - Prenatal maternal stress was not associated with levels of maternal CRP during pregnancy after adjustment for covariates - There was no evidence of mediation of the associations between prenatal maternal stress and children's internalizing and externalizing symptoms through maternal levels of CRP - Higher maternal CRP levels during pregnancy were associated with higher paternal-reported internalizing symptoms at 9 years of age
5	- Higher prenatal maternal stress was associated with higher levels of IL-6 in childhood, and with higher likelihood of generalized anxiety disorder and depression in adolescence - Higher levels of IL-6 during childhood were associated with diagnosis of generalized anxiety disorder in adolescence - The association between prenatal maternal stress and diagnosis of generalized anxiety disorder in adolescence was partially mediated by higher levels of IL-6 in childhood; this association remained significant after sensitivity analyses - No direct or indirect associations were observed with levels of CRP in childhood

6.2 Comparisons with and contributions to the existing literature

In line with the broader literature, findings from Chapters 2 through 5 of this thesis provide compelling evidence that prenatal maternal stress is associated with children's mental health throughout childhood and adolescence. Although few prior studies have utilized comprehensive prenatal maternal stress measures, these findings are in line with prior research demonstrating associations between prenatal depression, prenatal anxiety, and prenatal stressful life events and children's risk of mood and anxiety disorders (5–11). Findings are also in line with research

demonstrating associations between prenatal depression, prenatal anxiety, and prenatal stressful life events and externalizing problems in children (12–14).

A growing number of studies have examined the modifying role of the postnatal environment on the associations between prenatal maternal stress and children's developmental and mental health outcomes. For example, studies have reported that the associations between prenatal maternal stress and children's outcomes including cognitive ability and depressive symptoms were significant only among children exposed to negative postnatal influences, such as exposure to adversities and insecure maternal-infant attachment (15,16). Consistent with findings from Chapter 2, one study reported that the association between prenatal maternal anxiety and children's internalizing symptoms was modified by postnatal maternal stroking (a measure of caregiving), such that exposure to stroking in the first few weeks of life buffered the effects of prenatal maternal anxiety (17). Although few studies have directly examined the modifying role of parenting behaviours on these associations, parenting behaviors have been associated with both prenatal maternal stress and children's internalizing and externalizing symptoms (18,19). For example, exposure to positive parenting behaviours has been associated with lower risk of depression and externalizing problems among offspring (20,21), whereas exposure to negative parenting behaviours, such as harsh parenting and inconsistent discipline, has been associated with greater risk of these same outcomes (22,23). Findings from Chapter 2 extend this literature by demonstrating that parenting behaviours can modify the associations between prenatal maternal stress and children's outcomes.

Few studies have examined the modifying role of maternal positive mental health on the associations between prenatal maternal stress and children's mental health outcomes. In line with findings from Chapter 3, one prior study by Bolten and colleagues reported that the infants of mothers who reported higher prenatal stress as well as higher self-efficacy cried less than the infants of mothers who reported higher prenatal stress and lower levels of self-efficacy (24). Although infant crying is not a direct marker of children's wellbeing, persistent crying in infancy has been associated with poorer maternal-infant attachment (25,26), as well as greater risk of psychological difficulties later in childhood (27). Indicators of maternal positive mental health, including positive affect and optimism, have also been associated with improved coping in response to stressful situations (28,29), and improved parenting behaviours, both of which can improve developmental outcomes among children exposed to intrauterine stress (20,21,30). Although Chapter 3 reported that independent of prenatal maternal stress, maternal positive mental health was associated with lower internalizing and externalizing symptoms, few longitudinal studies have examined these direct associations; thus, these findings represent a unique contribution to the literature.

The findings from Chapters 2 and 3 also provide important evidence in support of the differential susceptibility hypothesis by demonstrating that exposure to positive influences after prenatal maternal stress exposure can potentially reduce risk towards mental health difficulties later in childhood (see Figure 1.1). This contrasts with the common diathesis-stress model, which suggests that prenatal maternal stress amplifies vulnerability towards negative postnatal influences, but which also stipulates that children exposed to prenatal stress do not substantially benefit from enriched environments (31,32).

