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# Maternal depression and children's cognitive development: The reasons and conditions of their associations

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Maternal depression and children's cognitive development:
The reasons and conditions of their associations

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**Résumé**

**Contexte :** Le développement cognitif est important pour la santé et le bien-être, car il permet aux individus de s'épanouir socialement, psychologiquement et physiquement. Pour assurer un développement cognitif optimal, nous devons mieux comprendre comment l'environnement de la petite enfance influence le développement du jeune enfant. La dépression maternelle au cours de la petite enfance est une problématique de santé prévalente (11-25%) et un facteur de risque reconnu pour les difficultés cognitives des jeunes enfants. Il existe des lacunes importantes dans notre compréhension des mécanismes longitudinaux via lesquels la dépression maternelle est associée au développement cognitif des enfants. Mieux comprendre comment la dépression maternelle est associée à un développement cognitif sous optimal et les conditions sous lesquelles cette association est plus ou moins forte permettrait l'élaboration d'interventions plus efficaces.

**Objectifs :** L'objectif général de cette thèse est d'examiner les médiateurs et modérateurs de l'association entre la dépression maternelle et le développement cognitif des enfants en utilisant le « *Developmental Model for Understanding Mechanisms of Transmission* » comme cadre conceptuel. Les objectifs spécifiques sont de : (1) résumer la littérature portant sur les médiateurs de l'association entre la dépression maternelle et le développement cognitif; (2) examiner le rôle médiateur des expériences scolaires dans l'association entre la dépression maternelle et la performance scolaire, ainsi que le rôle modérateur du sexe de l'enfant; (3) examiner le rôle des mécanismes gène-environnement dans l'association entre la dépression maternelle et la maturité scolaire; et (4) effectuer une méta-analyse sur le rôle modérateur du sexe dans l'association entre la dépression maternelle et les difficultés cognitives.

**Méthodes** : La réalisation d'une revue systématique et d'une méta-analyse a permis d'accomplir les objectifs 1 et 4. Les données de l'Étude Longitudinale du Développement des enfants du Québec ont été utilisées pour répondre à l'objectif 2 : la dépression maternelle a été auto-rapportée entre la naissance de l'enfant et ses 5 ans; la victimisation par les pairs et l'engagement scolaire ont été

rapportés par les parents, l'enseignant et l'enfant (entre 6 et 10 ans); la performance scolaire a été évalué à l'âge de 12 ans. Les données de l'Étude sur les Jumeaux Nouveau-nés du Québec ont été utilisées pour répondre à l'objectif 3 : la dépression maternelle a été auto-rapportée à 6 et 18 mois et la maturité scolaire a été évaluée lorsque l'enfant avait 5 ans. Des modèles d'équations structurelles, ajustés pour les facteurs de confusion, ont été utilisés pour estimer les associations dans les deux cohortes.

**Résultats :** Les articles dans cette thèse démontrent que (1) la majorité des études ont identifié les émotions, les cognitions, et les comportements maternels comme des médiateurs de l'association entre la dépression maternelle et le développement cognitif; (2) l'engagement scolaire est un médiateur de l'association entre la dépression maternelle et la performance scolaire, mais ce, seulement chez les filles; (3) il existe une interaction environnement-environnement dans l'association entre la dépression maternelle et la maturité scolaire; et (4) les garçons sont plus à risque que les filles d'obtenir de faibles scores cognitifs après avoir été exposés à la dépression maternelle.

**Conclusions :** Dans l'ensemble, les résultats suggèrent que la dépression maternelle est plus fortement associée au développement cognitif des garçons que celui des filles. De plus, pour les filles, l'engagement scolaire est un médiateur important de l'association entre la dépression maternelle et la performance scolaire. Enfin, promouvoir les pratiques parentales positives pourrait atténuer l'association négative entre la dépression maternelle et les faibles résultats cognitifs des enfants. Des études additionnelles portant sur d'autres médiateurs et modérateurs, en particulier chez les garçons, permettront d'améliorer nos connaissances sur l'association entre la dépression maternelle et le développement cognitif.

***Mots clés** : Développement cognitif; Dépression maternelle; Médiateurs; Modérateurs; Mécanismes gène-environnement; Revue systématique; Méta-analyse*

## Summary

**Context:** Cognitive development is an important building block of health and wellbeing because it equips individuals with the necessary skills to increase control over and improve their health as they age. To ensure healthy cognitive development, we need to better understand how the early childhood environment influences development. Maternal depression in early childhood is a prevalent (11-25%) public health problem and a robust risk factor for poor cognitive outcomes in the child. However, there remain important gaps in our understanding of the longitudinal mechanisms through which it influences children's cognitive outcomes. Understanding why and for whom this association exists can inform the development of interventions to promote healthy child development.

**Objectives:** The overall aim of this dissertation is to examine mediating and moderating factors of the association between maternal depression and children's cognitive development using the *Developmental Model for Understanding Mechanisms of Transmission* as a framework. Specific objectives – each corresponding to a research paper forming the body of this dissertation – are to: (1) summarize existing evidence on mediators of the association between maternal depression and children's cognitive development; (2) examine the mediating role of children's school experiences in the association between maternal depression and academic performance, including the moderating role of child's sex in these associations; (3) examine the role of gene-environment mechanisms in the association between maternal depression and children's cognitive school readiness; and (4) perform a meta-analysis of the moderating role of child's sex in the association between maternal depression and cognitive outcomes across childhood and adolescence.

**Methods:** Systematic review and meta-analytic methods were used to address objectives 1 and 4. For objective 2, data from the Québec Longitudinal Study of Child Development were used.

Maternal depression was self-reported (between child's ages 5 months and 5 years); peer victimization and school engagement were parent, teacher, and child-reported (6-10 years); and academic performance was assessed when children were 12 years. Data from the Québec Newborn Twin Study were used for objective 3: self-reported maternal depression (6 and 18 months) and assessment of children's cognitive school readiness (5 years). Structural equation models, adjusted for confounders where necessary, were used to estimate associations in both cohorts.

**Results:** The studies in this dissertation show that (1) only a handful of studies have examined mediators of the association between maternal depression and cognitive development, with most identifying maternal cognitions, behaviours, and affect as a mediator; (2) school engagement mediates the association between maternal depression and academic performance in girls only; (3) genetic contributions to children's cognitive school readiness decrease – while environmental contributions increase – as the level of maternal depression increases; and (4) sex moderates the association between maternal depression and cognitive development, with boys at higher risk of poor cognitive outcomes.

**Conclusion:** These findings suggest that addressing maternal cognitions, behaviours, and affect can help mitigate the negative effect of maternal depression on children's cognitive outcomes at the population level. They also suggest that boys are more negatively affected by maternal depression, and that for girls, addressing the impact of maternal depression on their school engagement may lead to improved cognitive outcomes. Further research on additional mediators and moderators can help strengthen our understanding of the association between maternal depression and children's cognitive development.

***Keywords****: Cognitive development; Maternal depression; Mediators; Moderators; Gene-environment mechanisms; Systematic review; Meta-analysis*

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## List of Abbreviations

CES-D – Centre for Epidemiologic Studies Depression Scale

DSM – Diagnostic and Statistical Manual for Mental Disorders

DZ – Dizygotic

EDI – Early Development Instrument

GxE – Gene-environment interaction

HOME – Home Observation for Measurement of the Environment

MDS – Maternal depressive symptoms

MZ – Monozygotic

QLSCD – Québec Longitudinal Study of Child Development

QNTS – Québec Newborn Twin Study

SEM – Structural Equation Modelling

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*"Here I raise my Ebenezer, hither by Thy help I'm come."*

-Robert Robinson

# Chapter 1. Introduction

## 1.1 Research problem

### 1.1.1 Children's cognitive development: The importance of the early childhood environment

The early childhood environment plays a significant role in child development. Evidence from many social science and health-related disciplines show that the origins of adult disease and wellbeing lie in the developmental processes that occur during early childhood (i.e., birth to age 5 years; Black et al., 2017; Council for Early Child Development, 2010; National Scientific Council on the Developing Child, 2020; O'Donnell & Meaney, 2017; Parsons, Young, Rochat, Kringelbach, & Stein, 2012; Richter et al., 2017; Shonkoff, Boyce, & McEwen, 2009; Shonkoff et al., 2012). Giving children the best start in life is therefore an important priority for promoting health across the lifespan (Black et al., 2017; Lund et al., 2018; Richter et al., 2017; WHO Commission on Social Determinants of Health & World Health Organization, 2008). Children's cognitive development – which refers to age-related increases in language, intellectual, and executive functioning capabilities – constitutes an important building block of social capital in modern societies (Grantham-McGregor et al., 2007; Walker et al., 2007; Walker et al., 2011). Cognitive skills allow children to think, learn, read, remember, reason, and pay attention, functions that enable them to increase control over and improve their health as they grow up (Black et al., 2017; Kickbusch, 2003; National Scientific Council on the Developing Child, 2020; Richter et al., 2017; World Health Organization, 1986) – the central aim of health promotion and the new public health (Baum, 2016).

From this health promotion perspective, it is necessary to understand the rearing environment within which children develop their cognitive skills, as these skills are influenced by genetic, biological, social, and psychological factors that can hinder or promote healthy

development – especially in early childhood (Baum, 2016; Black et al., 2017; Grantham-McGregor et al., 2007; National Scientific Council on the Developing Child, 2020; Walker et al., 2007, 2011). These factors include – but are not limited to – parental characteristics (e.g., parenting behaviours, mental health) and the context of early childhood care and education (Belsky & De Haan, 2011; Black et al., 2017; Eshel, Daelmans, Mello, & Martines, 2006; Gelaye, Rondon, Araya, & Williams, 2016; Grace, Evindar, & Stewart, 2003; Grantham-McGregor et al., 2007; Liu et al., 2017; Nakamoto & Schwartz, 2010; Parsons et al., 2012; Rogers et al., 2020; Roncallo, Barreto, & de Miguel, 2018; Ruiz, Quackenboss, & Tulve, 2016; Sanger, Iles, Andrew, & Ramchandani, 2015; Sohr-Preston & Scaramella, 2006; Stein et al., 2014; Teti, Cole, Cabrera, Goodman, & McLoyd, 2017; Upadyaya & Salmela-Aro, 2013; Walker et al., 2007, 2011; Wanless, Rosenkoetter, & McClelland, 2008). Given the large amount of time young children spend with their parents, particularly their mothers, parental characteristics play a vital role in children's cognitive development. Parents who stimulate and support their children's cognitive growth through verbal interactions, structured activities, and games encourage children's active exploration and engagement with their environments, leading to improvements in cognitive and academic outcomes (Aboud & Yousafzai, 2015; Jeong, Franchett, & Yousafzai, 2018; Teti et al., 2017; Zauche et al., 2017; Zauche, Thul, Mahoney, & Stapel-Wax, 2016). However, the extent to which parents can be involved in promoting their child's cognitive development can be influenced by other factors such as the experience of mental health problems. Although both parents are important for children's cognitive development, this dissertation focuses on mothers and their mental health as they are often the primary caregivers of young children (Ramchandani & Psychogiou, 2009; Richter et al., 2011).

### 1.1.2 The role of maternal depression in children's cognitive development

Maternal depression is a prevalent public health problem, with global prevalence estimates of 15-25% for sub-clinical symptoms and 11-13% for clinical diagnoses in the general population (Gelaye et al., 2016; Howard et al., 2014). It is characterized by the experience of sad mood or loss of pleasure in daily activities accompanied by cognitive or somatic symptoms that can persist over time across the perinatal period, from pregnancy to early childhood (American Psychiatric Association, 2013). Maternal depression – both sub-clinical and clinically significant symptoms – is a relevant public health issue not only because of its high prevalence, but also because of its adverse consequences on maternal health and child development (Arango et al., 2018; Edmond, 2017; Meaney, 2018; Moore Simas et al., 2019; O'Connor, Senger, Henninger, Coppola, & Gaynes, 2019; Stein et al., 2014). The experience of depressive symptoms is known to have a significantly negative impact on how mothers interact with and stimulate their children (Beck, 1995; Dix & Meunier, 2009; Downey & Coyne, 1990; Field, 2010; Logsdon, Wisner, & Pinto-Foltz, 2006; Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Meaney, 2018; Moore Simas et al., 2019; Murray, Cooper, & Hipwell, 2003). Maternal depression also has a consistent, albeit small, negative effect on children's cognitive development, including verbal and academic skills (Gelaye et al., 2016; Grace et al., 2003; Liu et al., 2017; Parsons et al., 2012; Rogers et al., 2020; Sanger et al., 2015; Stein et al., 2014). We know that screening for and preventing maternal depression leads to improvements in maternal mental health (Dennis & Dowswell, 2013; O'Connor et al., 2019; Rahman et al., 2018; Sockol, Epperson, & Barber, 2013). However, it is not clear whether such interventions also have an impact on children's cognitive outcomes (Goodman, Cullum, Dimidjian, River, & Kim, 2018; Letourneau, Dennis, Cosic, & Linder, 2017; Rahman et al., 2018).

Despite the significant body of research investigating the negative impact of maternal depression on children's cognitive development, few studies have investigated the underlying mechanisms of this association, that is the processes that explain why (mediators) and for whom (moderators) maternal depression has a negative impact on children's cognitive outcomes. As such, there are important gaps in our understanding of why children of mothers experiencing depression have a higher risk of developing poorer cognitive outcomes. These gaps can be addressed by answering questions such as: which factors mediate the association between maternal depression and children's cognitive development? Does maternal depression have a similar effect on boys' and girls' cognitive development? What are the roles of gene-environment mechanisms in the association between maternal depression and children's cognitive outcomes? Using longitudinal data to identify the modifiable factors through which maternal depression influences children's cognitive development and identifying the factors that alter the extent of its impact can help advance public health by informing the development of strategies to promote children's healthy cognitive development.

### 1.2 General objectives of the present dissertation

The present dissertation extends the current literature on the association between maternal depression and children's cognitive outcomes by using longitudinal population-based data and qualitative and quantitative review methods to examine mediating and moderating factors of this association. The specific objectives are to (1) summarize existing evidence on mediators of the association between maternal depression and children's cognitive development; (2) examine the mediating role of children's school experiences in the association between maternal depression and academic performance, including the moderating role of child's sex in these associations; (3)

examine the role of gene-environment mechanisms in the association between maternal depression and children's cognitive school readiness using a twin sample; and (4) perform a meta-analysis of the moderating role of child's sex in the association between maternal depression and cognitive outcomes. This dissertation is grounded in Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission* because it proposes potential mediators (i.e., negative maternal cognitions, behaviours, and affect; a stressful family environment; innate dysfunctional neuroregulatory mechanisms; and heritability) and moderators (i.e., timing and course of maternal depression; child's sex; and paternal characteristics) of the association between maternal depression and child development. Although this model was designed to explain the development of psychopathology in children exposed to maternal depression, the pathways proposed are relevant for understanding the association with cognitive development.

For the purpose of this dissertation, developmental periods are defined by age corresponding to three groups: (a) early childhood as ages 0-5 years; (b) (middle) childhood as ages 6-10 years; and (c) adolescence as ages 11-18 years. These ranges approximate conceptualizations of developmental periods as proposed by the American Academy of Pediatrics (i.e., childhood between 1 and 10 years and adolescence between 11 and 21 years; Hagan, Shaw, & Duncan, 2017).

Throughout the dissertation, the term "maternal depression" is used to refer to both sub-clinical (i.e., self-reported symptoms that do not meet established criteria) and clinical (i.e., diagnosed according to established criteria) levels of depression. In the Introduction, Literature Review, and Discussion, terms such as "effect", "impact", and "influences" are used to invoke causality (i.e., extent to which maternal depression causes poorer cognitive outcomes in children) in theoretical discussions of the association between maternal depression and children's cognitive

development (Ahern, 2018; Hernán, 2018). However, the causal nature of the association cannot be directly inferred with the study designs used for this dissertation. Nevertheless, statistical methods are used to estimate the adjusted association (i.e., accounting for observed variables that may confound the association) between maternal depression and children's cognitive development to reinforce confidence that the association is independent from known confounding factors.

### 1.3 Organization of the dissertation

The present dissertation is organized as follows: Chapter 1 (Introduction) presents cognitive development as a key building block of social capital and health outcomes, underscoring the importance of understanding how it is influenced by the early childhood environment. It also frames the purpose of the present dissertation by outlining how maternal depression – a prevalent public health issue – is etiologically associated with children's cognitive development and introduces a theoretical framework to understand this association. Finally, it presents the overall objectives of the current dissertation and an outline of the following chapters.

Chapter 2 (Literature Review) presents a detailed review of our current understanding of the association between maternal depression and children's cognitive outcomes. After a brief overview of cognitive development and the risk and protective factors in the early home and school environments that influence it, I present the definition and prevalence of maternal depression and discuss its implications for children's healthy cognitive development; review empirical evidence for each of the proposed mechanisms in Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission*; and discuss existing gaps in the literature. Reviewing this literature is relevant for public health and health promotion because it provides valuable information on what we know and what we do not know, thus enabling us to identify

relevant research questions that can help inform the elaboration of interventions to promote children's healthy cognitive development.

Chapter 3 (Methodology) presents the general objective of the present dissertation, as well as the specific objectives and hypotheses for each of the four research papers contained herein. This chapter also details the study design for each paper; describes the key variables used; and describes the statistical methods used for data analysis.

Chapter 4 (Results) contains all four research papers derived from the present dissertation in chronological order. Three manuscripts have been published in peer-reviewed journals and the fourth is currently undergoing peer review: *Article 1* entitled "Maternal depressive symptoms and early childhood cognitive development: A review of putative environmental mediators"; *Article 2* entitled "Maternal depressive symptoms and children's academic performance: Sex differences in the mediating role of school experiences"; *Article 3* entitled "Maternal depressive symptoms and children's cognitive school readiness: The role of gene-environment mechanisms"; and *Article 4* entitled "Sex differences in the association between maternal depression and child and adolescent cognitive development: A systematic review and meta-analysis".

I am the principal (first) author for each of these research articles. I was therefore responsible for conceptualizing the research questions, conducting literature reviews of existing studies, analyzing the data and interpreting the results, and preparing the first drafts of the manuscripts that I then revised based on co-authors' feedback. Co-authors contributed to the conceptualization of the research questions, supervision of data analysis, interpretation of results, and provision of critical feedback on drafts of the manuscripts. A detailed description of co-authors' contributions is provided before each article.

Chapter 5 (Discussion) reviews the main results of each research paper and discusses the findings in relation to scientific contributions, public health and health promotion implications, strengths and limitations, and emerging issues and future research in early childhood development. The conclusion is presented in the final section of this chapter.

# Chapter 2. Literature Review

This chapter presents a detailed literature review of cognitive development, maternal depression, and the association between them. It is organized into four sections: (1) a description of cognitive development and how it is influenced by the early childhood environment; (2) an overview of maternal depression and why it matters for child development; (3) a summary of what we know about the association between maternal depression and children's cognitive development, which consists of a literature review of empirical studies on each of the mechanisms outlined in Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission*; and (4) a reflection on the limitations of the extant literature (i.e., what we do not know) and how the present dissertation will address them.