The role of inflammation as a potential mechanism underlying the associations between prenatal maternal stress and children's development has long been hypothesized. For example, a 2019 review by Hantsoo and colleagues presented extensive animal evidence to support the role of maternal inflammation as a mediator of the associations between prenatal maternal psychosocial stress and neuropsychiatric outcomes in offspring (33). This work further highlighted that at the time of publication, no existing studies among humans had explored these associations. Since the publication of this review, emerging research has investigated the mediating role of maternal inflammation on the associations between prenatal maternal stress and children's development. Prior studies have reported that the associations between prenatal environmental adversities and offspring neurodevelopmental delay, and between prenatal depression and infant negative affect were partially mediated by maternal levels of CRP during pregnancy (34,35). Research has also reported that the association between socioeconomic disadvantage and offspring neurologic abnormalities in the first year of life was partially accounted for by maternal levels of interleukin 8 (IL-8) in the third trimester of pregnancy (36). The findings from Chapters 4 contribute to this emerging area of research by exploring the potential mediating role of maternal inflammation during pregnancy in the associations between prenatal maternal stress and children's internalizing and externalizing symptoms. Contrary to these other studies, significant mediation was not reported in Chapter 4, and direct associations between prenatal maternal stress and maternal inflammation were not observed. Notably, maternal CRP was measured in the Generation R cohort in the second trimester of pregnancy, which is typically conceptualized as an anti-inflammatory period (37). Similarly, a number of other studies have reported no associations between prenatal maternal stress and maternal inflammatory markers including

CRP, IL-6, and tumour necrosis factor alpha (TNF-α) when inflammation was measured in the second trimester (38–41).

Findings from Chapter 5 suggest that the association between prenatal maternal stress and adolescent diagnosis of generalized anxiety disorder is mediated by childhood levels of IL-6. These findings contrast with one prior study in the ALSPAC cohort, which did not find evidence of mediation when utilizing prenatal stressful life events as a measure of prenatal maternal stress; rather, this study suggested that higher IL-6 levels in children mediated the association between postnatal stressful life events and children's depressive symptoms (42). Results from Chapter 5 are in line with a range of studies that have demonstrated associations between measures of prenatal stress including prenatal maternal anxiety, prenatal maternal depression, prenatal stressful life events, and prenatal adversity and offspring levels of inflammation in infants and adults (5,43–45). Although few longitudinal studies have examined the associations between inflammation and risk towards generalized anxiety disorder, findings also align with a study in the ALSPAC cohort which reported a cross-sectional association between adolescent CRP levels and diagnosis of generalized anxiety disorder (46). Given that few studies have examined the mediating role of offspring inflammation in the associations between prenatal maternal stress and offspring mental health, the findings from Chapter 5 represent an important contribution to this growing area of research.

6.3 Strengths and limitations

Findings from this thesis should be interpreted in light of several limitations. First, across studies, many of the included measures utilized maternal self-reported data, and thus, findings

are prone to reporting bias. However, this is somewhat mitigated by the use of prospectively collected longitudinal data, as mothers reported on measures of prenatal stress years prior to reporting on measures of children's mental health. In addition, where possible, potential reporting biases associated with maternal-reported data on children's mental health were controlled for by adjusting analyses for postnatal maternal stress and/or depression, or utilizing paternal reported data. Second, there was substantial attrition across the three cohorts analyzed for this thesis. This attrition largely occurred among mothers who reported lower socioeconomic status and/or higher levels of prenatal maternal stress. However, explorations of selection bias in the ALSPAC cohort suggest that this attrition may lead to an underestimation of the effects of perinatal effects (including prenatal stress) (47), and analyses in the MoBa cohort suggest that attrition may not significantly impact estimates of exposure-outcome associations (48). It is possible that findings from this thesis may underestimate the true associations between prenatal maternal stress on children's mental health. Third, the studies examining the modifying roles of parenting and positive maternal mental health (Chapters 2 and 3) were limited to the use of maternal data; thus, we could not assess the effects of paternal measures on the associations under study. Paternal parenting behaviours and positive mental health are associated with children's mental health (49–51), and represent important avenues for future research. Fourth, studies involving data on inflammation (Chapters 4 and 5) were limited by the measurement of inflammation at single timepoints, as well as the lack of availability of a range of other inflammatory markers associated with both prenatal maternal stress and risk towards mental disorders. Reliance on a single measurement point is a particular limitation when assessing inflammation during pregnancy, as the inflammatory response varies greatly by trimester (37,52), and by individual (53). Fifth, the cohorts included in this thesis had limited racial, ethnic