## 2.1. Cognitive development: A brief overview

### 2.1.1. What is cognitive development?

Cognitive development is the process through which we acquire thought, language, memory, and reasoning capabilities (Aboud & Yousafzai, 2016). This process begins at conception and continues throughout childhood and into adolescence. Children progress through different developmental stages as they age, moving from responding to language as newborns to learning how to communicate verbally and non-verbally with people around them as infants and toddlers (Brazelton & Nugent, 1995). During the early childhood period (i.e., birth to age 5 years), the brain undergoes rapid development whereby connections between different parts of the brain are formed as children acquire new skills (Allen & Kelly, 2015; Black et al., 2017). The early childhood period is recognized as a sensitive period of development as this is when the brain is most malleable – that is, the brain is able to modify its connections in response to positive and negative external influences (Council for Early Child Development, 2010; National Scientific Council on the

Developing Child, 2020; Shonkoff et al., 2012). The cognitive skills acquired during this sensitive period then lay the foundation for key life skills – including logical reasoning and social relations – that can significantly influence an individual's health and social outcomes (Black et al., 2017; Heckman, 2006; National Scientific Council on the Developing Child, 2020; Park, Fertig, & Allison, 2011; Richter et al., 2017).

### 2.1.2. Childhood risk and protective factors for healthy cognitive development

Given the sensitivity of the developing brain to external influences prior to birth and during early childhood, it is important to understand the factors that can hinder or promote cognitive development. A large body of research has examined the risk and protective factors for children's healthy cognitive development (see Black et al., 2017; Grantham-McGregor et al., 2007; National Scientific Council on the Developing Child, 2020; Walker et al., 2007, 2011 for reviews). For the purposes of this dissertation, we will focus on risk and protective factors within what Bronfenbrenner (1979) termed microsystems, that is the systems of relations between the developing child and their immediate environments (e.g., home and school). This is similar to the health promotion concept of settings, which refers to the places or social contexts where individuals engage in daily activities through which environmental and personal factors interact to affect health and wellbeing (Nutbeam, 1998). The following paragraphs present research on risk and protective factors within these settings (note that the terms microsystems and settings are used interchangeably henceforth).

Within the home, parental characteristics are the primary factors that influence children's cognitive development. The nurturing care that parents provide consists of a core set of competencies including behaviours, attitudes, and knowledge regarding stimulation,

responsiveness towards the child, and the skills to support their child's development and wellbeing (Britto et al., 2017). The provision of cognitive stimulation (i.e., reading, singing, and playing), engagement in sensitive and responsive parent-child interactions (i.e., being aware of a child's signals and providing timely and developmentally appropriate responses; Eshel et al., 2006), and practice of warm, nurturing, and supportive behaviours have been repeatedly associated with improvements in various cognitive domains including academic performance, executive functioning (e.g., working memory, inhibitory control), and expressive and receptive language abilities in early childhood (Belsky & Haan 2011; Black et al., 2017; Britto et al., 2017; Eshel et al., 2006; Grantham-McGregor et al., 2007; Richter et al., 2017; Roncallo et al., 2018; Ruiz et al., 2016; Sohr-Preston & Scaramella 2006; Teti et al., 2017; Walker et al., 2007, 2011). Additionally, parental engagement (i.e., participation of parents in meaningful communication involving children's learning) and responsiveness have also been associated with academic performance in middle childhood and adolescence (Boonk, Gijselaers, Ritzen, & Brand-Gruwel, 2018; Fan & Chen, 2001; Jeynes, 2012; Pinquart, 2016).

Another important parental characteristic that has an impact on children's cognitive development is their socioeconomic status. Broadly speaking, socioeconomic status consists of an individual's income, educational attainment, and occupational status (Tucker-Drob, Briley, & Harden, 2013). Decades of social science and public health research show that children who grow up in poor/low socioeconomic status households have poorer cognitive outcomes across the lifespan (Aber, Bennett, Conley, & Li, 1997; Baker, Kainz, & Reynolds, 2018; Brooks-Gunn & Duncan, 1997; Heckman, 2011; Lacour & Tissington, 2011; Phillips & Shonkoff, 2000; Saitadze & Lalayants, 2020). Two perspectives have been proposed to explain these findings. The first is encapsulated in the *Family Investment Model* which posits that parents with higher incomes, levels

of education, and occupational status have the resources to provide the materials, experiences, and services to stimulate their child and invest in their education, thus leading to better cognitive outcomes (Conger & Elder, 1995). The second perspective – the *Family Stress Model* – postulates that living in poverty or having a low socioeconomic status increases parents' risk of experiencing stress and mental health problems, thereby limiting their capacity to engage in their children's cognitive development (Conger, Rueter, & Conger, 2000; Elder & Caspi, 1988). These perspectives are not mutually exclusive: it is possible that both having fewer economic resources and experiencing higher levels of stress explain the effect of poverty/low socioeconomic status on children's cognitive outcomes across the lifespan.

Yet another important parental characteristic that influences children's cognitive development is parental mental health. A handful of systematic reviews and meta-analyses report consistent and small-to-moderate negative effects of parental depression and anxiety on children's cognitive outcomes (Gelaye et al., 2016; Grace et al., 2003; Liu et al., 2017; Parsons et al., 2012; Rogers et al., 2020; Sanger et al., 2015; Stein et al., 2014; Wanless et al., 2008). Children exposed to maternal or paternal depression and anxiety are more likely to experience difficulties in various cognitive domains, with some studies suggesting that this effect persists into adolescence. To date, the majority of studies on parental mental health and children's cognitive development have examined the effects of maternal depression, which is the focus of the present dissertation. A more detailed review of studies examining this association is provided in section 2.2.

Different aspects of the school setting can also promote or hinder children's cognitive development. For example, the extent to which children actively invest in their learning activities (a term defined as school engagement) can influence their cognitive outcomes. School engagement is conceptualized as a three-dimensional construct consisting of cognitive (i.e., intellectual effort

devoted to learning tasks), behavioural (i.e., constructive or cooperative engagement in classroom activities), and emotional (i.e., feelings about peers, teachers, and schoolwork) engagement (Fredricks, Blumenfeld, & Paris, 2004). Numerous studies have reported positive associations between higher levels of all three dimensions of school engagement and cognitive outcomes such as increased memory retention, cognitive school readiness (i.e., cognitive and language skills that reflect a child's ability to function successfully in school contexts; La Paro & Pianta, 2000), and academic performance across elementary and secondary school (Chase, Hilliard, Geldhof, Warren, & Lerner, 2014; Dotterer & Lowe, 2011; Guay, Ratelle, & Chanal, 2008; Guay, Ratelle, Roy, & Litalien, 2010; Ladd & Dinella, 2009; Olivier, Archambault, De Clercq, & Galand, 2018; Upadyaya & Salmela-Aro, 2013).

Another predictor of cognitive development in the school setting is peer relations. A recent meta-analysis reported small-to-moderate effects of having reciprocal friendships and working on academic tasks with friends on children's cognitive outcomes (Wentzel, Jablansky, & Scalise, 2018). Conversely, peer victimization – the experience of being bullied or aggressed repeatedly over time by one or more peers (Ladd & Kochenderfer-Ladd, 2002) – is negatively associated with children's cognitive outcomes (Nakamoto & Schwartz, 2010). Systematic reviews and meta-analyses report that children who are victimized are more likely to experience psychological distress and feel less engaged with their learning environment, which increases their risk of poor cognitive outcomes (Espelage, Hong, Rao, & Low, 2013; Fry et al., 2018; Gardella, Fisher, & Teurbe-Tolon, 2017; Nakamoto & Schwartz, 2010).

Each of the aforementioned factors plays an important role in children's cognitive development. This dissertation specifically focuses on maternal depression and the proposed mechanisms through which it exerts an influence on children's cognitive outcomes.

## 2.2. Maternal depression: Understanding its effect on children's cognitive development

### 2.2.1. What is maternal depression?

I use the term maternal depression to refer to the experience of a depressive episode (i.e., clinical) or elevated depressive symptom levels (i.e., sub-clinical) in the perinatal period (i.e., during pregnancy and early childhood). Depressive episodes are diagnosed when an individual has five out of the six symptoms (i.e., depressed mood [including presence of recurrent negative thoughts], loss of interest or pleasure in previously pleasure-inducing activities, significant weight loss or gain, fatigue, lack of concentration, and suicidal ideation) specified in the Diagnostic and Statistical Manual for Mental Disorders (DSM) most of the day nearly every day for two weeks or more, and clinically significant distress or impairment in functioning (American Psychiatric Association, 2013). Sub-clinical depression is characterized by elevated depressive symptom levels that reflect both the number and severity of symptoms, but do not meet the criteria for a clinical diagnosis. Elevated levels of depressive symptoms may reflect the experience of numerous symptoms of a low severity or a high severity of a smaller number of symptoms. Importantly, both clinical and sub-clinical levels of maternal depression can be associated with impairments in psychosocial functioning, including how mothers interact with their children (Dix & Meunier 2009; Lovejoy et al., 2000; Meaney 2018; Moore Simas et al., 2019; Sohr-Preston & Scaramella 2006).

There are social inequalities in maternal depression, whereby its prevalence and incidence vary among individuals and social groups within a population (Arango et al., 2018; Kawachi, Subramanian, & Almeida-Filho, 2002; Lund et al., 2018). Individual and societal factors associated with an increased likelihood of maternal depression include a family history of depression or other mental health problems, living in poverty or having a low level of education

(i.e., low socioeconomic status), experiencing racism, discrimination, or xenophobia, single parenthood, and exposure to stressful life events (Coast, Leone, Hirose, & Jones, 2012; Falah-Hassani, Shiri, Vigod, & Dennis, 2015; Field, 2017; Fisher et al., 2012; Gelaye et al., 2016; Hammen, 2018; Howard et al., 2014; Lund et al., 2010; O'Connor et al., 2019; Reesor-Oyer, Cepni, Lee, Zhao, & Hernandez, 2021). Factors such as low socioeconomic status and the experience of stressful life events have also been found to co-occur with maternal depression within families, with studies suggesting that bidirectional associations may be at play (Coast et al., 2012; Hammen 2018; Howard et al., 2014). For example, contrary to the *Family Stress Model* which hypothesizes that having a low socioeconomic status increases stress and mental health problems, there is evidence that the experience of mental health problems such as maternal depression can result in people drifting into or remaining in conditions of economic deprivation (Coast et al., 2012; Lund et al., 2010; Reeser-Oyer et al., 2021). As explained in section 2.1.2, some of these co-occurring factors (e.g., low socioeconomic status) are also known to have a negative impact on children's cognitive outcomes. It will therefore be important to account for these factors, where possible, to understand how maternal depression influences children's cognitive outcomes over and above the effect of other risk factors for poor cognitive outcomes.

### 2.2.2. Why maternal depression matters for child development

Maternal depression can have a significant impact on the health and wellbeing of women (Field, 2017; Hammen, 2018; Letourneau et al., 2012; Moore Simas et al., 2019). It also has negative impacts on children's cognitive, socioemotional, behavioural, and physical development (Beck, 1999; Connell & Goodman, 2002; Cummings & Davies, 1994; Gelaye et al., 2016; Gentile, 2017; Goodman, 2007, 2020; Goodman & Gotlib, 1999; Goodman et al., 2011; Grace et al., 2003;

Liu et al., 2017; Martins & Gaffan, 2000; Moore Simas et al., 2019; Parsons et al., 2012; Richter et al., 2017; Rogers et al., 2020; Sanger et al., 2015; Stein et al., 2014; Surkan, Kennedy, Hurley, & Black, 2011; Wachs, 2009). Children exposed to both clinical and sub-clinical maternal depression – whether antenatally, postnatally, or both – are at increased risk of experiencing difficulties in a variety of cognitive outcomes, with meta-analytic effects of *Cohen's d* = 0.25 [95% confidence interval = -0.39 to -0.12] in early childhood and *Pearson's r* = -0.12 to -0.25 [-0.39 to -0.05] across childhood and adolescence (Gelaye et al., 2016; Grace et al., 2003; Liu et al., 2017; Parsons et al., 2012; Rogers et al., 2020; Sanger et al., 2015; Stein et al., 2014).

Several studies have also examined whether interventions that aim to treat or prevent maternal depression also have an effect on children's cognitive outcomes, but results are mixed (Cicchetti, Rogosch, & Toth, 2000; Cooper, De Pascalis, Woolgar, Romaniuk, & Murray, 2015; Hayden et al., 2012; Kersten-Alvarez, Hosman, Riksen-Walraven, Van Doesum, & Hoefnagels, 2010; Letourneau et al., 2011; Makrides et al., 2010; Maselko et al., 2015; Milgrom et al., 2015; Murray, Cooper, Wilson, & Romaniuk, 2003; Verduyn, Barrowclough, Roberts, Tarrier, & Harrington, 2003). Indeed, while some of these interventions successfully treat and prevent maternal depression, systematic reviews and meta-analyses have found that these improvements rarely translate into significant effects on children's cognitive outcomes (Goodman et al., 2018; Letourneau et al., 2017; Rahman et al., 2018; Tsivos, Calam, Sanders, & Wittkowski, 2015). This lack of overall effects on children's cognitive outcomes may be due to the fact that few of these interventions were specifically designed to assess impacts on child outcomes (O'Connor et al., 2019). This suggests that although screening and prevention efforts to reduce the prevalence of maternal depression are necessary for improving maternal mental health, further work is needed

to design interventions that can also lead to improvements in children's wellbeing (Dennis et al., 2013; O'Connor et al., 2019; Sockol et al., 2013).

The public health significance of maternal depression is reflected in prevention and health promotion efforts to reduce its prevalence and incidence in the general population. For example, both the *Institut National de Santé Publique du Québec* (Québec National Institute of Public Health) and the US Preventive Services Task Force strongly recommend regular screening for depressive symptoms and referral of at-risk women to appropriate psychosocial and/or pharmacological interventions during pregnancy (Gouvernement du Québec, 2019; O'Connor et al., 2019). The public health relevance of maternal depression is also highlighted by economic analyses that reveal that maternal mental health problems (e.g., depression, anxiety, psychosis) incur high health and social services costs of thousands of dollars ranging from $US 5,300 (~$CA 6,700) per year to lifetime costs of £75,728 (~$CA 134 277) per mother-child dyad (Bauer, Knapp, & Parsonage, 2016; Bauer, Parsonage, Knapp, Iemmi, & Adelaja, 2014; Bauer et al., 2015; Luca et al., 2020). These costs are generated through the increased use of health and social care services, decreases in disability-adjusted life-years (i.e., the loss of the equivalent of 1 year of full health; Gore et al., 2011), and loss of productivity (Bauer et al., 2016; Bauer et al., 2014; Bauer et al., 2015; Canadian Perinatal Mental Health Collaborative, 2018; Luca et al., 2020). Note that these are costs over and above those that would have been incurred anyway (e.g., costs of general health services). Furthermore, the majority of these costs derive from expenditures for the child such as special education needs, costs to the criminal justice system, and the social and economic costs of low levels of education (Bauer et al., 2014, 2015, 2016; Luca et al., 2020). These findings align with evidence showing that in the long-term, intervening early to improve child outcomes

generates high returns to investments, including improvements in population health (Arango et al., 2018; Heckman 2006; Richter et al., 2017).

Given the high malleability of the developing brain in early childhood, children are more likely to be responsive to interventions that target risk factors for poor development during this period (Black et al., 2017; Britto et al., 2017; Council for Early Child Development 2010; National Scientific Council on the Developing Child, 2020; Richter et al., 2017). We therefore need to better understand how maternal depression influences children's cognitive development during this period to subsequently inform the development of such interventions. This is especially important given the limited evidence on the efficacy of interventions targeting maternal depression on children's cognitive outcomes (O'Connor et al., 2019). By investigating the mechanisms through which maternal depression influences children's cognitive development, we can identify new targets for interventions that aim to mitigate the negative effect of maternal depression on children's cognitive outcomes. Below, I use a theoretical framework to structure a literature review of studies examining the mechanisms of the association between maternal depression and cognitive development across childhood and adolescence. I then highlight existing gaps in the current literature and propose research questions to address some of these gaps.

## 2.3. What do we know about the mechanisms of the association between maternal depression and children's cognitive development?

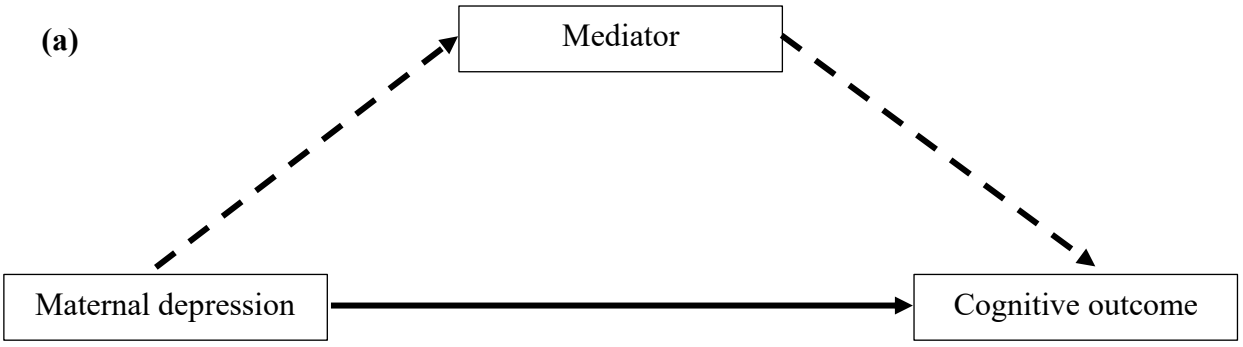
### 2.3.1. A conceptual framework for understanding how maternal depression influences children's cognitive development

It is necessary to anchor the research presented in this dissertation in a theoretical framework because theories enable us to describe, understand, and explain an ensemble of associations and thus advance scientific knowledge on a given phenomenon (Willett, 1996). A number of theoretical frameworks about the mechanisms of the association between maternal depression and child development have been proposed over the years. These include the *Developmental Model for Understanding Mechanisms of Transmission*, the *Family Stress Model*, and the *Determinants of Parenting Model* (Bandura, 1995; Belsky, 1984; Elder & Caspi, 1988; Goodman & Gotlib, 1999). Of all the aforementioned frameworks, Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission* is the most pertinent for the research presented in this dissertation as it provides a guide to identifying the processes that explain why (i.e., mediators) and for whom (i.e., moderators) maternal depression has an effect on child development. As mentioned in Chapter 1, although the model was designed to focus on mental health outcomes in children, some of the pathways proposed are relevant for understanding the association with cognitive development.

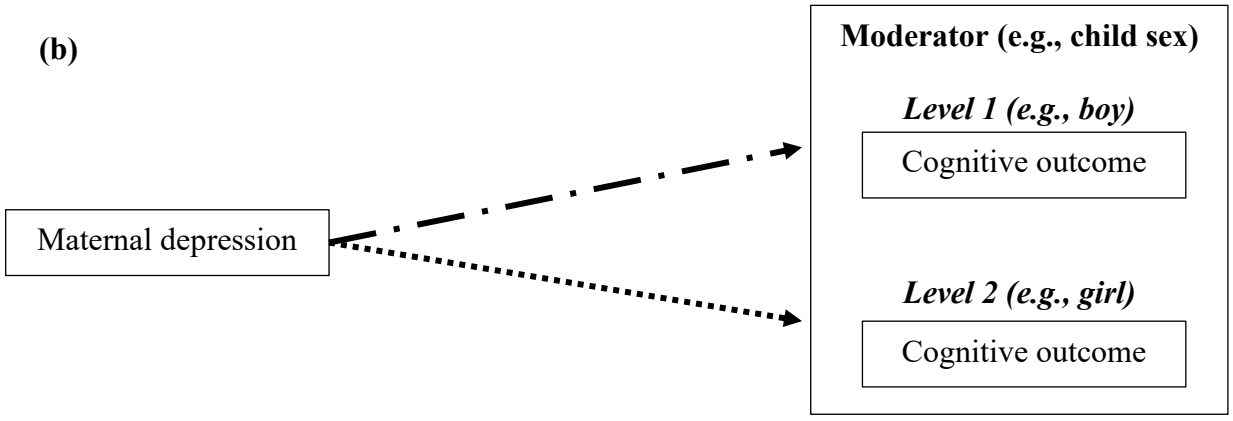
Within the model, mediation refers to intermediary factors that can explain the longitudinal effect of maternal depression on children's cognitive development (Goodman & Gotlib, 1999). To establish mediation, maternal depression must have an effect on the mediating (or intermediary) variable, which should in turn have an effect on children's cognitive outcomes. To respect the temporal nature of effects, maternal depression must occur in time before the mediator and a

cognitive outcome and the mediator must occur before the cognitive outcome (Glass, Goodman, Hernán, & Samet, 2013; Hill, 1965). On the other hand, moderation refers to a variable that acts as a modifier of the effect of maternal depression on children's cognitive outcomes such that this effect varies at different levels of the moderating variable (Goodman & Gotlib, 1999). For example, if the effect of maternal depression on boys' cognitive development is different from that of the effect on girls' cognitive development, child's sex is described as a moderator (or moderating variable) of the association between maternal depression and cognitive development. ***Figures 1a*** and ***1b*** provide visual representations of mediators and moderators, respectively.