and/or socioeconomic diversity – for example, the ALSPAC and MoBa cohorts were comprised primarily of White participants (>90%), and the majority of participants in the Generation R and MoBa cohorts reported high socioeconomic status. Thus, our findings may not generalize to more ethnically diverse or socioeconomically deprived regions. Sixth, the measure of prenatal maternal stress employed in all four studies did not contain markers of long-term maternal adversity, such as child maltreatment or adverse childhood experiences (ACEs). Studies suggests that the children of mothers who report a history of child maltreatment or ACEs tend to report higher internalizing and externalizing symptoms (5,54,55). It is possible that mothers who report a history of child maltreatment may experience distress during pregnancy due to ruminating on these past experiences as they transition to parenthood, and/or through experiencing ongoing symptoms of post-traumatic stress disorder stemming from past traumatic events. Finally, all four studies in this thesis used observational study designs, thus causality cannot be established, and the potential for residual confounding remains present across studies. Genetic confounding is a particular possibility, given that genetic data was not examined in analyses. Maternal genetic factors that can potentially influence vulnerability towards both prenatal maternal stress and psychopathology may be passed on to the child. Genetic factors may also modulate the impacts of prenatal maternal stress on the child (56), altering their risk towards poor mental health, or may serve as a mechanism underlying these association. For example, DNA methylation of genes implicated in the transmission of stress reactivity from mother to child, such as the NR3C1 gene that encodes the glucocorticoid receptor, has been associated with both intergenerational stress exposures and children's risk towards poor mental health (57–59).

The findings from this thesis also have several strengths. First, all four studies utilized a comprehensive measure of prenatal maternal stress that directly addresses the limitations inherent to many prior studies utilizing single measures of prenatal maternal stress (60). Importantly, the use of confirmatory factor analysis to generate these measures of prenatal maternal stress incorporates the shared variance across stress domains, and addresses the substantial overlap that exists over individual stress measures (61,62). Furthermore, when analyzed separately (Chapter 4), each of the included stress domains were associated with children's internalizing and externalizing symptoms. Second, findings from this thesis address important evidence gaps. Chapters 2 and 3 examined the moderating roles of parenting behaviours and maternal positive mental health, which have received limited focus in the broader literature. Chapter 4 contributed to a limited evidence base examine the mediating role of maternal inflammation during pregnancy on the associations between prenatal maternal stress and children's internalizing and externalizing symptoms throughout childhood. Chapter 5 represented one of the first studies to demonstrate significant mediation of these associations through children's inflammation. Third, consistent associations between prenatal maternal stress and children's mental health outcomes from early childhood to adolescence were found in all four studies. These associations were upheld after extensive adjustment for a range of potential confounding variables, including measures of postnatal risk (63). Although causality cannot be inferred due to the observational nature of this research, these findings add to a robust evidence base that supports associations between prenatal maternal stress exposures and children's risk towards mental health disorders. Finally, the use of data from three large prospective birth cohorts allowed for the adjustment of a range of potential confounding variables, the opportunity to appropriately assess for potential sex differences, as well as sufficient statistical power to

conduct complex statistical analyses (e.g., the latent moderated structural equations approach utilized in Chapters 2 and 3) to answer the outlined research questions.

6.4 Implications for public health and practice

Mental health disorders can have severe consequences for the individual, their families, and their broader communities. Experiencing depression during adolescence is associated with later risk towards depression and anxiety in adulthood, and lower socioeconomic status (64,65). Mental health disorders cost the Canadian economy at least $51 billion per year (66); from a global perspective, 2010 estimates suggest that mental disorders cost the world economy over $2 trillion per year due to health care costs and reduced productivity, with this figure expected to almost triple by 2030 (67). Thus, the identification of factors that can mitigate risk towards poor mental health outcomes represents a priority for research, public health, and clinical practice. The overarching objective of this thesis was to identify biological and psychosocial factors that influence the associations between prenatal maternal stress and children's mental health outcomes, in order to provide data that can fuel initiatives designed to improve quality of life for parents and their children. Parenting behaviours and maternal positive mental health are modifiable (68–70), and have been independently associated with children's development and mental health (71–76). The findings from Chapters 2 and 3 of this thesis demonstrate that parenting behaviours and maternal positive mental health can alter the strength of the associations between prenatal maternal stress and children's internalizing and externalizing symptoms. This suggests that among children exposed to adversity, interventions targeted towards enriching their environments, such as those designed to improve parenting behaviours or parental mental health, may mitigate later risk towards poor mental health outcomes. These