**Figure 1.** Visual representations of (a) mediation and (b) moderation of the association between maternal depression and children's cognitive development



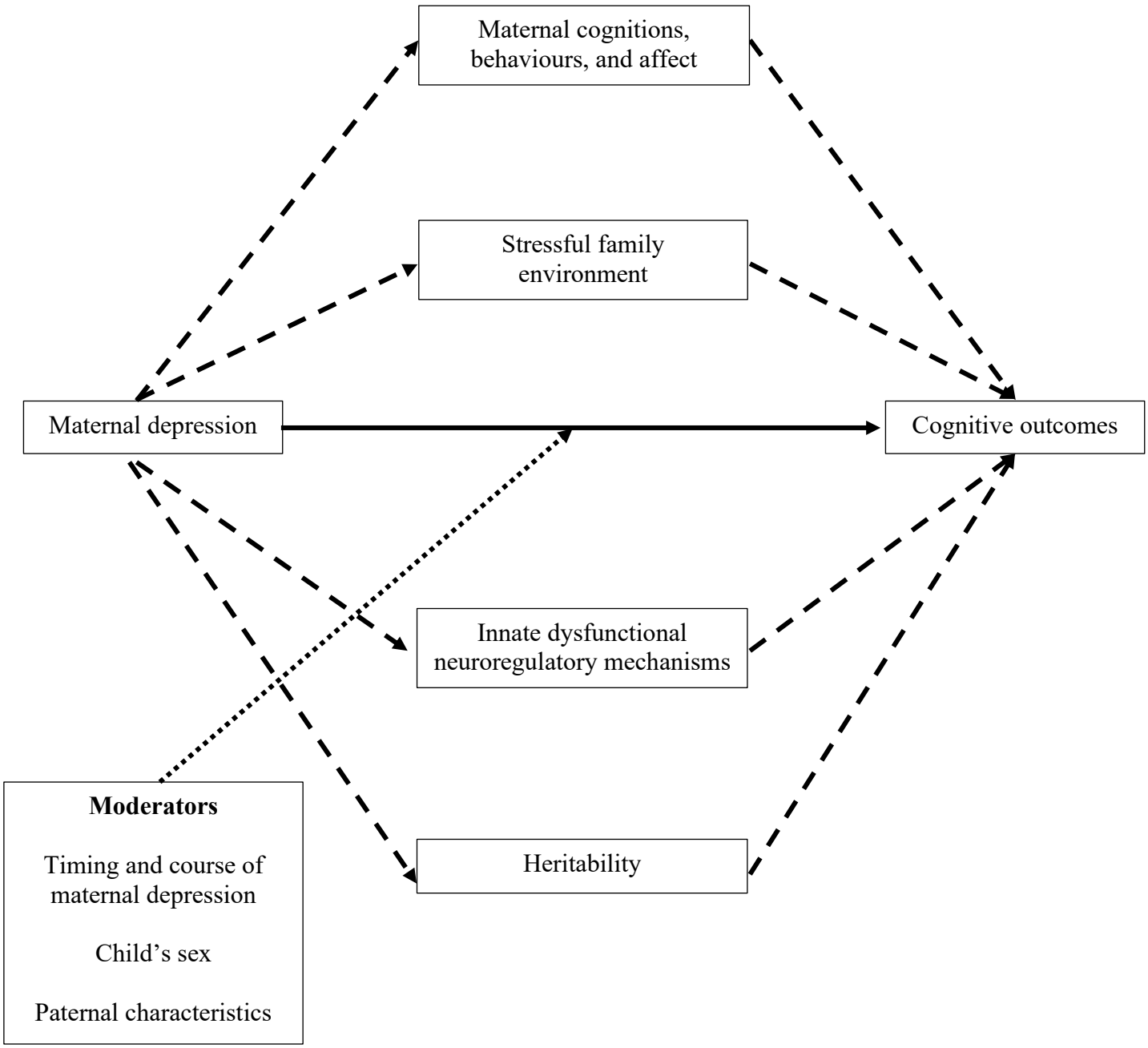

The solid arrow represents the *direct* effect of maternal depression on children's cognitive outcomes. The dashed arrows represent the *indirect* effect of maternal depression on children's cognitive outcomes *via* the mediator.




The dashed-dotted line represents the effect of maternal depression on children's cognitive outcomes at the *first level* of the moderator and the dotted line represents the effect at the *second level*.

In the *Developmental Model for Understanding Mechanisms of Transmission*, Goodman & Gotlib propose four potential mediators (i.e., negative maternal cognitions, behaviours, and affect; a stressful family environment; innate dysfunctional neuroregulatory mechanisms; and heritability) and three potential moderators (i.e., timing and course of maternal depression; child's sex; and paternal characteristics) of the association between maternal depression and child development (Goodman & Gotlib, 1999). The following paragraphs describe each of these mediators and moderators and provides a corresponding review of empirical studies testing the proposed mechanism with respect to children's cognitive outcomes. ***Figure 2*** provides a visual representation of the model.

**Figure 2.** Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission*




The solid arrow represents the *direct* effect of maternal depression on children's cognitive outcomes. The dashed arrows represent the *indirect* effect of maternal depression on children's cognitive outcomes *via* the proposed mediators. The dotted line represents the *moderating effect* of the proposed moderators on the direct effect of maternal depression on children's cognitive outcomes.

Adapted from Goodman & Gotlib, 1999

#### 2.3.1.1. Proposed mediators of the association between maternal depression and children's cognitive development

***Negative maternal cognitions, behaviours, and affect***

According to Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission*, one of the four potential mediators of the association between maternal depression and children's cognitive development is exposure to the negative cognitions, behaviours, and affect that occur in mothers experiencing depression. These characteristics are hypothesized to interfere with a mother's ability to actively engage with her child and can therefore negatively affect the development of cognitive skills by increasing risk for poor cognitive outcomes.

Five narrative reviews of observational studies report significant associations of maternal depression with negative maternal perceptions of normal child behaviour, reduced maternal sense of enjoyment in the parenting role, lower quality mother-child interactions, and flat and negative emotional expression (Downey & Coyne 1990; Dix & Meunier 2009; Field 2010; Logsdon et al., 2006; Murray et al., 2003). These findings are supported by meta-analytic findings of moderate-to-large effects of maternal depression on the quality of mother-child interactions (*Pearson's r* = 0.32-0.50 [95% confidence interval = 0.24-0.56]; Beck 1995) and maternal parenting behaviours (*Cohen's d* = 0.40 [0.31-0.49]; Lovejoy et al., 2000). However, evidence of this association in intervention studies is mixed. Two reviews found that although treating maternal depression reduced depressive symptoms, there was no overall effect of interventions on maternal cognitions, behaviours, and affect (Letourneau et al., 2017; Tsivos et al., 2015). Conversely, another review found significant positive effects of maternal depression treatment interventions on mother-child interactions (Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2015). However, the authors of

the latter review caution that results must be interpreted prudently due to sub-optimal study quality and heterogeneity in the assessment tools used.

Regarding the association of negative maternal cognitions, affect, and behaviour with children's cognitive development, there is ample evidence from both observational and intervention studies that improving different dimensions of maternal parenting (e.g., warmth, sensitivity, responsiveness, cognitive stimulation) leads to improved cognitive outcomes in children – as described in section 2.1.2 (Aboud & Yousafzai, 2015; Belsky & De Haan, 2011; Black et al., 2017; Daelmans et al., 2015; Dowdall et al., 2020; Eshel et al., 2006; Grantham-McGregor et al., 2007; Jeong et al., 2018; Roncallo et al., 2018; Ruiz et al., 2016; Sanders, Kirby, Tellegen, & Day, 2014; Sohr-Preston & Scaramella, 2006; Teti et al., 2017; Walker et al., 2007, 2011). However, only a handful of studies have quantitatively examined whether negative maternal cognitions, affect, and behaviour mediate the association between maternal depression and cognitive development. To date, only one study has systematically reviewed this literature.

Goodman and colleagues (2020) reviewed studies that examined different dimensions of maternal parenting behaviours as a mediator of the longitudinal association between maternal depression and various child outcomes and provided meta-analytic effects of: (1) the association between maternal depression and maternal parenting behaviours; (2) the association between maternal depression and child outcomes; (3) the association between maternal parenting behaviours and child outcomes; and (4) the indirect effect of maternal depression on child outcomes via maternal parenting behaviours. Of the 37 studies included in the meta-analysis, eight (from six publications) used a measure of cognitive development as the child outcome (Gueron-Sela, Camerota, Willoughby, Vernon-Feagans, & Cox, 2018; McManus & Poehlmann, 2012; Ng-

Knight, Shelton, Frederickson, McManus, & Rice, 2018; Psychogiou, Russell, & Owens, 2019; Stein, Malmberg, Sylva, Barnes, & Leach, 2008; Wu et al., 2019).

All of these studies used a validated measure of sub-clinical maternal depression (e.g., Centre for Epidemiologic Studies Depression Scale [CES-D]; Radloff, 1977). However, there was some heterogeneity in the dimensions of maternal parenting behaviours and children's cognitive outcomes assessed across studies. All but two studies (Ng-Knight et al., 2018; Psychogiou et al., 2019) assessed maternal parenting using observer ratings with scales such as the Home Observation for Measurement of the Environment (HOME; Caldwell & Bradley, 1985). The dimensions of maternal parenting behaviours assessed included maternal caregiving, the quality and quantity of support for cognitive development available in the home, mother-child interactions during play activities, and mother and child-reports of maternal warmth and hostility. Various domains of cognitive outcomes (e.g., academic performance, executive functioning) were also assessed using standardized tests such as the Bayley Scales of Infant Development (Bayley, 2006) and school records of academic performance. Despite this heterogeneity across studies, (1) maternal depression was associated with both positive (e.g., responsiveness; *Pearson's r* = 0.14 [95% confidence interval = 0.11-0.16], where higher scores represent less positive) and negative (e.g., hostility; 0.12 [0.09-0.14], where higher scores represent more negative) maternal parenting behaviours; (2) maternal depression was associated with children's cognitive outcomes (0.08 [0.07-0.10]); (3) maternal parenting behaviours were associated with children's cognitive outcomes (0.22 [0.17-0.27]); and (4) maternal parenting behaviours mediated the longitudinal association between maternal depression and children's cognitive outcomes (0.02 [0.01-0.03]) (Goodman et al., 2020).

### *A stressful family environment*

The second mediator in Goodman & Gotlib's (1999) model is the exposure to a stressful family environment. The authors argue that children of mothers experiencing depression are not only exposed to their mother's depression, but also to a variety of stressors that are associated with maternal depression and can negatively impact child development. The framework particularly focuses on relationship discord (i.e., stress generated from the relationship between a mother and her partner; Goodman & Gotlib, 1999). However, the extent to which it mediates the association between maternal depression and cognitive development is not clear, as there can be bi-directional associations between relationship discord and maternal depression (Goodman 2007, 2020). The following paragraphs summarize evidence of the associations of relationship discord – and other family stressors – with maternal depression and with children's cognitive outcomes.

The experience of recurrent negative thoughts in individuals who are depressed can interfere with their capacity to respond to their interpersonal environment, including their relationships with their partners (American Psychiatric Association, 2013; Hammen, 2006). Several studies have found that mothers experiencing depression are more likely to experience interparental conflict and relationship discord, and they are more likely to be victims of intimate partner violence (Howard et al., 2014; Najman et al., 2014, 2017; Stein et al., 2014). Conversely, there is also evidence that experiences of interparental conflict, relationship discord, and intimate partner violence are important risk factors for maternal depression in the perinatal period (Dadi, Miller, Bisetegn, & Mwanri, 2020; Field, 2017; Fisher et al., 2012; Howard, Oram, Galley, Trevillion, & Feder, 2013; Hutchens & Kearney, 2020; Pilkington, Milne, Cairns, Lewis, & Whelan, 2015; Whisman, 2001). Indeed, recent evidence suggests that there is a bi-directional association between these two factors over time: difficulties in the interparental relationship

increase the risk of maternal depression, which can in turn exacerbate interparental difficulties (Goldfarb & Trudel, 2019; Hammen, 2018; Najman et al., 2014, 2017). Nevertheless, given that the purpose of the present dissertation is to understand the pathways through which maternal depression influences children's cognitive outcomes, we will subsequently focus on research examining relationship discord as a mediator of the longitudinal association between maternal depression and children's cognitive outcomes.

The association between relationship discord and child outcomes is well established (Cummings & Davies, 1994; Cummings & Davies, 2002; Grych, Fincham, Jouriles, & McDonald, 2000). Evidence from systematic reviews and meta-analyses suggest that relationship difficulties between a mother and her partner may 'spillover' into parent-child interactions and negatively impact child outcomes (Cummings & Davies, 2002; Erel & Burman, 1995; Krishnakumar & Buehler, 2000). Specifically, the Emotional Security Theory suggests that factors – such as interparental conflict – that threaten children's feelings of safety and security have the potential to negatively affect their wellbeing (Davies & Cummings, 1994). The overwhelming majority of studies have focused on children's behavioural and emotional outcomes, with only a few examining how exposure to relationship discord influences children's cognitive outcomes (Artz et al., 2014). These studies show that exposure to relationship discord, particularly to intimate partner violence, is associated with increased risk of experiencing poorer cognitive outcomes across childhood and adolescence (Artz et al., 2014; Fry et al., 2018; Pendry & Adam, 2013; Supol, Satyen, Ghayour-Minaie, & Toumbourou, 2020). Although a number of studies have found interparental conflict to mediate the association between maternal depression and children's emotional and behavioural outcomes, no study to date has examined the mediating role of relationship discord in the association with cognitive outcomes (Cummings, Cheung, Koss, &

Davies, 2014; Goodman, 2007; Goodman, 2020; Hammen, 2018; Hanington, Heron, Stein, & Ramchandani, 2012). Furthermore, only a handful of studies have examined whether other aspects of a stressful family environment (e.g., household chaos, family dysfunction) mediate the longitudinal association between maternal depression and children's cognitive development (Chen et al., 2013; Hay et al., 2001; Hur, Buettner, & Jeon, 2015; Letourneau, Tramonte, & Willms, 2013; Piteo, Yelland, & Makrides, 2012). Only one of these studies (Chen et al., 2013) identified a stressful family environment as a significant mediator, however, the use of a cross-sectional study design limits the ability to establish the temporality of associations (Maxwell, Cole, & Mitchell, 2011).

***Innate dysfunctional neuroregulatory mechanisms***

In the third mediation pathway of Goodman & Gotlib's (1999) model, dysfunctional neuroregulatory mechanisms are hypothesized to mediate the association between exposure to maternal depression during pregnancy and children's cognitive development. Antenatal maternal stress – including maternal depression – activates stress hormones such as glucocorticoids that regulate foetal brain development (Glover, O'Donnell, O'Connor, & Fisher, 2018; Meaney, Szyf, & Seckl, 2007; O'Donnell & Meaney, 2017). Because it can be difficult to obtain detailed information on foetal brain development using serial ultrasound scans, most studies use proxy measures – including birth weight, premature birth, head circumference, and ponderal index – to assess the direct effect of maternal mental health on brain development (Schlotz & Phillips, 2009). Several studies have found that children exposed to antenatal maternal depression are more likely to be born prematurely and have low birth weight (see Dadi et al., 2020; Field 2017 for reviews). In turn, children born prematurely and with low birth weight are more likely to experience poorer

cognitive outcomes across the lifespan (Aylward, Pfeiffer, Wright, & Verhulst, 1989; Farajdokht et al., 2017; Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2015; Mulder, Pitchford, Hagger, & Marlow, 2009; Orri et al., 2021). However, the extent to which these proxy measures of dysfunctional neuroregulatory mechanisms mediate the association between maternal depression and children's cognitive development has not been tested (O'Donnell & Meaney 2017). Further research is needed to determine whether exposure to maternal stress hormones in utero does indeed explain the association between antenatal maternal depression and children's cognitive outcomes.

### *Heritability*

The fourth and final mediation pathway in Goodman & Gotlib's (1999) model is directly applicable when examining children's mental health outcomes, as evidence suggests that depression is heritable and that children whose mothers experience depression have a genetic vulnerability that increases their risk of experiencing depression (Beardslee, Gladstone, & O'Connor, 2011; Goodman, 2007, 2020; Rice, Harold, & Thapar, 2002). There is no clear evidence, however, that children of mothers who experience depression have a genetic vulnerability that puts them at risk of specifically experiencing poor cognitive outcomes. We cannot therefore conceptualize heritability as a mediator in the context of the association between maternal depression and children's cognitive development. Nevertheless, behavioural genetic models can be used to examine gene-environment mechanisms that may potentially explain this association.

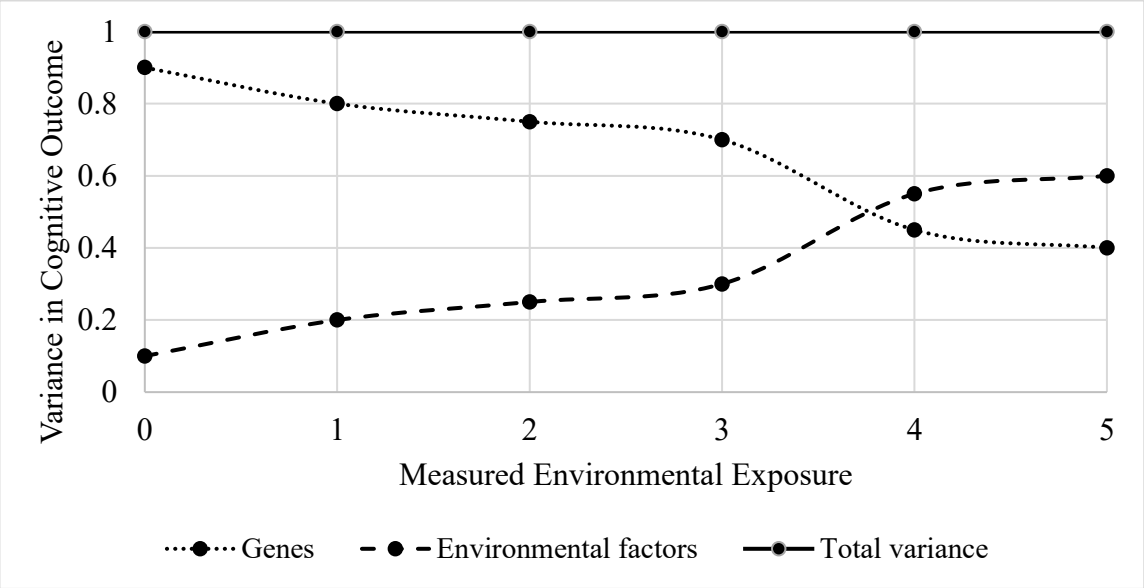
In behavioural genetic modelling, the environment is broadly defined as any non-genetic factor. Models are used to estimate the aggregate contribution of genes and environmental factors to a specific trait by exploiting differences in genetic relatedness between monozygotic (MZ) and

dizygotic (DZ) twin pairs (Price & Jaffee, 2008). By estimating the relative contributions of genetic and environmental factors to a given trait, these models quantify the proportion of a trait's variance explained by genes and environmental factors. The process of estimating a behavioural genetic model (also known as classic twin modelling) is further described in Chapter 3. For now, I focus on explaining a specific gene-environment mechanism this type of modelling is often used to estimate.