findings are particularly important, given that common diathesis-stress thinking suggests that children exposed to early life adversity may not benefit from enriched environments. Those directly and indirectly involved in children's lives, including their parents, relatives, teachers, and broader systems such as school boards, medical services, community and non-profit organizations, and governmental organizations may benefit from learning about and applying these findings as relevant to their roles. In particular, potential stakeholders of this research may apply these findings in order to improve child care, facilitate access to mental health resources and supports, and assist in the development and provision of intervention and prevention strategies designed to improve children's early life environments. Findings from Chapters 4 and 5 of this thesis further suggest that targeting children and the family unit early in development is essential, as findings suggest that prenatal maternal stress is associated with children's internalizing and externalizing symptoms as early as 36 months of age, and the processes that may underlie and drive these short- and long-term associations (i.e., inflammation) can begin in childhood.

There is growing literature on the potential effectiveness of parenting and positive psychological interventions on improving both parent and child outcomes. Among at-risk families, parenting interventions in the first year of life can lead to improvements in child behaviour, and the parent-child relationship (77); parenting interventions have also demonstrated positive outcomes for child and youth mental health in low- and middle-income countries (78). Research suggests that parenting and other psychosocial interventions may improve children's cortisol regulation (79,80). One study examining the effects of a psychosocial intervention designed to improve parenting and youth competencies, and strengthen family relationships in a sample of low-SES African American families reported that youth who received the intervention had significantly

lower inflammation compared to controls eight years later (81). These findings are promising given that families that present the greatest challenges to parenting intervention programs tend to be from at-risk groups (e.g., groups reporting lower SES, single parent homes, and/or racialized groups). Challenges with adherence often occur because these families may have had negative experiences with the health care system and social services (e.g., through facing stigma or discrimination from health care providers), and/or may face additional stressors associated with poverty or ethnicity, such as financial stress or discrimination. In turn, these experiences can interfere with parents' abilities to cultivate nurturing home environments for their children. Interventions that have reported positive outcomes despite these challenges have included group-based therapeutic activities, which can promote social support (82); psychoeducation to parents and children about how to navigate specific stressors, such as racism and discrimination (81); and role-playing scenarios between parents and children to practice skills learned from interventions (81). These strategies are further reinforced by recent qualitative research among low-income mothers about their priorities for stress- and parenting-related interventions (82); this research suggests that effective interventions should include components that cultivate social supports, train providers on explicit and implicit biases to reduce judgmental perspectives, and consider other potential sources of stress in the household, such as unstable housing or employment, concerns about documentation of citizenship, and step-parenting (82). Thus, clinicians and researchers may seek to incorporate these components into parenting and stress-reduction interventions to improve treatment efficacy and effectiveness among diverse populations.

Parenting interventions can also have impacts on indicators of positive mental health; for example, parenting interventions have been shown to increase levels of parental self-efficacy and positive affect (83,84), and parental self-efficacy has been linked to improved parenting behaviours, such as parental warmth (85). Positive psychological interventions, such as interventions including gratitude journaling and mindfulness-based stress reduction, can also have substantial impacts on parent and child mental health, as meta-analyses of randomized trials support the efficacy of these interventions in improving participant well-being and alleviating symptoms of depression (69). Positive psychological interventions during pregnancy and after birth can lower symptoms of maternal depression, and improve maternal affect (86–88). Limited research has examined the effects of positive psychological interventions among lower-income or minority families; however, pilot research suggests that mindfulness-based interventions are acceptable and potentially effective in these groups (89). In all, the highlighted clinical research coupled with the findings from this thesis suggest that the provision of interventions designed to improve parenting behaviours and that integrate positive psychological components may improve the mental health and wellbeing of parents and children.

6.5 Implications for future research

The studies comprising this thesis highlight a number of avenues for future research in the epidemiological and clinical spheres. A particular criticism regarding prior studies utilizing prenatal maternal stress measures is that the definition and measurement of stress varies considerably among studies (60); the inconsistent measurement of stress may hamper the ability of researchers and knowledge users to compare findings between studies. To address this issue, a comprehensive measure of prenatal maternal stress developed for use in the ALSPAC and

Generation R cohorts was also adapted for use in the MoBa cohort (90,91), and then employed across the four studies included in this thesis. The consistent findings between prenatal maternal stress and children's mental health outcomes demonstrated in Chapters 2 through 5 may serve to encourage future use of comprehensive stress measures in order to enhance comparability among studies and to better ascertain the impacts of stress exposure, which in itself is a broad concept, on children's development.

Given that few studies have examined the modifying impacts of postnatal influences on the associations between prenatal maternal stress and children's mental health outcomes, the findings from this thesis highlight the need for additional inquiry into these associations. For example, paternal parenting behaviours and paternal mental health have received comparatively less attention compared to their maternal-reported analogues. Given that paternal parenting behaviours and paternal mental health have demonstrated associations with children's mental health (49–51), further study into how paternal exposures may buffer the deleterious effects of prenatal maternal stress on children's development is important. Analysis of other factors in the child's environment, including sibling relationships, friendships, and neighbourhood exposures may also represent important areas for further study. For example, poorer sibling relationships have been associated with later risk towards depression (92), and higher social support and friendship quality has been associated with lower internalizing and externalizing symptoms in children (93,94). Children who live in neighbourhoods with low or declining cohesion may be more likely to experience depression and externalizing behaviours (95), and higher neighbourhood cohesion has demonstrated protective effects on the associations between children's exposure to stressful events and later depression, anxiety, suicidal ideation, and

externalizing behaviours (96). Analyses of these associations in diverse samples is also important, as is ascertaining whether these associations differ based on sociodemographic factors including but not limited to socioeconomic status, race or ethnicity, and sex and gender. As an extension of the work presented in Chapters 2 and 3, researchers may also seek to examine whether parenting and positive psychological interventions improve outcomes among children exposed to early life adversity.

Few longitudinal studies have been conducted to ascertain how maternal and child inflammation mediate the associations between prenatal maternal stress and children's mental health outcomes. To extend and improve upon existing research, it is important to examine inflammation utilizing a range of markers and by measuring inflammatory markers at several time points. For example, studies including the measurement of maternal inflammation during pregnancy should strive to assess maternal inflammatory marker levels during each trimester, to account for pregnancy-related fluctuations and individual differences in the inflammatory response. Researchers may also seek to supplement assessments of inflammatory marker levels with the examination of epigenetic changes to key genes involved in immune function and inflammation, as methylation of these genes has been associated with postnatal depression and offspring-related health outcomes (97,98). Furthermore, research to date has not examined how maternal and child inflammation may work together to influence these associations; thus, researchers may seek to examine how maternal and child inflammation interact in concert using methods such as serial mediation analyses, which hypothesize a causal chain linking two or more mediators. Finally, since research, including findings from this thesis, suggests that postnatal factors may influence children's outcomes, future studies may benefit from examining how these factors interact with

these mediation models. Examining how the postnatal environment modifies these complex relationships extends the work highlighted in this thesis, and will provide important information to better understand how early life experiences interact to influence children's mental health and wellbeing.

6.6 Conclusions

The findings from this thesis clearly demonstrate that exposure to prenatal maternal stress is associated with poorer mental health throughout childhood and adolescence. Importantly, these findings further suggest that modifiable psychosocial factors, including parenting behaviours and indicators of maternal wellbeing, may buffer the detrimental impacts of prenatal maternal stress on children's outcomes. In addition, results suggest that the associations between prenatal maternal stress and mental health in adolescence may be partially mediated by childhood inflammation; by comparison, we did not find evidence of mediation through maternal inflammation during pregnancy. However, these mixed findings provide important data towards better understanding the potential biological mechanisms underlying the associations between prenatal maternal stress and offspring mental health. Collectively, the studies comprising this thesis suggest that expecting and new parents, as well as the broader environment that children are born into, represent important intervention targets in order to minimize the long-term risks associated with exposure to prenatal maternal stress.