Gene-environment interaction (GxE) occurs when the genetic contribution to a given trait varies as a function of a measured environmental exposure (Price & Jaffee, 2008). In other words, the proportion of variance explained by genetic and environmental factors is not the same at different levels of a given environmental exposure. A hypothetical consideration of how genetic and environmental contributions to children's cognitive outcomes may vary at different levels of an environmental risk exposure is presented in ***Figure 3***. This information is important, as it would suggest that the same intervention aiming to modify environmental risk factors would be more effective in some contexts than others. In trying to understand the role GxE plays in the association between maternal depression and children's cognitive outcomes, Bronfenbrenner & Ceci's (1994) *Bioecological Model of Development* may be a more appropriate framework than Goodman & Gotlib's (1999) model. Bronfenbrenner & Ceci's (1994) model suggests that high quality environments that provide children with more opportunities for cognitive stimulation and learning can enable greater genetic contributions to cognitive outcomes. Alternatively, environments that do not promote cognitive stimulation can override genetic contributions and have a negative impact on cognitive outcomes. For example, studies show that there is a GxE between socioeconomic status and genetic contributions to children's cognitive outcomes, whereby genes explain less of the variance in cognitive school readiness among children from low socioeconomic

status families compared to those from high socioeconomic status families. Conversely, environmental factors explain more of the variance in cognitive school readiness among children from low socioeconomic status families (Rhemtulla & Tucker-Drob 2012; Tucker-Drob & Bates 2016; Tucker-Drob et al., 2013; Tucker-Drob, Rhemtulla, Harden, Turkheimer, & Fask 2011). Improving families' socioeconomic status could therefore minimize the impact of environmental factors on children's cognitive school readiness.

**Figure 3.** Hypothetical consideration of how proportion of variance in a cognitive outcome accounted for by genes and environmental factors varies as a function of a measured environmental exposure.




Behavioural genetic (or classic twin) modelling explains variations in a trait by identifying the proportion of the total variance explained by genes and environmental factors (also including measurement error), with these two components adding up to 100%. Therefore, decreases in the contribution of genes means that the contribution of environmental factors will increase and vice versa. In this figure, we conceptually represent a hypothetical GxE by showing how the contribution of genes and environmental factors to a cognitive outcome (i.e., the proportion of variance in the cognitive outcome explained by genes and the environment; y-axis) would vary at different levels of a measured environmental exposure (e.g., an adverse environment; x-axis). At level 5 of the environmental exposure (i.e., high adversity) genes would explain 40% of the variance versus 60% explained by environmental factors. Whereas at level 1 (i.e., no/low adversity), genes would explain 80% of the variance while environmental factors now only explain 20%. This suggests that there would be a moderating effect of the adverse environment on the relative proportions in the cognitive outcome explained by genes and environmental factors (i.e., there is GxE). Therefore, if the level of adversity in the environment were diminished, environmental factors would have less of an impact on the cognitive outcome.

We know that maternal depression is associated with decreased levels of maternal engagement in cognitive stimulation (Goodman et al., 2020; Goodman 2020), yet we do not know the role GxE may play in the association between maternal depression and children's cognitive outcomes. Understanding the role of GxE in this association can help strengthen our understanding of the contexts within which interventions can have a significant impact on the cognitive outcomes of children exposed to maternal depression (Jaffee & Price 2007; Khoury et al., 2011; Price & Jaffee 2008).

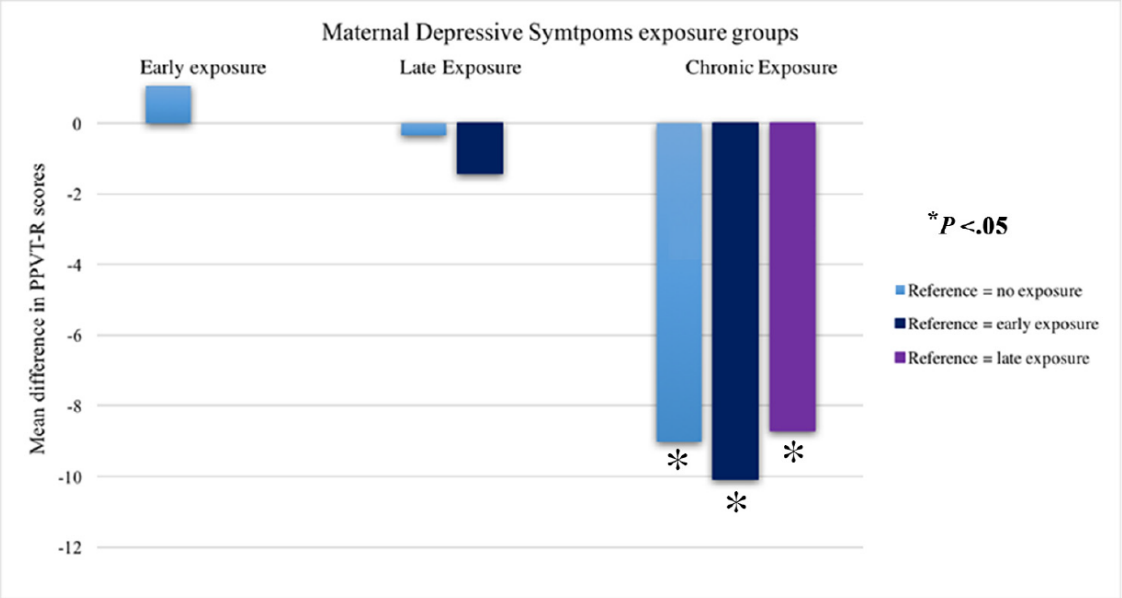
#### 2.3.1.2. Proposed moderators of the association between maternal depression and children's cognitive development

***Timing and course of maternal depression***

The *Developmental Model for Understanding Mechanisms of Transmission* (Goodman & Gotlib, 1999) posits that the timing and course of maternal depression can moderate its association with children's cognitive outcomes. A growing number of studies have investigated this association, examining whether exposure during a specific period of development (e.g., antenatal, early postnatal [~birth to 3 years], late postnatal [~3-5 years]) has a greater impact on later development, or whether it is the chronicity of exposure over a significant period of time that has a more detrimental impact on children's cognitive outcomes (Ahun et al., 2017; Brennan et al., 2000; Evans et al., 2012; Netsi et al., 2018; Sutter-Dallay et al., 2011). During my Master's, my colleagues and I used data from a population-based cohort in Québec to test this association. We found that children exposed to maternal depression in a sensitive period for the development of language skills (i.e., first 3 years of life; Zauche et al., 2017) had comparable verbal ability scores in middle childhood (6-10 years) compared to those exposed to maternal depression later in the

postnatal period (i.e., 3-5 years) (Ahun et al., 2017). However, children exposed chronically to maternal depression across the early childhood period (i.e., birth to 5 years) had significantly worse verbal ability scores compared to children exposed never, early, or late to maternal depression (see ***Figure 4***). These findings contribute to evidence that the timing and course of maternal depression does moderate its association with a variety of cognitive outcomes, with chronic exposure putting children at highest risk for poorer cognitive outcomes (Brennan et al., 2000; Evans et al., 2013; Netsi et al., 2018; Sutter-Dallay et al., 2011).

**Figure 4.** Mean difference in children's verbal abilities across maternal depression exposure groups (Ahun et al., 2017)




Mean differences obtained from multivariate model including all covariates (n = 1073). Covariates included in model: PPVT administration language, maternal anxiety, maternal antisocial behaviour (during her youth), maternal age at birth of target child, maternal verbal IQ, family socioeconomic status, mother-child interactions (verbalization, stimulation), and maternal native language.

Adapted from Ahun et al., 2017

### *Child's sex*

Goodman & Gotlib's (1999) model also postulates that the association between maternal depression and children's cognitive outcomes may not be the same in boys and girls. Understanding the extent to which this association differs in boys and girls is relevant for the implementation of interventions that aim to mitigate the negative effects of maternal depression on children's cognitive outcomes, as it may suggest different approaches for boys and girls (Goodman et al., 2020). From a theoretical perspective, biological and developmental factors can contribute to variations in how boys and girls react to maternal depression (Kraemer, 2000). For example, it is possible that male foetuses' increased vulnerability to antenatal maternal stress (including depression) and its neurodevelopmental consequences may put them at risk of experiencing poorer cognitive outcomes when exposed to (antenatal) maternal depression (Bale & Epperson, 2015; Dadi et al., 2020; DiPietro & Voegtline, 2017; O'Donnell & Meaney, 2017; Linsell et al., 2015; Sandman, Glynn, & Davis, 2013). Another factor possibly contributing to sex differences is the maturational advantage held by girls in cognitive skills (e.g., language, reading) in early childhood, which might protect from the negative impact of maternal depression on cognitive outcomes (Galsworthy, Dionne, Dale, & Plomin, 2000; Grace et al., 2003; Logan & Johnston, 2010; Sohr-Preston & Scaramella, 2006). Overall, theory suggests that boys exposed to maternal depression are more likely to experience poorer cognitive outcomes compared to girls.

From an empirical perspective, systematic reviews of the association between maternal depression and children's cognitive development present mixed evidence of moderation by child's sex. Narrative reviews that have considered sex differences report that overall, boys exposed to maternal depression have lower scores on measures of cognitive outcomes than girls across childhood and adolescence (Ebeid, 2018; Grace et al., 2003; Sanger et al., 2015). However, some

of the studies included in these reviews reported no moderation by child's sex (e.g., Galler et al., 2004). Furthermore, studies published after these reviews continue to report mixed findings, with some studies reporting a stronger association in girls (e.g., Shen et al., 2016) and others finding no effect of moderation by child's sex (e.g., Ng-Knight et al., 2018). Although there have been two recent meta-analyses of the association between maternal depression and cognitive outcomes across childhood and adolescence (Liu et al., 2017; Rogers et al., 2020), neither have advanced our understanding of the moderating role of child's sex in this association.

### *Paternal characteristics*

The final moderator proposed in Goodman & Gotlib's (1999) model consists of paternal mental health and parenting behaviours. The authors propose that these paternal characteristics can either increase or decrease the risk for poor cognitive outcomes in children exposed to maternal depression. This proposition is encapsulated in two alternative hypotheses that reflect the importance of paternal engagement for healthy cognitive development and outline how maternal depression can influence fathers' engagement (Jeong, McCoy, Yousafzai, Salhi, & Fink, 2016; Rollè et al., 2019). The *spillover hypothesis* posits that maternal depression can negatively influence fathers' well-being (e.g., via the stress and burden that can be placed on romantic partnerships when one partner is depressed; Egmose, Tharner, Liebenberg, Steenhoff, & Væver, 2020; Najman et al., 2014; Thiel, Pittelkow, Wittchen, & Garthus-Niegel, 2020; Whisman, 2001) and thus lead to decreased paternal involvement with their child (Kouros, Papp, Goeke-Morey, & Cummings, 2014; Margolin, Christensen, & John, 1996; Nelson, O'Brien, Blankson, Calkins, & Keane, 2009). Conversely, the *compensatory/buffering hypothesis* posits that fathers may try to

compensate for – or buffer – depression in their partner by becoming more involved in caring and providing for their child (Belsky, 1984; Nelson et al., 2009).

There is empirical evidence for both hypotheses, with some studies finding that higher levels of maternal depression are associated with greater paternal involvement (i.e., *compensatory/buffering hypothesis*; Paulson, Dauber, & Leiferman, 2006; Sejourne, Vaslot, Beaumé, Goutaudier, & Chabrol, 2012) and others finding that higher levels of maternal depression are associated with lower paternal involvement (i.e., *spillover hypothesis*; Edhborg, Lundh, Seimyr, & Widström, 2003; Maselko et al., 2019; Vakrat, Apter-Levy, & Feldman, 2017). One study found evidence of both hypotheses: maternal depression was associated with greater paternal involvement in the first 6 months after birth but was associated with lower paternal involvement in the second half of the first year of life (Goodman, Lusby, Thompson, Newport, & Stowe, 2014). This suggests that fathers may be able to compensate for/buffer maternal depression up to a point and that paternal involvement is likely lower when maternal depression is chronic (Goodman et al., 2014; Maselko et al., 2019; Newkirk, 2018).

In the context of child outcomes, the majority of studies have focused on children's mental health, and there is mixed evidence that paternal characteristics moderate its association with maternal depression (Fredriksen, von Soest, Smith, & Moe, 2019; Lewis, Neary, Polek, Flouri, & Lewis, 2017, 2018; Mezulis, Hyde, & Clark, 2004; Pietikäinen et al., 2020; Wanless et al., 2008). Only two studies have examined the role of this moderator in the association with children's cognitive outcomes and neither of them reported a moderating effect of paternal characteristics (Fredriksen et al., 2019; Paulson, Keefe, & Leiferman, 2009). Although it is not the focus of the present dissertation, it should be noted that the associations of maternal characteristics with paternal characteristics are bidirectional, and that studies have found paternal depression to be

independently associated with cognitive outcomes in the offspring (Barker, Iles, & Ramchandani, 2017; Fredriksen et al., 2019; Paulson et al., 2009; Ramchandani & Psychogiou, 2009; Wanless et al., 2008).

### 2.4. Limitations of extant studies and objectives of present dissertation

This literature review provides a summary of what we know and what we do not know about children's cognitive development, maternal depression, and the mechanisms of the association between the two. We know that early childhood is a sensitive period for cognitive development and that exposure to maternal depression during this period has been associated with poor social, economic, and health outcomes across the lifespan (Bauer et al., 2014, 2015, 2016; Black et al., 2017; Council for Early Child Development 2010; Luca et al., 2020; Simas et al., 2019; Stein et al., 2014). Moreover, in the two decades since the publication of Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission*, we have learned that negative maternal cognitions, behaviours, and affect mediate the association between maternal depression and children's cognitive outcomes and that this association is moderated by the timing and course of maternal depression (Ahun et al., 2017; Goodman et al., 2020; Netsi et al., 2018). However, there still remain important gaps in our understanding of the mechanisms of this association. Some of these gaps are addressed in the present dissertation.

First, although some studies have explored maternal cognitions, behaviours, and affect, stressful family environments, and innate dysfunctional neuroregulatory mechanisms as potential mediators of the association between maternal depression and children's cognitive outcomes, no study has provided a review of this literature. I address this gap in the first objective of my dissertation, which is to summarize existing evidence on the mediators of the association between

maternal depression and children's cognitive development (*Article 1*). This is necessary as reviews provide clear and succinct summaries of available knowledge and are useful tools for the development of evidence-based recommendations for practice and interventions to promote health (Khoury, Gwinn, & Ioannidis, 2010).

Second, few studies have gone beyond the proposed model to examine how factors in the different settings children inhabit influence this association. It is important to explore this because population health is the result of a complex interplay between individuals and their environment, and we know that factors within the home and school microsystems influence cognitive development across the lifespan (Bronfenbrenner, 1979; Stronks & Nicolaou, 2018). I address this gap in my second objective by testing the mediating role of school experiences in the association between maternal depression and academic performance in a longitudinal population-based cohort (*Article 2*). This objective also extends Goodman & Gotlib's (1999) model by not only exploring the moderating role of child's sex in the direct effect of maternal depression on children's cognitive outcomes, but also testing whether sex moderates the mediation pathways.

Third, we do not know the role of gene-environment mechanisms in the association between maternal depression and children's cognitive development. Understanding how genetic and environmental factors interact to influence the association between maternal depression and children's cognitive outcomes can shed light on the contexts within which interventions aiming to modify environmental risk factors can be more effective. To this end, I address this gap by providing the first examination of the role of GxE in the association between maternal depression and children's cognitive school readiness in a population-based cohort of twin pairs (*Article 3*).

Fourth and lastly, we do not know whether the association between maternal depression and cognitive outcomes differs in boys versus girls. This gap is addressed in my final objective

which is to review and meta-analyze sex-specific estimates of the association between maternal depression and cognitive outcomes across childhood and adolescence (*Article 4*).

# Chapter 3. Methodology

This chapter is organized into four parts: (1) an outline of the objectives corresponding to the four research papers forming the main body of this dissertation; (2) descriptions of the study designs of the Québec Longitudinal Study of Child Development (*Article 2*) and the Québec Newborn Twin Study (*Article 3*); (3) a detailed description of the exposure, outcome, mediator, and confounder variables for *Articles 2* and *3*; and (4) a description of our analytical strategy, including the statistical analyses (*Articles 2, 3,* and *4*) and search strategies (*Articles 1* and *4*) employed in each of the research papers.

### 3.1 Objectives of the present dissertation

The overall aim of this dissertation is to use longitudinal population-based data and qualitative and quantitative review methods to examine mediating and moderating factors of the association between maternal depression and children's cognitive development across childhood and adolescence. Specific objectives and their corresponding hypotheses are specified below:

*Article 1 – Maternal depressive symptoms and early childhood cognitive development: A review of putative environmental mediators*

Objective – to summarize existing evidence on the mediators of the association between maternal depression and children's cognitive development in early childhood (0-5 years).

Hypothesis – using Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission* as a framework, we hypothesized that negative maternal cognitions, behaviours, and affect; a stressful family environment; and innate dysfunctional neuroregulatory mechanisms would mediate the association between maternal depression and children's cognitive development in early childhood.

*Article 2 – Maternal depressive symptoms and children's academic performance: Sex differences in the mediating role of school experiences*

Objective – to build on previous literature by examining the mediating role of school experiences (i.e., peer victimization and school engagement) in middle childhood (6-10 years) in the association between exposure to maternal depression in early childhood (0-5 years) and academic performance in adolescence (12 years) in a population-based cohort, and to determine whether these associations differ by child's sex.

Hypothesis – based on prior literature, we hypothesized that exposure to maternal depression in early childhood would be negatively associated with school engagement and positively associated with peer victimization in middle childhood. In turn, school engagement would be positively associated with adolescent academic performance whereas peer victimization would be negatively associated with performance. Due to the mixed literature on the presence of sex differences in these associations, we did not formulate an a priori hypothesis regarding sex differences.

*Article 3 – Maternal depressive symptoms and children's cognitive school readiness: The role of gene-environment mechanisms*

Objective – to examine the role of GxE in the association between maternal depression (6-18 months) and children's cognitive school readiness (5 years) in a population-based cohort of twins

Hypothesis – using the *Bioecological Model of Development* as a framework (Bronfenbrenner & Ceci, 1994), we hypothesized that the genetic contribution to children's cognitive school readiness would decrease – and thus environmental contributions would increase – as the level of maternal depression increased (i.e., there would be GxE).

*Article 4 – Sex differences in the association between maternal depression and child and adolescent cognitive development: A systematic review and meta-analysis*

Objectives – to (1) summarize the literature on longitudinal associations between maternal depression and cognitive development across childhood and adolescence (0-18 years) in boys and girls; (2) conduct a meta-analysis of the sex-specific estimates of this association; and (3) examine whether the sex-specific associations vary as a function of (a) time of exposure to maternal depression (pregnancy versus after birth), (b) method of measuring maternal depression (rating scale versus diagnostic interview), (c) child's age at cognitive outcome assessment (childhood [0-10 years] versus adolescence [11-18 years]), and (d) length of time between assessments of maternal depression and cognitive outcome (short [≤1 year] versus long [>1 year]).

Hypothesis – due to the mixed literature on the presence of sex differences in these associations, we did not formulate an a priori hypothesis regarding sex differences.

## 3.2 Description of cohorts

### 3.2.1 The Québec Longitudinal Study of Child Development (*Article 2*)

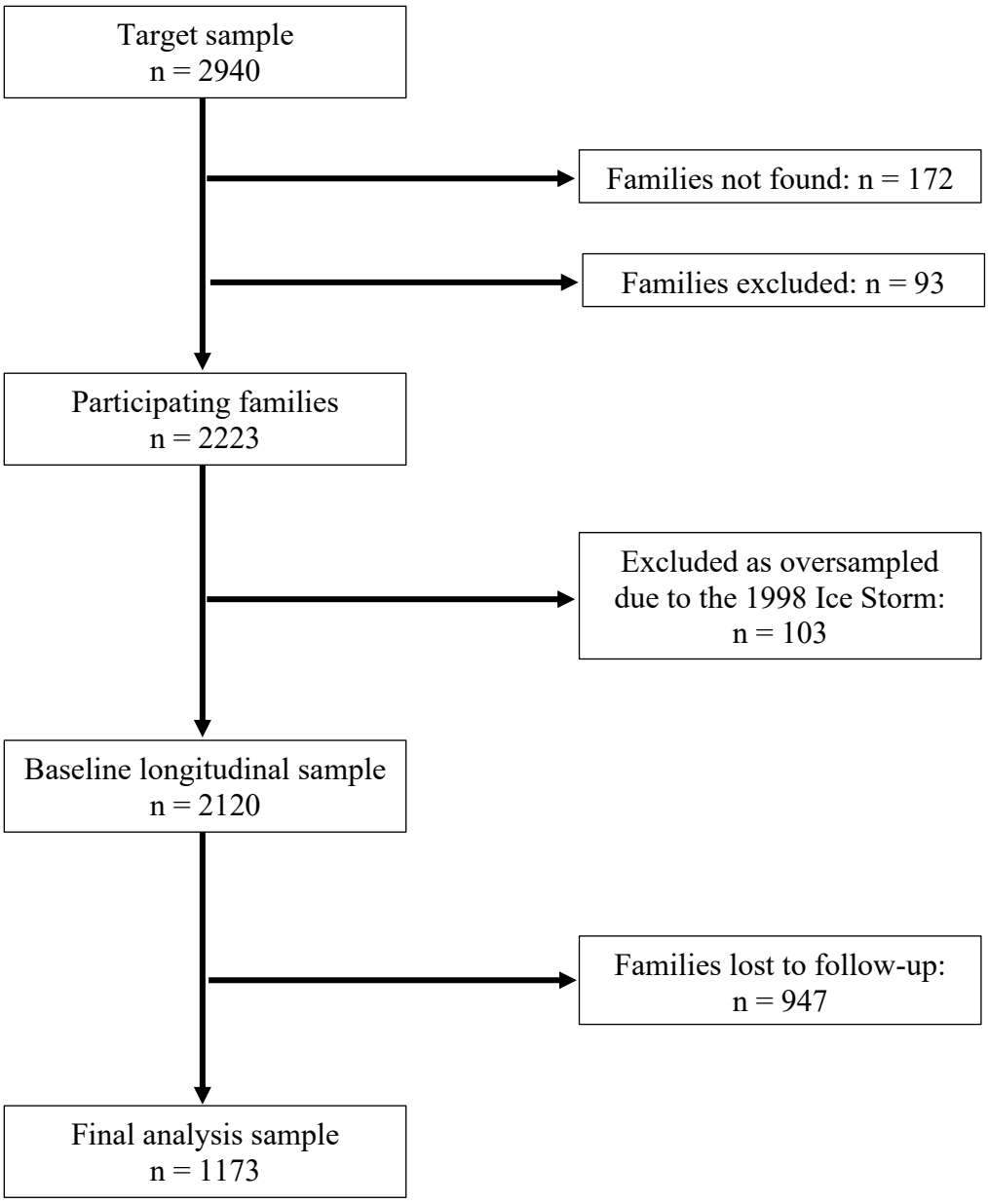
The Québec Longitudinal Study of Child Development (QLSCD) is an ongoing population-based longitudinal study of children born in 1997-1998 and followed-up prospectively between the ages of 5 months and 21 years (Orri et al., 2020). The last completed data collection of the children was in 2020. The main objective of the QLSCD is to study the long-term associations of preschool physical, cognitive, social, and emotional development with long-term academic performance and biopsychosocial development (Orri et al., 2020). The QLSCD protocol was approved by the *Insitut de la Statistique du Québec* (Québec Institute of Statistics) and the Sainte-Justine Hospital Research Center ethics committees (see Appendix I). The QLSCD follows

strict ethical guidelines, in that all matters relating to confidentiality and informed consent are observed. Written informed consent was obtained from all respondents and data were coded for confidentiality at each assessment.

The QLSCD target population included singleton infants who were born between October 1997 and July 1998 to mothers residing in each geographic area of the Canadian province of Québec. Infants born in Northern Québec, Cree Territory, Inuit Territory, and Aboriginal reserves (2.2% of all Québec births), as well as those whose mothers spoke neither English nor French, those whose gestational age was unknown, and those born before 24 weeks (1.3% of all Québec births) were excluded from the study (Orri et al., 2020). The Québec Master Birth Registry of the *Ministère de la Santé et des Services Sociaux* (Ministry of Health and Social Services) was used to select a representative sample of 2940 families. From this sample, 2223 families were available to participate in the first data collection when children were on average 5 months old (75.6% response rate). This included an over-represented sub-sample of 103 families from the Montérégie region to cross-sectionally investigate the impact of the highly disruptive ice storm in January 1998 on infant outcomes (Orri et al., 2020). Only the remaining 2120 families participated in subsequent data collections (response rate of 72.1%) and constituted the final longitudinal sample. Data were collected annually during the first 8 years of life, after which the interview schedule shifted to a biennial design. Assessments were conducted by trained research assistants through home interviews directed to the person most knowledgeable about the child (mothers in the majority of cases; Orri et al., 2020) and direct evaluations of children. The QLSCD also incorporates data obtained from multiple informants including fathers, teachers, target children, and government-level academic performance data. All assessments were conducted in either English or French.

*Article 2* of the present dissertation draws on QLSCD data collected between 1997-1998 and 2010 (birth to ~12 years). We used data from ten assessment points when children were aged (on average) 5 months, 1½, 3½, 4½, 5, 6, 7, 8, 10, and 12 years. When participants were 12 years old, 1173 families from the baseline sample remained in the study (i.e., 55% retention rate). Although this attrition compromises the initial representativeness of the sample, it is comparable with that of other longitudinal studies such as the Avon Longitudinal Study of Parents and Children (ALSPAC; Fraser et al., 2013). Furthermore, as described in section 3.4, inverse probability weights were used to minimize the impact of attrition on analyses. The majority of QLSCD participants were White (84%). The remaining 16% were of African (1%), Native American (3%), and other (12%; including Asian, Arab, Latinx, and bi/multi-ethnic) ethnic origins. See ***Figure 5*** for a flow diagram of the QLSCD sample used in *Article 2*.

**Figure 5.** Flow diagram of the Québec Longitudinal Study of Child Development sample




Adapted from Orri et al., 2020

### 3.2.2 The Québec Newborn Twin Study (*Article 3*)

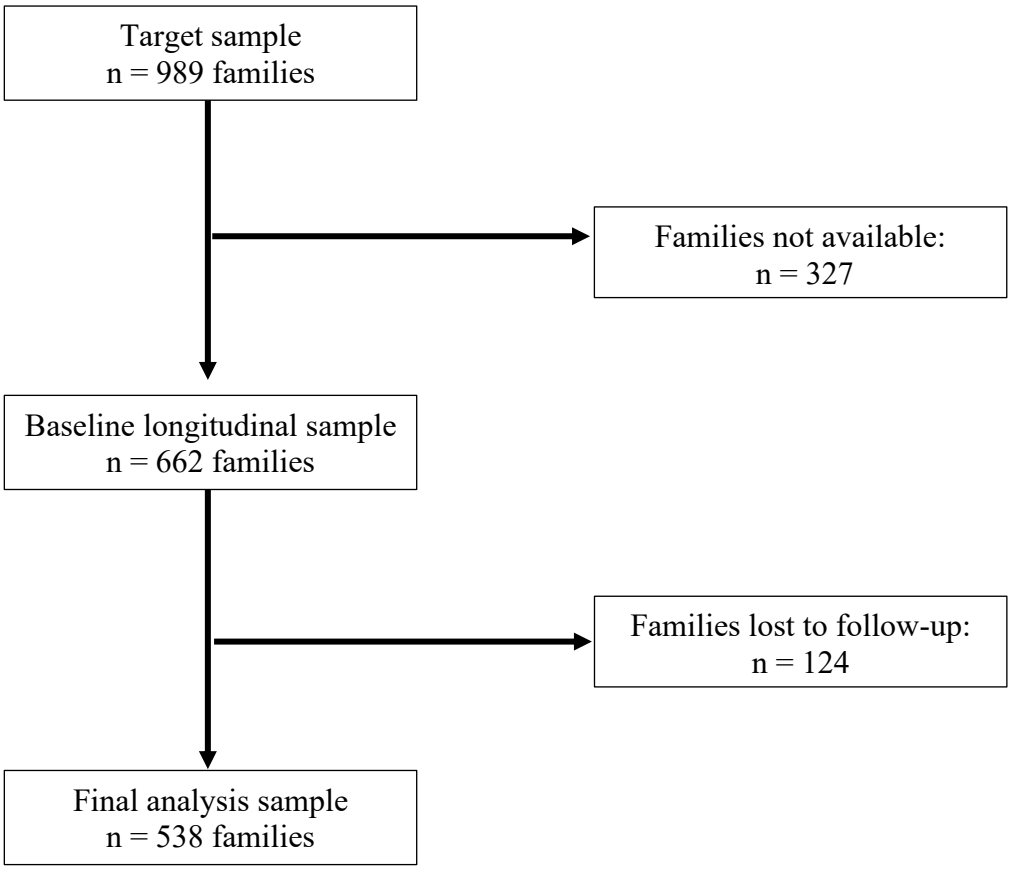
The Québec Newborn Twin Study (QNTS) is an ongoing population-based longitudinal study of twin pairs born between 1995 and 1998 and followed-up prospectively between the ages of 6 months and ~23 years (Boivin et al., 2013, 2019). The last completed data collection of the sample was in 2019. The main objective of the QNTS is to document individual differences in cognitive, behavioural, and socioemotional development across childhood, their early bio-social determinants, and their putative role in later socioemotional adjustment, school, and health outcomes (Boivin et al., 2013). The QNTS protocol was approved by the *Université Laval* (Laval University) and the Sainte-Justine Hospital Research Center ethics committees (see Appendix I). The QNTS follows strict ethical guidelines, in that all matters relating to confidentiality and informed consent are observed. Written informed consent from was obtained from all respondents and data were coded for confidentiality at each assessment.

The QNTS target population included MZ and DZ twin pairs who were born between April 1995 and December 1998 to mothers residing in seven administrative social health districts comprising and surrounding the Greater Montréal area. No other inclusion criteria were specified. The Québec Bureau of Statistics registry was used to recruit a sample of 989 families. From this sample, 662 families were available to participate in the first data collection when twins were on average 6 months old (66.9% response rate). Zygosity was initially assessed via questionnaire (Hill Goldsmith, 1991) and ascertained with a 96% correspondence through genotyping (Forget-Dubois et al., 2003). Data were collected annually during the first 6 years of life, and quasi-annually thereafter. Assessments were conducted by trained research assistants through home interviews directed to the person most knowledgeable about the twins (mothers in the majority of cases; Boivin et al., 2013) and direct evaluations of twins. The QNTS also incorporates data obtained

from multiple informants including fathers, teachers, peers, and target twins. All assessments were conducted in either English or French.

*Article 3* of the present dissertation draws on QNTS data collected between 1995-1998 and 2003 (0 to ~5 years). We used data from three assessment points when twins were aged (on average) 6 months, 1½, and 5 years. When twins were 5 years old, 538 families from the baseline sample remained in the study (i.e., 81.3% retention rate), suggesting a low rate of attrition (National Heart Lung and Blood Institute: National Institutes of Health, 2014). The majority of twins were White (89%). The remaining 11% were of African (2%), Asian (3%), Native American (0.2%), and other (5.8%; including Arab, Latinx, and bi/multi-ethnic) ethnic origins. See ***Figure 6*** for a flow diagram of the QNTS sample used in *Article 3*.

**Figure 6.** Flow diagram of the Québec Newborn Twin Study sample



### 3.3 Description of variables

The items used to assess the exposure (maternal depression) and mediator (school engagement, peer victimization, mother-child interactions) variables are in Appendix II. I could not include the items of the cognitive outcome measures due to copyright reasons. The QLSCD and the QNTS were designed by the same group of researchers and there is therefore an overlap in some of the measurement tools used.

#### 3.3.1 Primary outcomes

##### *3.3.1.1 Article 2* – Academic performance

The primary outcome for *Article 2* was the QLSCD participants' academic performance at the end of primary school (corresponds to age 12 in Québec). In Québec, every student must write exams administered by the *Ministère de l'Éducation et de l'Enseigment Supérieur* (Ministry of Higher Education and Teaching) to be admissible to high school. With parents' informed consent, we linked the QLSCD participants to their performance on the mathematics, reading, and writing exams. The following evaluation criteria and weights were used to assess competencies and score each subject: (1) mathematics – task comprehension, mobilizing concepts and processes, and solution explanation (30% of grade) and analyzing and making informed choices, applying solution, and justifying (70% of grade); (2) reading – extraction of pertinent explicit and implicit information (75% of grade), text interpretation (8% of grade), and pertinent reactions to literary and informational texts (17% of grade); and (3) writing – relevance and adequacy of ideas, appropriate organization of the text, syntax and punctuation, vocabulary, and spelling (100% of grade). The grades for each exam were scored as a percentage, with possible ranges of 22-100%

for mathematics, 6-100% for reading, and 32-100% for writing. Continuous scores from each exam were examined as separate outcomes.

#### *3.3.1.2 Article 3* – Cognitive school readiness

The primary outcome for *Article 3* was cognitive school readiness as assessed by the Lollipop Test when the QNTS participants were 5 years old. Cognitive school readiness involves the cognitive and language skills that reflect a child's ability to function successfully in school contexts (La Paro & Pianta 2000). The Lollipop test is a well-validated multidimensional diagnostic measure of cognitive school readiness consisting of four subtests: identification of colours and shapes and copying shapes; picture description, position, and spatial recognition; identification of numbers and counting; and identification of letters and writing (Chew, 1989). Trained research assistants administered the subtests to each twin separately during home visits when they were 5 years old, on average. We created a total score – with a theoretical range of 0-69 – by summing up the four subtests for each twin (Cronbach's α [across twins] = 0.73) and used this score in analyses.

### 3.3.2 Exposure variable: Maternal depression

In both the QLSCD (*Article 2*) and the QNTS (*Article 3*), sub-clinical levels of maternal depression, as assessed with the short (12-item) version of the CES-D (Radloff 1977), were used as the exposure variable. The short CES-D is a reliable and psychometrically sound measure of sub-clinical levels of depression, assessing the occurrence and severity of depressive symptoms in the past 7 days (Poulin, Hand, & Boudreau, 2005). For both *Articles 2* and *3*, the CES-D was used dimensionally, with mothers reporting the frequency of each symptom as "none, some, or a little

of the time [1-2 days]"; "occasionally or a moderate amount of time [3-4 days]"; and "most or all of the time [5-7 days]". Items included symptoms such as "I felt that I could not shake off the blues even with help from my family or friends", "I felt that everything I did was an effort", and "I felt depressed". Total scores were scaled to a range from 0 to 10 in the QLSCD and 12 to 48 in the QNTS, with higher scores in both samples indicating more elevated levels of depression. Note that the association between maternal depression and children's cognitive outcomes has already been established in the QLSCD (Abitan, 2008; Ahun et al., 2017).

#### *3.3.2.1 Article 2* – Maternal depression from 5 months to 5 years

In *Article 2*, we created a mean score of maternal depression by averaging maternal self-reported depression scores at child age's 5 months ($\alpha = 0.81$), 1½ ($\alpha = 0.82$), 3½ ($\alpha = 0.81$), and 5 ($\alpha = 0.82$) years. The correlation between the scores at each age ranged from Pearson's $r = 0.35$ to 0.44 ($p<0.001$). When we applied the conventional cut-off from the original CES-D (16/60, which is equivalent to 2.67/10 in these data; Weissman, Sholomskas, Pottenger, Prusoff, & Locke, 1977) to the mean score, we found that 11.5% of mothers in the analysis sample (n = 1173) had elevated levels of depression. This is comparable to the prevalence of maternal depression in high-income countries (8-13%; Howard et al., 2014; Lanes, Kuk, & Tamim, 2011).

#### *3.3.2.2 Article 3* – Maternal depression from 6 months to 1½ years

A mean score of maternal depression was also used as the exposure variable in *Article 3*. We created this score by averaging maternal self-reported depression scores when twins were 6 months ($\alpha = 0.82$) and 1½ years ($\alpha = 0.82$) old. The correlation between these two scores was $r = 0.48$ ($p<0.001$). When we applied the conventional cut-off from the original CES-D (12.8/48 in

these data) to the mean score, we found that 18.1% of mothers in the analysis sample (n = 538 twin pairs) had elevated levels of depression.

### 3.3.3 Potential mediators

#### *3.3.3.1 Article 2* – Peer victimization and school engagement

We used peer victimization and school engagement – two core aspects of the school setting (Ladd, Ettekal, & Kochenderfer-Ladd, 2017) – to examine the mediating role of children's school experiences in the association between maternal depression and academic performance.

In the QLSCD, peer victimization was assessed using items from an adapted version of the self-report victimization scale (Ladd & Kochenderfer-Ladd, 2002). Data were collected from parents (when children were 6 years), teachers (6, 7, 8, and 10 years), and children themselves (6, 7, 8, and 10 years). Each respondent rated how often (never, sometimes, often) children were "hit or pushed", "laughed at", and "called names or had mean things said to them" by other children in the past 12 months. Items from all respondents at all ages of assessment were used to create a latent score using the correlated traits-correlated (methods-minus-one) approach (Papa, Litson, Lockhart, Chassin, & Geiser, 2015). This approach allows for a more comprehensive and effective use of multi-informant data which provide important, non-overlapping information on peer victimization and are better predictors of academic performance than single-informant reports (Ladd & Kochenderfer-Ladd, 2002; Nakomoto & Schwartz 2010). The model used to estimate the latent peer victimization variable showed a good fit to the data (Root Mean Square Error of Approximation [RMSEA] = 0.02 [values < 0.06 indicate good fit]; Comparative Fit Index [CFI] = 0.99 [values > 0.95 indicate good fit]). Participants with higher scores were victimized by peers on a more frequent basis. Note that participants in this sample attended co-educational day schools.