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Appendix 1. Additional Methodological Detail, Chapters 2-5

Cohort descriptions

MoBa cohort profile. The studies from Chapters 2 and 3 utilized data from the Norwegian Mother, Father and Child Cohort Study (MoBa), a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. The aims of MoBa are to: 1) detect causes of serious diseases through the estimation of exposure-outcome associations among parents and children, and 2) to provide data on the social determinants of health, and how health serves as a potential determinant of children's socioeconomic achievement (1). To fulfill these aims, data collection involved collecting as much information as possible on a range of exposures, mediators, moderating variables, and outcomes (1).

Recruitment of the MoBa cohort began in 1999, and ended in 2008. All pregnant women in Norway were eligible for inclusion, with the caveat that women were able to read in Norwegian in order to complete study questionnaires. Sampling was initially opportunistic due to funding restrictions, but gradually expanded to include almost all of Norway's hospitals with maternity units. In all, women consented to participation in 41% of pregnancies. Following the end of recruitment, the cohort comprised over 95,200 mothers, 75,200 fathers, and 114,500 children (1). Response rates at the 17th and 30th week of gestation, and at 18 months, and 5 years after birth were 95.1%, 91.4%, 87.0% and 54.0%, respectively (2).

Pregnant women were invited to participate prior to their routine ultrasound scan at 17 weeks' gestation. Questionnaires were provided at this time, as well as at 30 weeks' gestation, and

included questions on background information, and previous and current health problems and exposures. A food frequency questionnaire was also distributed at 22 weeks' gestation. Birth records from the Medical Birth Registry of Norway were integrated into the MoBa database, and additional questionnaires at child ages 6 months, 18 months and 3 years collected information on child development, maternal-child health, and lifestyle questionnaires. At child ages 5 and 8 years, questionnaires included items on children's learning, language and neurocognitive development (1). Data collection is ongoing, with children's self-reported data beginning collection at child age 13 years. Ethics approval for both studies (Chapters 2 and 3) was received by The Regional Committees for Medical and Health Research Ethics (#2013/2061), and the University of Ottawa Research Ethics Board (REB #H-09-19-4923).

Generation R cohort profile. The study from Chapter 4 utilized data from the Generation R study, a population-based prospective cohort study in Rotterdam, the Netherlands. Generation R focuses on four areas of research: 1) growth and physical development; 2) behavioural and cognitive development; 3) diseases in childhood; and 4) health outcomes and healthcare for pregnant women and their children (3,4). The main outcomes for these areas of research have been described in detail elsewhere (3). The primary aims of the Generation R study were to: 1) provide descriptions of normal and abnormal growth patterns, development, and physical and mental health from fetal life through young adulthood; 2) to identify determinants of these outcomes; and 3) to develop and test prevention and early intervention strategies for at-risk groups (3).

Eligible mothers represented those who were residents of Rotterdam at their delivery date, with delivery dates between April 2002 and January 2006. The Generation R cohort aimed to enrol mothers prior to 18 weeks' gestation, but enrolment was allowed until the birth of their child(ren). Baseline response rates were 61%, with approximately 80% of enrolled children followed up to 10 years of age (3). 9,778 mothers were enrolled in the study, with a total of 9749 live births; 6,347 fathers were also included. Study assessments began in early pregnancy (< 18 weeks' gestation), and continued through mid- and late pregnancy; fathers were assessed once in the prenatal period. From birth of the child to the age of 4 years, data collection was performed with an at-home visit at 3 months, eight questionnaires between 2 and 48 months, and 11 clinic visits between 2 and 45 months (3). Between 6 and 10 years, children and their parents participated in additional in-clinic measurements, behavioural observations, biological sampling, and MRI scans. Parents received 6 questionnaires during this four-year period, and children began self-reporting on questionnaires at 10 years old. Data collection for the cohort is still ongoing, with children being re-invited at 13 and 16 years of age for continued assessment. The study from Chapter 4 was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, and Ethics, and the University of Ottawa Research Ethics Board (REB #H-09-19-4923), with written informed consent obtained from adult participants.

ALSPAC cohort profile. The study from Chapter 5 utilized data from the Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC is population-based, prospective pregnancy cohort based in the former county of Avon, in southwest England. The cohort was established to ascertain how genetic and environmental factors influenced the health and development of parents and their children. ALSPAC includes several components, such as questionnaires, which

are completed by carers (typically the mother), partners and/or fathers, children, and schools; as well as a range of detailed cognitive and physical examinations, biological sampling, and genome-wide screens (5).