All three dimensions of school engagement (cognitive, behavioural, emotional) were repeatedly assessed from ages 6 to 10 years in the QLSCD. Cognitive engagement was assessed using items from the Early Development Instrument (EDI), a well-validated measure of children's school engagement (Janus & Offord, 2007). When children were 6, 7, 8, and 10 years old, their teachers reported the frequency of cognitive engagement (never, rarely, sometimes, often, always) in the past 12 months: "is curious about the world", "is willing to play a new game", "challenges the teacher in a positive way", "is capable of resolving problems" ($\alpha = 0.85$-$0.86$). Teacher ratings of cognitive engagement were strongly correlated with each other over time ($r = 0.49$-$0.57$, $p<0.001$). We created a cognitive engagement score scaled 0 to 10 by averaging across all time points. Higher scores indicate more frequent cognitive engagement behaviours. Behavioural engagement was also reported by teachers when children were 6-, 7-, and 8-years using age-appropriate items from the EDI (Janus & Offord 2007). Teachers reported how often (never, rarely, sometimes, often, always) students displayed the following behaviours in the past 12 months: "listens attentively", "follows instructions", "is capable of resolving daily problems on their own", "works autonomously" ($\alpha = 0.84$-$0.85$). We created a mean behavioural engagement score scaled 0 to 10 by averaging across all time points ($r = 0.50$-$0.67$, $p<0.001$). Higher scores indicate more frequent behavioural engagement behaviours. Finally, emotional engagement was self-reported by children when they were 6-, 7-, and 8-years using items to assess their feelings toward the school environment (Hill & Werner, 2006). Children reported the extent to which they agreed (strongly disagree, disagree, uncertain, agree, strongly agree) with the following statements based on their experiences in the past 12 months: "I am happy to be studying at this school", "I am proud to be studying at this school", "I like my school", "Most mornings, I feel like going to school", "I feel safe at my school" ($\alpha = 0.60$-$0.61$). A mean emotional engagement score was created by averaging

across all time points ($r$ = 0.27-0.39, $p$<0.001). High scores indicate greater levels of emotional engagement.

### 3.3.4 Confounders

#### *3.3.4.1 Article 2*

Using the existing literature as a guide, we searched for variables that could confound (i.e., explain away) the associations between our exposure, mediator, and outcome variables (Augustine, 2010; Claessens, Engel, & Curran, 2015). We followed epidemiological guidelines for modelling longitudinal data in this process, selecting variables that were (1) correlated with maternal depression and any of the mediators or outcomes and (2) assessed as close to baseline as possible, to avoid selecting variables that might potentially fall on the mediation pathway between maternal depression and the mediators or maternal depression and the outcomes (Greenland & Morgenstern, 2001; Pearce & Greenland, 2005). This process enabled us to understand the association between maternal depression and children's cognitive outcomes over and above the influence of other risk factors for poor cognitive outcomes (e.g., low socioeconomic status).

The following variables in the QLSCD were included as confounders. Unless otherwise specified, all variables were assessed at baseline (i.e., child's age 5 months). Maternal verbal IQ was assessed by trained research assistants using the Peabody Picture Vocabulary Test (Dunn & Dunn, 1981) when children were 5 years old. Given the stability in verbal IQ over time, it is unlikely that this changed significantly between children's ages 5 months and 5 years (Deary, 2014). Maternal age at child's birth was used as a dichotomous confounder (≤21 years versus >21 years) because becoming a mother before 21 years has been previously shown to be a risk factor for poor child outcomes in the Québec population (Tremblay et al., 2004). Generalized trait-

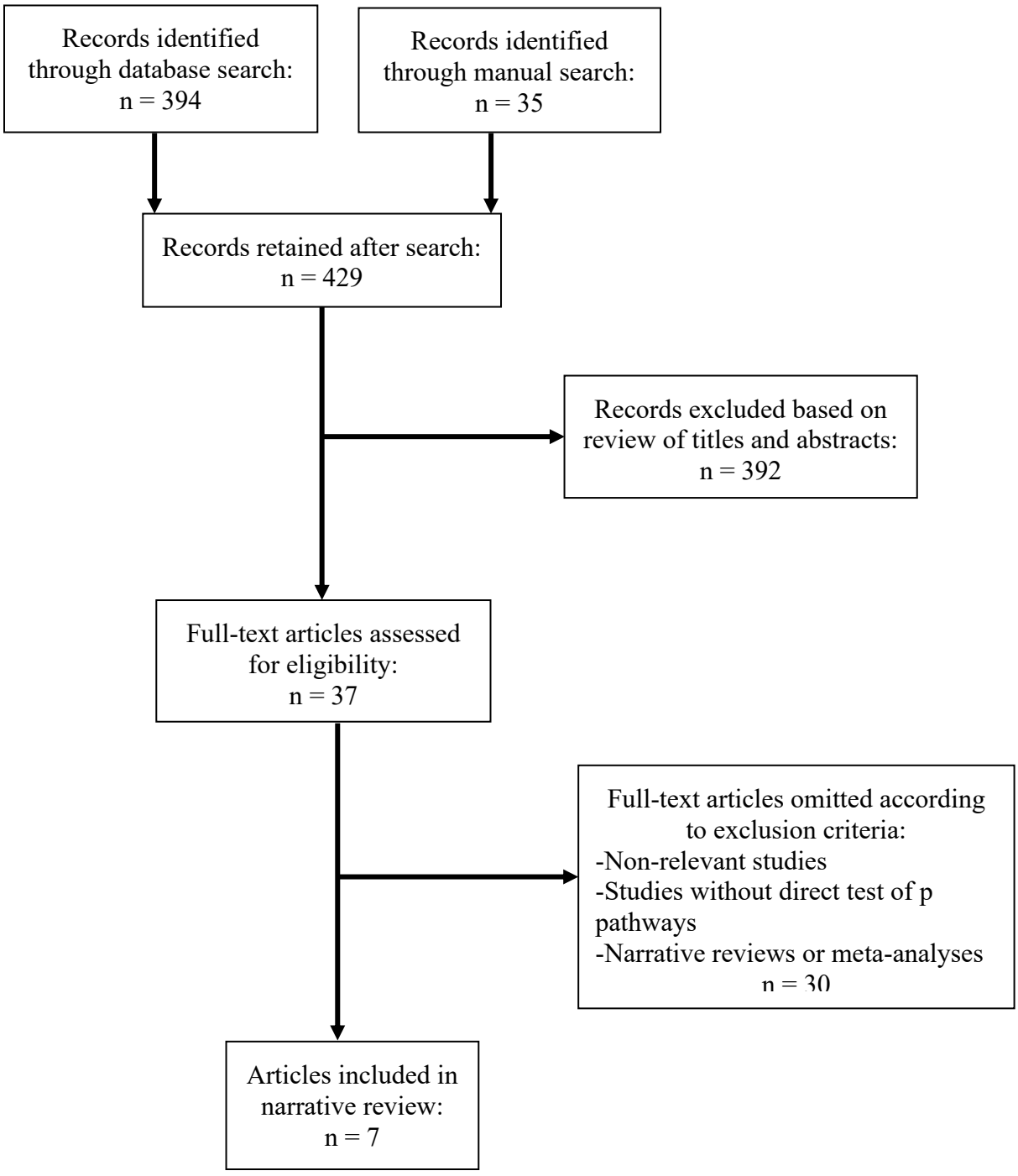
anxiety symptoms in mothers was self-reported using a 10-item screening tool (based on criteria from the 4th edition of the DSM; Shapiro, Seguin, Muckle, Monnier, & Fraser, 2017) for parental anxiety in large-scale longitudinal studies when children were 4½ years. Antisocial behaviour in mothers during their youth was assessed with a 5-item screening tool of conduct problems based on 4th edition DSM criteria (Zoccolillo, Paquette, & Tremblay, 2005). Trained research assistants conducted in-home observations and ratings of mother-child interactions (stimulation and verbalization dimensions) using the HOME (Caldwell & Bradley 1985). The person most knowledgeable about the child (mothers in 95% of cases in the QLSCD; Orri et al., 2020) reported the status of the family (single-parent versus two-parent), the family's socioeconomic status (derived from maternal and paternal education and occupational status and household income), and levels of family dysfunction as assessed by the Family Dysfunction Scale (Byles, Byrne, Boyle, & Offord, 1988). Mothers reported their children's behavioural and depressive and anxiety symptoms when children were 1½ years old using validated items from the Child Behaviour Checklist (Achenbach & Edelbrock, 1991). To account for children's baseline cognitive development, we used scores from the Lollipop test (Chew 1989) which was administered by trained research assistants when children were 5 years old. To account for baseline peer victimization, we included mother- and father-reported scores of peer victimization when children were 3½, 4½, and 5 years old. Data on baseline school engagement was not available and we could therefore not include it as a cofounder.

## 3.4 Analytical strategy

### 3.4.1 *Article 1* – Narrative review search strategy

To identify studies examining mediators of the association between maternal depression and children's cognitive development, electronic searches were carried out in two relevant databases – PubMed and PsycNet – from their inception through to March 2018. The following broad search terms were used to capture as many relevant articles as possible: "maternal depressive symptoms" (or "maternal depression") AND "cognitive development". In both databases I searched for articles that had these search terms in their titles and/or abstracts. The references of articles were also manually searched to identify additional articles. I retrieved 88 articles from PubMed, 306 from PsycNet, and 35 from manual searches. An article was considered eligible for inclusion if it (i) quantitatively assessed associations between maternal depression and children's cognitive development; (ii) assessed maternal depression in the postnatal period; (iii) was published in a peer-reviewed journal; (iv) included putative mediator variables involved in the association between maternal depression and children's cognitive development; and (v) was written in either English or French. No other restrictions were applied. My co-author and I screened the title and abstracts of all 429 articles identified in the electronic and manual searchers using these criteria. After this stage, 37 articles were retained and read in full by my co-author and I. Seven articles met the inclusion criteria and were retained for the review (***Figure 7***). *Article 1* was a qualitative review of the literature; therefore, no statistical analyses were conducted.

**Figure 7.** Flow diagram of study selection procedure in *Article 1*




Adapted from Ahun & Côté 2019

### 3.4.2 *Article 2* – Structural Equation Modelling (mediation)

I used Structural Equation Modelling (SEM) to examine the mediating role of peer victimization and school engagement in the association between maternal depression and academic performance. SEM is a robust statistical method that allows for the simultaneous testing of multiple pathways through which a given exposure may influence an outcome. This method is a preferred alternative to other mediation methods such as Baron and Kenny's (1986) 3-step approach because it allows for direct estimation of the indirect (mediation) effect in a single analysis and provides greater statistical power to estimate direct and indirect effects (Hayes, 2017). Furthermore, longitudinal mediation analyses provide necessary – albeit insufficient – evidence of causation (Tryon, 2018). In *Article 2*, I used SEM to estimate the direct and indirect (i.e., via peer victimization and school engagement) association between maternal depression and academic performance (i.e., mathematics, reading, and writing exam scores). I adjusted for confounder variables in the association between maternal depression and each potential mediator, between maternal depression and each outcome, and between each potential mediator and each outcome. Mediation was tested via the significance of the indirect effect from the exposure variable via the mediators to the outcomes (Holmbeck, 2002). The indirect effect is significant if the product of the coefficient of the pathway from the exposure to the mediators and the coefficient of the pathway from the mediators to the outcomes is significant (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002).

To test for the moderating role of sex in this association, I compared the fit of a freely estimated model (i.e., all estimated coefficients allowed to freely vary between sexes) with the fit of a model in which all estimated coefficients were constrained to be equal across sexes (Kline, 2015). I calculated the differences in fit between the freely estimated and constrained models by

hand using the Satorra-Bentler scaled chi-square (Muthén & Muthén). If the freely estimated model (which has more parameters) is a better fit to the data than the constrained model, this suggests that the associations between the exposure, mediator, and outcome variables are different in boys and girls and they should therefore be reported separately by sex. However, if the freely estimated model does not provide a better fit to the data than the constrained model, that suggests that the associations between the exposure, mediator, and outcome variables are not different in boys and girls.

Finally, to account for the loss of participants over time, I used inverse probability weighting – where weights represent the probability of being included in the analysis sample – in all analyses (Seaman & White, 2013). Traditionally, the simplest approach to dealing with missing data is to restrict analysis to complete cases. However, because participants with data at 12 years (n = 1173) were different from those lost to follow up (n = 947), restricting our analyses to those with data would bias our results. Differences between these two groups (n = 1173 vs n = 947) were that participants included in the analysis sample were less likely to be male, to come from a low socioeconomic status family, to live in a single-parent household, and to experience higher levels of family dysfunction compared to those excluded from analyses. The analysis sample also had higher scores on a test of cognitive school readiness, received higher levels of stimulation and verbalization in mother-child interactions, and had mothers with lower levels of depressive symptoms and higher levels of verbal IQ. I therefore created and applied weights to the analysis sample by first regressing a binary variable indicating whether or not participants were in the analysis sample onto each of these variables to obtain the probability of being included in the analysis sample. These probabilities were then transformed into weights by dividing 1 by each probability. Each participant in our analysis sample (n = 1173) therefore had a weight reflecting

their probability of being lost to follow up based on the afore-mentioned baseline characteristics. This process assigns larger weights to participants who are more similar to those lost to follow up, therefore reducing the extent to which attrition influences the results (Seaman & White 2013).

I used Mplus version 8.6 (Muthén & Muthén, 2019) to estimate the SEM using the robust maximum likelihood estimator. The R-Mediation package (Tofighi & MacKinnon, 2011) in R version 4.0.3 (R Core Team, 2019) was used to build unbiased confidence intervals for indirect effects because normal parametric tests would be biased due to the non-normal distribution of the indirect effect. Missing data in covariates were handled using the full information maximum likelihood. Descriptive statistics, correlations, and unadjusted regressions for this *Article* were obtained using SAS version 9.4 (SAS Institute Inc, 2013).

### 3.4.3 *Article 3 – Structural Equation Modelling (twin modelling)*

The analyses in *Article 3* were conducted in two steps.

First, I tested a full univariate ACE twin model to estimate genetic and environmental contributions to children's cognitive school readiness. As introduced in Chapter 2, this model is based on a comparison of the covariance between MZ and DZ twins for a given measure, knowing that MZ twins share 100% of their genes whereas, on average, DZ twins share 50%. The model partitions the variance of measures between additive genetic (A) and environmental (C and E) sources (Plomin, DeFries, & McClearn, 2008). The extent to which MZ twins are more similar than DZ twins on a given variable reflect additive genetic factors (A). The environmental variance is further decomposed to estimate the proportion of variance attributable to the shared environment (C), which includes all non-genetic factors that augment the similarity between twins regardless of zygosity, and to the unique environment (E), which includes all non-genetic factors that make

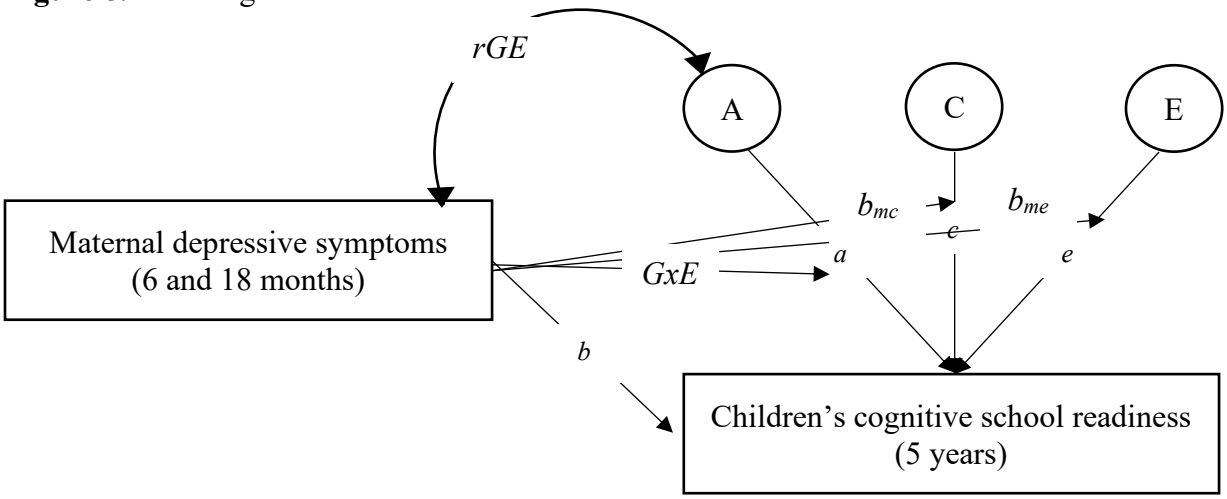
twins of a pair more different from each other (Turkheimer & Waldron, 2000). Measurement error is also encompassed in the unique environment factor (E). The model assumes that both MZ and DZ twins share 100% of the shared environment (C) and 0% of the unique environment (E).

Second, I used a non-additive twin model that estimated GxE and the residual direct contribution of our measured environmental variable (i.e., maternal depression) to our child outcome (i.e., cognitive school readiness). The strength of this model lies in its joint estimation of GxE and gene-environment correlation (i.e., the correlation between genetic and environmental factors), as classic twin models only estimate GxE. It is necessary to estimate both GxE and gene-environment correlation because if a potential environmental moderator such as maternal depression is correlated with the genetic factors associated with a trait such as children's cognitive school readiness (which means gene-environment correlation exists), GxE will be overestimated (Price & Jaffee, 2008). This overestimation occurs because the correlation between the environmental moderator and the genetic factors is wrongly interpreted by the classic twin model as stemming from GxE alone. Therefore, by also estimating the gene-environment correlation, the advanced model rightly partitions the variance in the association between maternal depression and children's cognitive school readiness into GxE and gene-environment correlation, as well as the remaining direct contribution of maternal depression to children's cognitive school readiness.

In this model, cognitive school readiness with beta coefficients *a*, *c*, and *e* load on the latent sources of variance A, C, and E, respectively. In addition to these parameters, the model estimates the moderation of genetic contributions to children's cognitive school readiness by maternal depression (GxE), the moderation of shared and nonshared environmental contributions to children's cognitive school readiness, the residual direct contribution of maternal depression to children's cognitive school readiness (*beta (b)*), and the correlation between maternal depression

and the genetic contributions to children's cognitive school readiness (rGE). In the output, *a* represents the genetic contributions to children's cognitive school readiness, *GxE* the moderation of this genetic contribution by maternal depression, $b_{mc}$ the moderation – by maternal depression – of shared environmental contribution to children's cognitive school readiness, $b_{me}$ the moderation of nonshared environmental contributions, *b* the residual direct contribution of maternal depression to children's cognitive school readiness, and *rGE* the correlation between maternal depression and the genetic contributions to children's cognitive school readiness (***Figure 8***).

**Figure 8.** Path diagram of advanced twin model




I conducted all analyses with SEM in Mplus 8.6 (Muthén & Muthén 2019). The full information maximum likelihood estimator permitted the use of all available data. I used the Mplus Automation package (Hallquist & Wiley, 2018) in R version 4.0.3 (R Core Team, 2019) to prepare the data and the R Mediation package (Tofighi & MacKinnon, 2011) to build unbiased confidence intervals for indirect effects using the distribution of the product method in the mediation model

(Hayes, 2017). Descriptive statistics and Pearson's correlations were obtained using the Statistical Package for the Social Sciences version 25 (IBM Corporation, 2017).

### 3.4.4 *Article 4* – Systematic review and meta-analysis

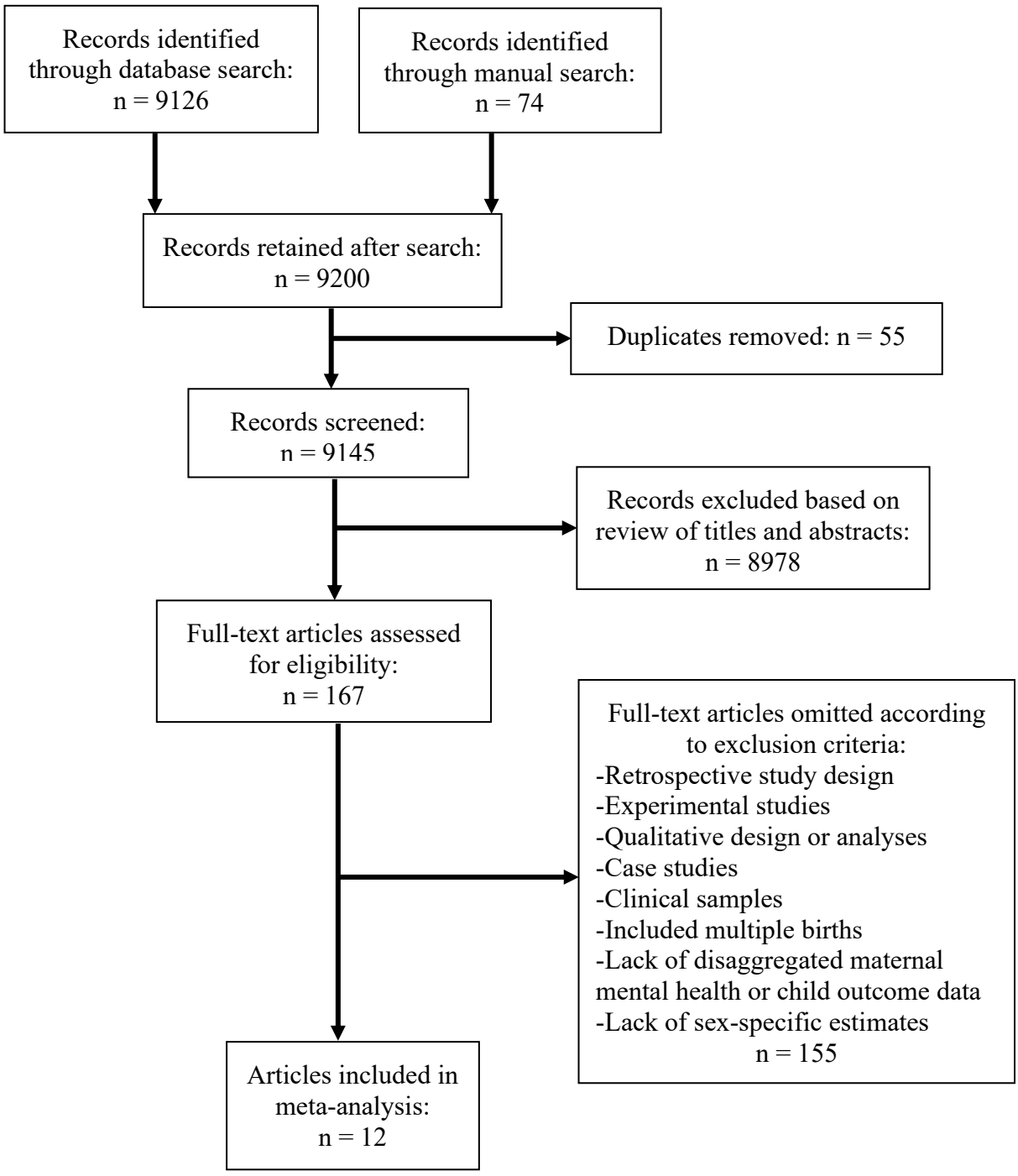
***Search strategy***

To identify studies examining sex differences in the association between maternal depression and cognitive outcomes across childhood and adolescence I carried out – with the help of a University librarian – electronic searches in seven databases from their inception through to January 2020: PubMed MEDLINE, Embase, ERIC, PsycINFO, CINAHL, Scopus, and ProQuest Dissertations and Theses Online. Search terms included the concepts of maternal depression "[(postnatal or postpartum or perinatal or peri-natal or antenatal or maternal or mother) AND (depression or depressive symptoms)] OR major depression OR minor depression" and cognitive development "child development OR cognition OR [cognitive or language or verbal or intelligence or academic or reading or writing or development or learning]". The search concepts were combined using the Boolean operator "and". Across databases I searched for articles that had these search terms in their titles, abstracts, and/or keywords. I conducted follow-up manual searches from the reference lists of systematic reviews, meta-analyses, and theses retrieved from the electronic search (Ebeid, 2018; Grace et al., 2003; Liu et al., 2017; Sanger et al., 2015).

I retrieved 9126 articles from electronic searchers and 74 from manual searches. After the removal of duplicates, I retained 9145 articles. An article was considered eligible for inclusion if it (i) provided sex-specific estimates of the quantitative association between maternal depression and child and adolescent cognitive outcomes in a longitudinal study; (ii) was published in a peer-reviewed journal in English or French; (iii) assessed cognitive outcomes in children and

adolescents 18 years old or younger; (iv) did not use data from a case study or randomized controlled trial (to avoid bias introduced by the potential impact of the trial on the association of interest); and (v) had a population-based sample of children and mothers in that context. If the study population was described as a specific subset of children/adolescents (e.g., born prematurely) or mothers (e.g., recruited because they had a medical condition or were taking medication, alcohol, or other drugs), the study was excluded. No other restrictions were applied. One of my co-authors and I screened the title and abstracts of all 9145 articles identified in the electronic and manual searchers using these inclusion criteria (Cohen's $\kappa = 0.76$). After this stage, 167 articles were retained. We read all articles in full and retained those meeting inclusion criteria for the review (n = 12) (***Figure 9***). Any disagreements between myself and the co-author reviewing the articles were resolved in team discussions with all other co-authors.

**Figure 9.** Flow diagram of study selection procedure in *Article 4*



Once all relevant articles were identified, a co-author and I independently abstracted core data from each article onto a standardized form. This data included, authors, year of publication, country where the study was conducted, study population, sample size, study design, exposure and outcome measures, age of the child/adolescent at exposure and outcome assessments, and sex-specific estimates. We also extracted the necessary information to assess risk of bias using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, which was designed to examine study quality according to Cochrane collaboration criteria (National Heart Lung and Blood Institute: National Institutes of Health, 2014). The tool includes items assessing the clarity of the research question and the study design (i.e., definition of sample, presentation of selection criteria, reporting of attrition), the use of valid exposure and outcome measures, and whether key potential confounding variables were included in analyses. Each item is scored as yes, no, or not reported.

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for standard reporting (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). The protocol for this review was preregistered on the PROSPERO international prospective register of systematic reviews (registration number CRD42020161001). The only deviation we made from this protocol was the addition of a new subgroup in the meta-regression analyses as specified below.

***Meta-analysis***

I performed a meta-analysis using the *metafor* version 2.0 and *robumeta* version 2.0 (Fisher, Tipton, & Zhipeng, 2017) packages in R version 4.0.3 (R Core Team, 2019). The *robumeta* package uses a robust variance meta-analysis approach that accounts for multiple effects from the

same sample (Hedges, Tipton, & Johnson, 2010). All studies reported offspring cognitive outcomes as continuous variables using a variety of measures. We used maternal depression as our exposure to capture studies using either a rating scale or a diagnostic interview to assess depression. If a study assessed depression at several time points, we used the mean of children/adolescents' age at those time points. When a study used more than one measure to assess depression or cognitive outcomes, we gave priority to the measure that was more commonly used (i.e., more frequently cited) in the literature. If a study used both a rating scale and a diagnostic interview to assess depression, the association with the diagnostic interview measure was used.

I converted sex-specific estimates of the association between maternal depression and child/adolescent cognitive outcomes to a common bias-corrected metric of *Hedges' g* (Borenstein, Hedges, Higgins, & Rothstein, 2011; Lüdecke, 2019), which represents the difference between two group means (cognitive scores for daughters and sons of mothers with high versus low/no depression or higher versus lower levels of depression) divided by the pooled standard deviation (Cohen, 1988; Hedges, 1981). This metric uses a weighted pooled standard deviation to provide an effect size estimate that is not biased by small samples. Where studies did not provide all the relevant data to convert sex-specific estimates into *Hedges' g*, I reached out to authors to provide said data. Out of seven authors contacted, three provided data. I examined the crude effect of maternal depression on child and adolescent cognitive outcomes using *Hedges' g* and used guidelines to interpret effect sizes that are meaningful, where 0.10 is small, 0.20 is medium, 0.30 is large, and greater than 0.40 is very large (Funder & Ozer, 2019). I used standard meta-analytical methods to estimate the summary effect sizes using the inverse variance approach and robust variance random-effects models.

Heterogeneity was assessed by calculating the $I^2$ index. I also conducted subgroup analyses by comparing sex-specific estimates across the following categorical variables: time of exposure to maternal depression (exposure during pregnancy versus after birth), method of measuring maternal depression (rating scale versus diagnostic interview), child age at cognitive outcome assessment (childhood [birth to 10 years] versus adolescence [11 to 18 years]), and length of time between assessments of exposure and outcome (short [≤1 year] versus long [>1 year]). All subgroups except the length of time between exposure and outcome were prespecified in the registered protocol. Meta-regressions were conducted to determine whether the sex-specific associations between maternal depression and offspring cognitive outcomes varied within these subgroups. Two-sided $p < .05$ indicated significance based on the regression of sex-specific meta-analytic estimates onto each of these subgroups. I ran sensitivity analyses to determine whether an outlier (Ng-Knight et al., 2018) affected reported estimates. Results were similar with and without this study, so the former are henceforth reported.

To assess publication bias, I regressed studies' effect estimates onto their standard errors using Egger's linear regression test and a funnel plot (Borenstein et al., 2011). A significant result of the test suggests that the plot is asymmetric, and bias is present, while a non-significant result suggests minimal bias.

# Chapter 4. Results

This chapter contains the four articles forming the main body of the present dissertation – three published and the fourth currently under review. The articles are presented in the following order:

**4.1 *Article 1* – Maternal depressive symptoms and early childhood cognitive development: A review of putative environmental mediators**

Ahun, M.N., and Côté, S.M. (2019). Maternal depressive symptoms and early childhood cognitive development: a review of putative environmental mediators. *Archives of Womens Mental Health, 22*, 15-14. DOI: https://doi.org/10.1007/s00737-018-0870-x

**4.2 *Article 2* – Maternal depressive symptoms and children's academic performance: Sex differences in the mediating role of school experiences**

Ahun, M.N., Psychogiou, L., Guay, F., Boivin, M., Tremblay, R.E., and Côté, S.M. (2020). Maternal depressive symptoms and children's academic performance: sex differences in the mediating role of school experiences. *Psychological Medicine*, 1-10. DOI: https://doi.org/10.1017/S0033291720004298

**4.3 *Article 3* – Maternal depressive symptoms and children's cognitive school readiness: The role of gene-environment mechanisms**

Ahun, M.N., Brendgen, M.R., Côté, S.M., Girard, A., Vitaro, F., Tremblay, R.E., Boivin, M., and Dionne, G. (*under review*) Maternal depressive symptoms and children's cognitive school readiness: The role of maternal gene-environment mechanisms.

**4.4 *Article 4* – Sex differences in the association between maternal depression and child and adolescent cognitive development: A systematic review and meta-analysis**

Ahun, M.N., Gapare, C., Gariépy, G., and Côté, S.M. (2021). Sex differences in the association between maternal depression and child and adolescent cognitive development: A systematic review and meta-analysis. *Psychological Medicine*. DOI: https://doi.org/10.1017/S0033291721001689

## 4.1 *Article 1*

**Maternal depressive symptoms and early childhood cognitive development: A review of putative environmental mediators***

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**Authors' contributions.** M.N. Ahun developed the study concept, conducted the literature review, and prepared the first draft of the manuscript under the supervision of S.M. Côté. S.M. Côté assisted in the literature review and provided critical feedback on drafts of the manuscript.

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****Note that this article was published before Goodman et al.'s (2020) systematic review of parenting as a mediator of the association between maternal depression and child development. Their review is therefore not referenced in this article.*

**Abstract**

Despite the abundance of research investigating the associations between maternal depressive symptoms (MDS) and children's cognitive development, little is known about the putative mechanisms of this association. The aim of this review was to summarize the literature on the proposed mediators (i.e., negative maternal cognitions, behaviours, and affect; a stressful family environment; innate dysfunctional neuroregulatory mechanisms) of the association between MDS and children's cognitive development. Studies were selected from online databases (PubMed, PsycNet) and manual searches. Only studies that quantitatively assessed associations between MDS and children's cognitive development and examined the role of mediator variables were included in the review. Seven studies, five longitudinal and two cross-sectional, were included. Six out of the seven studies identified mediating maternal responsiveness, parenting style, the quality of the home environment, and maternal caregiving practices as mediators of the association between MDS and children's cognitive development.

## Introduction

Maternal depressive symptoms (MDS) consist of the experience of sad mood or loss of pleasure accompanied by cognitive or somatic symptoms. These symptoms can occur during pregnancy and/or the early childhood years (American Psychiatric Association, 2013). MDS persist for longer periods of time (months-years) than postpartum blues (hours-days) but may not necessarily reach levels of severity that qualify for major depression (Robertson, Grace, Wallington, & Stewart, 2004). A wide range of prevalence estimates have been reported (Marcus, 2009; Walker et al., 2011), but most recent estimates of MDS in high-income countries suggest that approximately 10% of mothers are affected in the first few years after birth (Howard et al., 2014; Lanes, Kuk, & Tamim, 2011; Pearson, Janz, & Ali, 2013).

MDS are a public health concern, not only because of their high prevalence, but also because of their adverse consequences on maternal health and child development (Piteo, Yelland, & Makrides, 2012). Children's early life experiences (up to age 5 years) provide the foundation for future life success, and failure to cultivate cognitive skills during this period impedes their ability to learn at later ages (Heckman, 2006). Exposure to MDS in this sensitive period is a risk factor for poor cognitive development (Liu et al., 2017). There has been a recent interest in identifying the potential mediators of this association to improve our understanding of its underlying mechanisms. This review provides a summary of factors in the early childhood family environment that putatively mediate the association between MDS and children's cognitive development.

Evidence suggests that MDS negatively affect children's cognitive, behavioural, and socioemotional development (Goodman et al., 2011; Grace, Evindar, & Stewart, 2003; Liu et al., 2017; Wachs, Black, & Engle, 2009). Cognitive development refers to age-related increases in

language, intellectual, and executive functioning capabilities, all of which are affected by genetic, biological, social, and psychological factors that are sensitive to broader contextual determinants (Grantham-McGregor et al., 2007; Walker et al., 2011). Four reviews (Field, 1995; Grace et al., 2003; Sohr-Preston & Scaramella, 2006; Wachs et al., 2009) and two meta-analyses (Beck, 1998; Liu et al., 2017) have summarized the research findings linking MDS and children's cognitive development, however, there is no synthesis of studies that have tested the role of putative mediating variables in this association.

A number of theoretical frameworks about the putative pathways through which MDS may influence children's cognitive development have been proposed (Bandura, 1995; Belsky, 1984; Bowlby, 1988; Bronfenbrenner, 1979; Goodman & Gotlib, 1999; Minuchin, 1985). An often-cited framework is Goodman and Gotlib's *Developmental Model for Understanding Mechanisms of Transmission* (Goodman & Gotlib, 1999). This model identifies four pathways through which children could be at risk for less optimal development: (1) negative maternal cognitions (i.e., thoughts), behaviours, and affect; (2) stressful context of children's lives; (3) innate dysfunctional neuro-regulatory mechanisms; and (4) heritability of depression. Studies have empirically tested these pathways as mechanisms through which MDS are associated with children's cognitive outcomes either by testing the associations between (a) MDS and putative mediator variables or (b) mediators and children's cognitive development. The following paragraphs provide a brief summary of these studies.

### *Maternal cognitions, behaviours, and affect*

Numerous studies (Beck, 1995; Logsdon, Wisner, & Pinto-Foltz, 2006; Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Murray, Cooper, & Hipwell, 2003) have investigated the impact of

MDS on negative maternal cognitions, behaviours, and affect. The minds of depressed mothers can be dominated by recurrent negative thoughts which in turn interfere with their capacity to respond to their interpersonal environment (Stein, Malmberg, Sylva, Barnes, Leach, et al., 2008), including their interactions with their children. Two systematic reviews (Logsdon et al., 2006; Murray, Cooper, & Hipwell, 2003) found that MDS predicted negative maternal perceptions of normal child behaviour and reduced mothers' sense of enjoyment in the maternal role. In addition, one meta-analysis (Beck, 1995) reported that MDS have a negative, moderate-to-large effect on the quality of mother-child interactions ($d$=.68 - .78). Another review (Lovejoy et al., 2000) found that depressive symptoms increased the likelihood of negative parenting practices ($d$=.40) such as low sensitivity, hostility, and negative parent-child interactions. Maternal sensitivity, responsiveness, and affect have in turn been consistently associated with young children's cognitive development (Sohr-Preston & Scaramella, 2006; Walker et al., 2007).

There is evidence that the quality of care provided by mothers to their children, including their responsivity and cognitive stimulation, influences children's early cognitive development (Sohr-Preston & Scaramella, 2006). Experimental intervention studies assessing the effect of cognitive stimulation on children report that those who received additional cognitive stimulation had higher cognitive functioning scores than non-stimulated controls (Grantham-McGregor et al., 2007; Walker et al., 2007). Furthermore, interventions that enhanced mother-child interactions and increased the provision of learning activities in the home found positive associations with children's cognitive development (Walker et al., 2011).

***Stressful family environment***

There is empirical and theoretical support for the association between MDS and stressful family contexts in children's lives. Although Elder and Caspi's (Elder & Caspi, 1988) *Family Stress Model* suggests that low-income impacts maternal mental health which then influences children's development through parenting practices, the mechanisms of the association between low-income and maternal mental health are not clear. Conditions of economic deprivation such as stress, worse physical health, and reduced access to health care could facilitate the development of mental ill-health (Lund et al., 2010). Or perhaps, the experience of mental ill-health could result in people drifting into or remaining in conditions of economic deprivation (Lund et al., 2010). Importantly, MDS could foster a stressful context of children's lives through its association with family functioning (Burke, 2003; Letourneau et al., 2012). Thus, even if there is no clear evidence to show that MDS cause economic problems or vice versa, MDS and economic difficulties are important contributors to the levels of stress in the family and should be accounted for in models on the impact of MDS on children's outcomes.

***Innate dysfunctional neuroregulatory mechanisms***

Evidence also suggests that innate dysfunctional neuroregulatory mechanisms, which can be inferred through proxy measures such as low birth weight and premature birth, are associated with both maternal depression and children's cognitive development (Glover, O'Donnell, O'Connor, & Fisher, 2018; Meaney, Szyf, & Seckl, 2007; O'Donnell & Meaney, 2017; Schlotz & Phillips, 2009). Several studies show that children exposed to maternal depression are more likely to be born prematurely and have low birth weight (Dadi et al., 2020; Field 2017). In turn, children born prematurely and with low birth weight are more likely to experience poorer cognitive

outcomes across the lifespan (Aylward, Pfeiffer, Wright, & Verhulst, 1989; Farajdokht et al., 2017; Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2015; Mulder, Pitchford, Hagger, & Marlow, 2009; Orri et al., 2021). However, the extent to which these proxy measures of dysfunctional neuroregulatory mechanisms mediate the association between maternal depression and cognitive development has not been tested (O'Donnell & Meaney 2017).

### *Our Study*

Understanding the putative pathways through which MDS influence children's cognitive development in early childhood can lead to the development of targeted interventions to minimize the impact of depressive symptoms in this critical developmental period. From a public health perspective, research identifying these pathways can be used to develop population-level interventions for depressed mothers and their families, which act directly on these factors and improve children's cognitive development. This review provides a summary of such research. Specifically, our objective was to summarize the empirical literature on the putative mediators through which MDS are associated with children's cognitive development.

## Methods

### *Search strategy*

Studies included in this review were identified using both electronic and manual searches. Two electronic databases, PubMed and PsycNet (through to March 2018), were searched for relevant studies on MDS and child cognitive development using the following search terms: 'maternal depressive symptoms' (or 'maternal depression') AND 'cognitive development'.