Pregnant women residing in Avon County with delivery dates between April 1, 1991 and December 31, 1992 were enrolled into the cohort; detailed recruitment methods can be found elsewhere (6). In total, a cohort of 14,541 pregnancies were initially enrolled; 674 were excluded, for a total of 13,867 pregnancies remaining (comprising 13,761 unique women). Additional participants were also recruited and added to the cohort when children were school-aged (5). Response rates declined slightly over pregnancy and the first three years after birth, and remained constant at approximately 70% until 12–13 years after birth; after this period, there was another decline in response rate, with response rates decreasing to approximately 50% at 220 months after birth (5). Data collection is ongoing in the cohort, with data available through child age 24 years, and current recruitment for a focused clinic at child age 30 years, which will involve data collection from study children, as well as their parents and their own children. The study from Chapter 5 received ethical approval from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees, and the University of Ottawa Research Ethics Board (REB #H-09-19-4923).

Missing data approaches

Both full information maximum likelihood (FIML) and multiple imputation (MI) are considered state of the art missing data techniques, because these approaches require less strict assumptions regarding missingness compared to approaches such as complete case analysis, and yield

unbiased estimates with missing completely at random (MCAR) and missing at random (MAR) data mechanisms. MCAR assumes that missingness does not depend on observed or missing values, whereas MAR assumes that missingness depends on observed values but not on missing values (7,8). FIML was utilized in Chapters 2, 3, and 5; multiple imputation by chained equations procedures (MICE) was utilized in Chapter 4. Both approaches are considered asymptotically equivalent (i.e., they yield roughly equal estimates at large sample sizes). General descriptions of FIML and MICE are provided below.

Full information maximum likelihood. The FIML approach to addressing missing data involves an "implicit imputation" method, which is based on estimating unbiased parameters through the assumption of an underlying joint distribution for the data (9,10). This approach does not impute missing values, but rather, directly estimates model parameters and standard errors using available raw data (see highlighted description below). The FIML estimator maximizes a likelihood function that is the sum of *n* case-wise likelihood functions, where *n* represents the number of respondents included in the analysis (9,10). In the context of latent variable interactions (such as those included in Chapters 2 and 3), FIML produces unbiased parameter estimates, accurate Type I error rates, and high statistical power for moderation effects (11).

Description of FIML estimation (adapted from Enders et al., 2001)(10):

- A hypothetical model has 4 variables – *X1, X2, X3, X4*
- The likelihood value for a subject with missing data on *X1* will be a function of the values for the other three variables (*X2, X3,* and *X4*); missing values on *X1* are conditionally dependent on the values of the other variables (MAR assumption)

- FIML is analogous to generating predicted scores for the missing data on *X1* by regressing *X1* on the other variables used in the analysis
- This also applies for the other variables – for example, the likelihood value for a subject with missing data on *X2* is a function of the values of *X1, X3,* and *X4*, and missing data on *X2* are conditionally dependent on the values of these variables

Multiple imputation by chained equations. MICE differs from FIML in that it does not start with the construction of a well-defined joint distribution for the variables to be imputed. Rather, MICE begins with a collection of univariate conditional distributions for variables with missing data in terms of all other variables included in the model. A sequence of univariate conditional models is constructed for each potentially missing variable with fully conditional specifications of prediction equations, and other variables (missing or complete) are used as explanatory variables in each univariate imputation model. In simpler terms, MICE involves filling in missing values multiple times, which generates multiple "complete" datasets (12). MI approaches account for statistical uncertainty in the imputations, are flexible, can handle variables of varying types (e.g. continuous, categorical), and can accommodate complexities such as survey skip patterns (12). Specification requires consideration of the target analytical model – contrasted with FIML, this requires the need to take into account anticipated analytic complexities such as potential interactions or non-linearities.

Steps for MICE (adapted from Azur et al., 2011)(12)***:***

- **Step 1:** A simple imputation (e.g., mean imputation) is performed for every missing value in the dataset, serving as "place holders."

- **Step 2:** The "place holder" imputations for one variable (*X1*) are set back to missing.
- **Step 3:** The observed values from the variable *X1* in Step 2 are regressed on the other variables in the imputation model
- **Step 4:** The missing values for *X1* are then replaced with predictions (imputations) from the regression model.
- **Step 5:** Steps 2–4 are repeated for each variable with missing data (e.g., *X2, X3*…*Xn*). Cycling through each of these variables constitutes one iteration, and iterations are then repeated a specified number of times (e.g., 20 iterations)

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Appendix 2. Research Ethics Board Approval, University of Ottawa

10/09/2021

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

CERTIFICAT D'APPROBATION ÉTHIQUE I CERTIFICATE OF ETHICS APPROVAL

Numéro du dossier / Ethics File Number	H-09-19-4923
Titre du projet / Project Title	Biological and Psychosocial Influences of Relationships between Prenatal Stress and Offspring Mental Health Outcomes
Type de projet / Project Type	Thèse de doctorat / Doctoral thesis
Statut du projet / Project Status	Renouvelé / Renewed
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	09/10/2019
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Office of Research Ethics and Integrity

Le Comité d'éthique de la recherche (CÉR) de l'Université d'Ottawa, opérant conformément à l'*Énoncé de politique des Trois conseils* (2014) et toutes autres lois et tous règlements applicables, a examiné et approuvé la demande d'éthique du projet de recherche ci-nommé.

L'approbation est valide pour la durée indiquée plus haut et est sujette aux conditions énumérées dans la section intitulée "Conditions Spéciales ou Commentaires". Le formulaire « Renouvellement ou Fermeture de Projet » doit être complété quatre semaines avant la date d'échéance indiquée ci-haut afin de demander un renouvellement de cette approbation éthique ou afin de fermer le dossier.

Toutes modifications apportées au projet doivent être approuvées par le CÉR avant leur mise en place, sauf si le participant doit être retiré en raison d'un danger immédiat ou s'il s'agit d'un changement ayant trait à des éléments administratifs ou logistiques du projet. Les chercheurs doivent aviser le CÉR dans les plus brefs délais de tout changement pouvant augmenter le niveau de risque aux participants ou pouvant affecter considérablement le déroulement du projet, rapporter tout évènement imprévu ou indésirable et soumettre toute nouvelle information pouvant nuire à la conduite du projet ou à la sécurité des participants.

The University of Ottawa Research Ethics Board, which operates in accordance with the *Tri-Council Policy Statement* (2014) and other applicable laws and regulations, has examined and approved the ethics application for the above-named research project.

Ethics approval is valid for the period indicated above and is subject to the conditions listed in the section entitled "Special Conditions or Comments". The "Renewal/Project Closure" form must be completedfour weeks before the above-referenced expiry date to request a renewal of this ethics approval or closure of the file.

Any changes made to the project must be approved by the REB before being implemented, except when necessary to remove participants from immediate endangerment or when the modification(s) only pertain to administrative or logistical components of the project. Investigators must also promptly alert the REB of any changes that increase the risk to participant(s), any changes that considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project or the safety of the participant(s).

Safaa LAMHOUJEB
Coordonnateur de l'éthique / Ethics Coordinator
Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences de la santé et sciences / Health Sciences and Sciences Research Ethics Board**

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Appendix 3. Confirmation of manuscript submission (Chapter 3) to *European Child & Adolescent Psychiatry*

ECAP-D-21-00632: Submission Confirmation for Positive maternal mental health attenuates the associations between prenatal stress and children's internalizing and externalizing symptoms - [EMID:9a423dad10a9a5d9]

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on behalf of
European Child & Adolescent Psychiatry (ECAP) <em@editorialmanager.com>
Thu 2021-11-11 11:24 PM
To: Zahra Clayborne[redacted]
Attention : courriel externe | external email

CC: "Wendy Nilsen" [redacted] "Fartein Ask Torvik" [redacted] "Kristin Gustavson" [redacted] "Mona Bekkhus" [redacted] "Stephen E Gilman" [redacted], "Golam M Khandaker" [redacted], "Deshayne B Fell" [redacted] Ian Colman" [redacted]

Dear Ms Clayborne,
Your submission titled "Positive maternal mental health attenuates the associations between prenatal stress and children's internalizing and externalizing symptoms" has been received by European Child & Adolescent Psychiatry.

The submission id is: ECAP-D-21-00632

Please refer to this number in any future correspondence.

You have listed the following authors: Zahra M Clayborne; Wendy Nilsen; Fartein Ask Torvik; Kristin Gustavson; Mona Bekkhus; Stephen E Gilman; Golam M Khandaker; Deshayne B Fell; Ian