Follow-up manual searches were conducted from the citations in articles retrieved from the electronic search.

### *Study inclusion criteria*

A study was considered eligible for inclusion if it: (i) quantitatively assessed associations between maternal depression or depressive symptoms and child cognitive development; (ii) assessed maternal depression or depressive symptoms in the postnatal period (iii) was published in a peer-reviewed journal; (iv) included putative mediator variables involved in the association between maternal depression or depressive symptoms and child cognitive development; and (v) was written in a language in which the author could read scientific articles (English/French). No other restrictions were applied.

### *Study selection*

The selection of studies was conducted in two steps. First, titles and abstracts of the retrieved studies were screened by the authors. Studies deemed to not fulfill the criteria were excluded. Second, the remaining studies were read in full by both authors and selected for inclusion if the study met inclusion criteria.

## Results

We retrieved 88 citations from PubMed and 306 citations from PsycNet. Additional relevant articles were found through manual search. Thirty-seven potentially relevant studies were identified by screening the titles and abstracts received from the electronic and manual searches (***Figure 1***). Among these, seven studies meeting the selection criteria were included in the review.

Studies were conducted across the UK, Australia, Canada, Taiwan, and the USA. Two studies were cross-sectional, and the other five used longitudinal designs, among which four assessed MDS at least twice. MDS were assessed between the ages of 6-weeks and 5-years, and cognitive outcomes between 6-months and 5-years. ***Table 1*** presents a summary of these studies. The results of studies that included more than one variable is reported under the relevant sub-headings. Note that the term "effect" is used to refer to longitudinal and sequential associations tested in mediating models, and not to causality.

***Negative maternal cognitions, behaviours, and affect***

Stein and colleagues (Stein, Malmberg, Sylva, Barnes, & Leach, 2008) examined the associations between MDS, maternal caregiving – assessed by trained interviewers in two-hour home observations – and children's language development in a British sample. Using SEM, the authors found that MDS at 10-months or 36-months did not directly predict children's language development at 36-months. There was, however, an indirect effect of MDS on children's language. In other words, higher levels of MDS were associated with lower quality of maternal caregiving, and this was in turn associated with poorer language outcomes.

Kiernan and Huerta (Kiernan & Huerta, 2008) also found no direct effect of MDS on children's cognitive outcomes using data from the Millennium Cohort Study, a large-scale survey of British children born in 2001-2. They then tested whether MDS were associated with maternal parenting behaviours, disciplinary practices, and mother-child interactions and whether these variables were in turn associated with child outcomes. MDS were not assessed with a direct measure, rather, they were derived from three items assessing whether or not mothers had symptoms in the postnatal period, whether or not mothers had been diagnosed by a doctor, and

items derived from the Rutter Malaise Invetory (Kelly, Bartley, Schoon, & Hope, 2004). Information on reading activities, mother-child interactions, and disciplinary parenting practices were self-reported by mothers. They found that depressed mothers (at age 9-months) were less likely to engage in reading activities and positive mother-child interactions at age 3-years, which in turned predicted lower concurrent cognitive scores. Thus, the association between MDS and lower child cognitive development came about via lower levels of maternal stimulation and mother-child interactions as well as less efficient parenting. Depressed mothers were also more likely to engage in coercive disciplinary practices (e.g., smacking the child, shouting at the child if they are naughty), however, these practices were not significantly associated with children's lower cognitive scores at age 3.

Milgrom and colleagues (Milgrom, Westley, & Gemmill, 2004) reported that children of depressed mothers had lower Full IQ scores and lower cognitive/language profile scores than children of non-depressed mothers at 42-months in a small (n=56) Australian sample. Baron & Kenny's (Baron & Kenny, 1986) mediation approach was used to formally test whether observed maternal responsiveness at age 6-months mediated these associations. Maternal responsiveness fully mediated the association between MDS and children's IQ, however, there was no indirect effect of MDS in the association with children's cognitive/language profile scores (Milgrom et al., 2004). That is, the association between MDS and lower cognitive profile was not mediated by maternal responsiveness. These results should be interpreted with caution as Baron and Kenny's (Baron & Kenny, 1986) approach does not provide a clear test of the indirect effect (Hayes, 2009). Rather, it infers mediation based on the reduction of significance in the association between the exposure and the outcome once the mediator is entered into the model.

In a cross-sectional study (Zajicek-Farber, 2010), MDS was indirectly associated with children's language competencies (assessed as understanding and producing age-expected vocabulary) at age 16 to 18-months in a low-income non-white sample. The results indicated that depressed mothers were less likely to engage in stimulating activities with their children, and this in turn was associated with poorer language development. (Zajicek-Farber, 2010). The cross-sectional nature of the study greatly limits the interpretation of a mediation process as it is plausible that there is a bi-directional association between MDS and the potential mediator, as well as between the mediator and child outcomes.

On the other hand, a longitudinal study in a Canadian sample found direct, as well as indirect, association between MDS and children's receptive vocabulary at ages 4 to 5-years (Letourneau, Tramonte, & Willms, 2013). Children of chronically and concurrently depressed mothers had lower receptive vocabulary scores. Exposure to higher neglectful parenting style was identified as a partial mediator. This means that parenting style explained part of the association between MDS and children's vocabulary. MDS were still significantly associated with children's receptive vocabulary after parenting style was included in the model.

***A stressful family environment***

Two studies (Chen et al., 2013; Piteo et al., 2012) used measures of the quality of the home environment (e.g., organization, learning materials, variety of daily stimulation) to test whether it mediated the association between MDS and children's cognitive development. The home environment when children were 18-months old did not mediate the association between MDS at 6-weeks and 6-months postpartum and children's concurrent cognitive development in an ethnically homogenous American sample of full-term and pre-term infants (Piteo et al., 2012).

Conversely, Chen and colleagues (Chen et al., 2013) found an indirect association through the quality of the home environment in a cross-sectional study of immigrant mothers in Taiwan. In other words, the home environment fully mediated the association between MDS and children's cognitive and language development. Because of the cross-sectional nature of the study, the results do not provide information about the directionality of the exposure-mediator and mediator-outcome associations.

Letourneau and colleagues (2013) tested whether family dysfunction mediated the association between MDS and children's receptive vocabulary. Family functioning (i.e. cohesiveness and adaptability of family) was reported using the McMaster Family Assessment Device (Epstein, Baldwin, & Bishop, 1983) by the person who knew the child best (the mother in most cases) when children were 4 to 5-years old. Similar to their results with parenting style, they found that the influence of family dysfunction reduced the negative impact of early depressive symptoms on children's receptive vocabulary. However, family dysfunction was not significantly associated with vocabulary scores, and therefore did not mediate the association between MDS and vocabulary scores. (Letourneau et al., 2013). Note that the authors do not report associations between MDS and the potential mediators (i.e., parenting style and family functioning).

## Discussion

This review summarized the small but emerging literature investigating the pathways through which MDS are associated with children's cognitive development in early childhood. Of the seven studies included in the review, two found direct and indirect associations, four found no direct but some indirect associations, and one found no direct nor indirect associations between MDS and children's cognitive development. Among studies using statistical methods providing

robust test of mediation hypotheses, such as SEM, maternal responsiveness and the quality of maternal caregiving were identified as mediators of the association between MDS and children's cognitive development in early childhood. These advance the field by identifying the aspects of the family environment likely to be affected by MDS, which can then be targeted as part of comprehensive intervention programs.

The mediator variables tested in the seven studies can be categorized into two of the four pathways identified in Goodman and Gotlib's *Developmental Model for Understanding Mechanisms of Transmission*: negative maternal cognitions, behaviours, and affect (i.e., mother-child interactions and maternal parenting behaviours) and stressful context of children's lives (i.e., family dysfunction) (Goodman & Gotlib, 1999). Four studies specifically tested the extent to which exposure to negative maternal, cognitions, behaviours, and affect – operationalized as maternal affect, mother-child interactions, maternal responsiveness, and maternal parenting practices – were pathways of transmission of risk for the development of children with depressed mothers. Kiernan & Huerta were concerned with both negative maternal cognitions, behaviours, and affect, and the stressful context of children's lives as measured by low-income status (Kiernan & Huerta, 2008). However, they tested the role of MDS as a mediator of the association between low-income status (a proxy for stressful environment) and child development, rather than testing the mediating role of low-income in the association between MDS and child development. The direction of causality in the association between low-income and mental health problems continues to be a subject of debate amongst researchers (Elder & Caspi, 1988; Lund et al., 2010). The remaining studies focused on the stressful context of children's lives, through measurement of the quality of the home environment (e.g., organization) and family functioning, as putative pathways of risk.

***Potential explanations for divergent findings***

There are a few potential explanations for the conflicting results presented in the reviewed studies. The first is that MDS, the mediators, and child outcomes were measured at different ages. For example, a parenting practice that mediates the association between MDS and cognitive outcomes for an infant, may not be a significant mediator for a preschooler. The time elapsed between the exposure, mediator, and outcome variables also differed across studies. Although previous research suggests that there is no effect of timing of exposure to MDS on cognitive outcomes (Ahun et al., 2017; Brennan et al., 2000), it is plausible that the strength of the association between MDS exposure at an earlier point in time and child outcomes decreases as the child gets older, especially if the symptoms are of a low severity and do not persist over time (Brennan et al., 2000). Only one of the reviewed studies accounted for the chronicity of MDS, and they reported a significant association between chronic MDS and child outcomes at 4 to 5-years, compared to a non-significant association for early MDS (Letourneau et al., 2013). One conceptual difference between studies was the choice of potential confounders included in the mediation models. Two of the reviewed studies did not include any confounders, and only three of the remaining studies considered maternal education. Failure to account for the role of potential confounds may have led to an overestimation of the direct and indirect effects of MDS on children's cognitive outcomes.

Another potential explanation for the differences in results, is the use of maternal report to assess putative mediators. For example, MDS have been found to predict mother-reported but not externally observed mother-child interactions (Chi & Hinshaw, 2002). Population-based studies typically rely on maternal ratings of MDS, child behaviours, and the overall family environment, and such ratings can be biased by depressive/negative cognitions (Chi & Hinshaw, 2002; Letourneau et al., 2013). Research suggests that behaviours self-reported by depressed mothers

are more likely to be identified as mediators compared to external observations of these same behaviours (Chi & Hinshaw, 2002; Gartstein, Bridgett, Dishion, & Kaufman, 2009; Herbers, Garcia, & Obradović, 2017). Moving forward, researchers should prioritize multi-informant reports and direct observations of the home environment, mother-child interactions, and parenting practices in samples of depressed mothers.

Given the correlational nature of the majority of MDS studies, it is important that robust statistical techniques be used to test associations and that conclusions are drawn with caution since causality cannot be determined. Despite its widespread use, Baron and Kenny's (Baron & Kenny, 1986) mediation approach has been criticized on multiple grounds, including its low power for testing intervening variable effects (Fritz & Mackinnon, 2007; Hayes, 2009; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). It is therefore not the most appropriate means for testing mediation. Only one study used this approach. Some studies were limited by their use of a cross-sectional design, as they were unable to account for reciprocal associations between MDS, mediators, and child outcomes. For example, MDS are associated with parenting behaviours (e.g., hostility) that influence child outcomes (Goodman & Tully, 2008; Lovejoy et al., 2000). Children's behaviour, in turn, can exacerbate later MDS in a transactional relationship (Bagner, Pettit, Lewinsohn, Seeley, & Jaccard, 2013). Furthermore, cross-sectional approaches to mediation generate substantially biased estimates of longitudinal parameters by implying the existence of a significant indirect effect when the true longitudinal indirect effect is zero (Maxwell & Cole, 2007; Maxwell, Cole, & Mitchell, 2011). It is therefore important to rely on longitudinal designs to determine the direction of associations in mediation models.

***Strengths and limitations***

This review provides a summary of the potential pathways through which MDS are associated with children's cognitive development. It draws upon developmental theoretical models, particularly Goodman & Gotlib's *Developmental Model for Understanding Mechanisms of Transmission* (Goodman & Gotlib, 1999), to understand and interpret existing empirical evidence. This model focuses specifically on pathways within the family environment, and we are therefore unable to comment on the role of putative mediators in other childhood environments (e.g., school). We reviewed studies that formally tested putative mediators of the association between MDS and children's cognitive development, and thus only a small number of studies were included. These studies were limited by their use of relatively small sample sizes, lack of repeated assessments of MDS, mediators, and child outcomes over the early childhood period, and failure to include pertinent confounders in the mediation models. The latter limitation threatens the internal validity of a given study as the reported associations between MDS, a mediator, and an outcome may be confounded by an unobserved variable. It should be noted, however, that not all reviewed studies were subject to each of these limitations.

Lack of knowledge on the associations between MDS and paternal characteristics, and the latter's impact on children's cognitive development represents a substantive limitation of these studies. Paternal depressive symptoms have been associated with more withdrawn behaviour in father-child interactions (Paulson & Bazemore, 2010; Sethna, Murray, Netsi, Psychogiou, & Ramchandani, 2015) and poorer cognitive outcomes in young children (Malin et al., 2012; Paulson & Bazemore, 2010; Wanless, Rosenkoetter, & McClelland, 2008). Additional research is needed on the combined and independent effects of maternal and paternal depressive symptoms on child outcomes to better understand the pathways through which they influence child development (see

Goodman, 2004; Paulson & Bazemore, 2010 for reviews of the associations between maternal and paternal depressive symptoms).

## Conclusion

The most significant mediators through which MDS are associated with children's cognitive development in early childhood are negative maternal cognitions, behaviours, and affect. But these effects are mixed. To improve our understanding of the pathways through which MDS are associated with children's cognitive development, future research should identify sources of variation in the mediating factors. These include variation as a function of the family context, age of the child, type of cognitive outcome, and nature of depressive symptoms. This information is needed to design interventions that target the family processes affected by maternal depressive symptoms within a comprehensive approach fostering family health and well-being.

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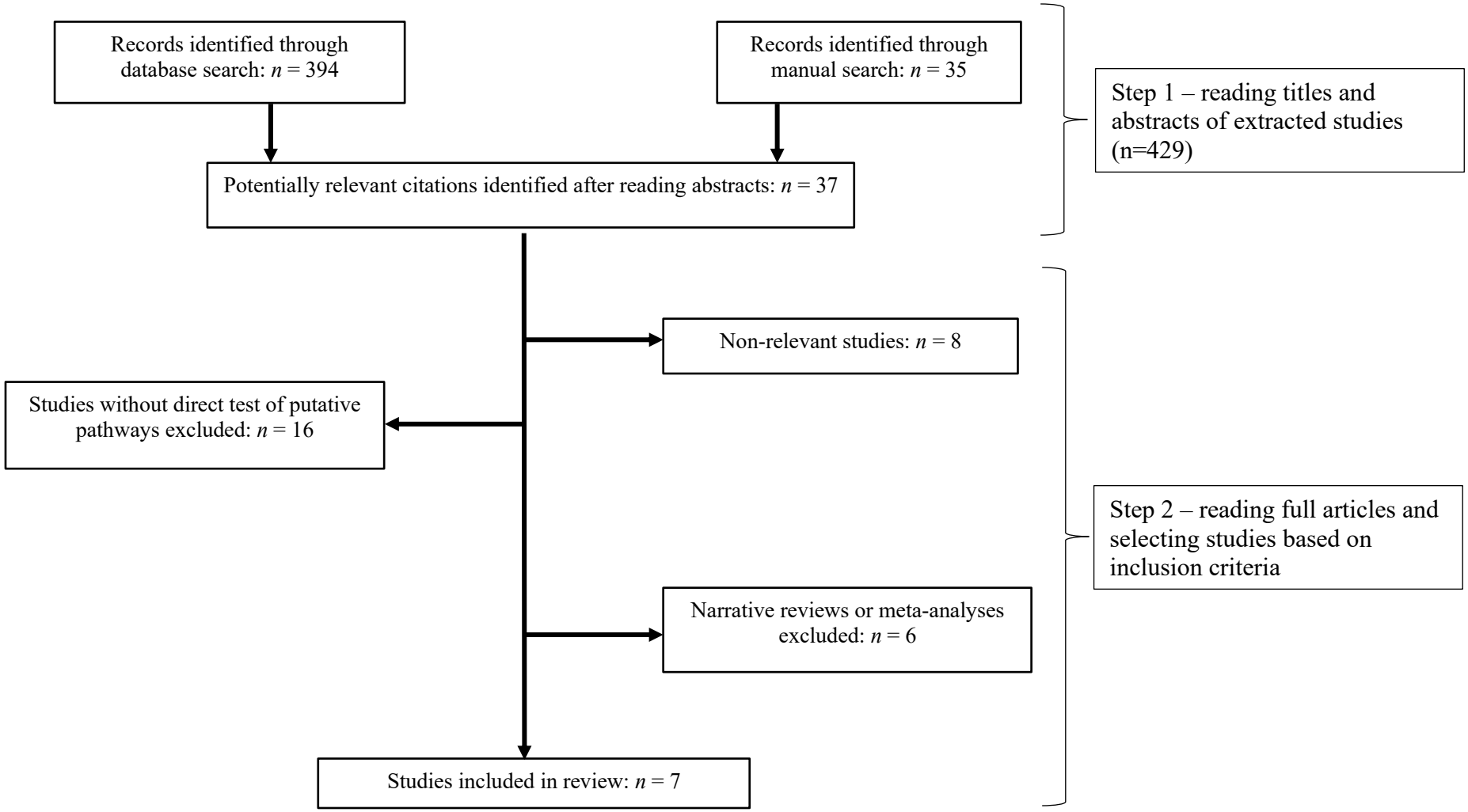


**Figure 1**. Flow diagram of study selection procedure

**Table 1.** Summary of articles examining mediators of the maternal depressive symptoms-child cognitive development association.

| Name and country | Study design | Participants | Measures[a] | Putative mediators | Strength of direct and indirect associations |
|---|---|---|---|---|---|
| Milgrom et al., 2004 Australia | Longitudinal | Mothers aged 19-39 years, infants aged 15.8 weeks (SD=7.1) at recruitment. N=56 | Hamilton Depression Rating Scale at recruitment, 6, 12, 24, and 42 months.<br><br>Maternal responsiveness measure adapted from rating scales (Brazelton, Koslowski, & Main, 1974; Censullo, Lester, & Hoffman, 1985) and assessed at 6 months<br><br>Wechsler Preschool Primary Scale of Intelligence (Revised) | Mother-child interactions (maternal responsiveness) | MDS to child IQ (when maternal responsiveness is in model): b= –0.1, p=0.44 |

| | | | | | |
|---|---|---|---|---|---|
| | | | and Early Screening Profiles at 42 months | | |
| Kiernan & Huerta 2008 United Kingdom | Longitudinal | Millennium Cohort Study. N=13,877 | Maternal depression was derived from 3 items of information at 9 months<br><br>Reading activities, mother-child interactions, and disciplinary practices were assessed by maternal report at 3 years<br><br>Bracken Basic Concept Scale at 3 years | Maternal parenting behaviours (disciplinary practices)<br><br>Mother-child interactions | MDS to reading activities: b= –0.05, p<.05<br><br>Reading activities to child cognitive scores: b= 0.42, p<.001<br><br>MDS to mother-child interactions: b= –0.12, p<.001<br><br>Mother-child interactions to child |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | cognitive scores: b= 0.08, p<.001<br><br>MDS to coercive disciplinary practices: b= 0.17, p<.001<br><br>Coercive disciplinary practices to children's cognitive scores: b= 0.03, p>.05 |
| Stein et al United Kingdom | Longitudinal | Subjects were recruited at antenatal and post-natal baby clinics. N=944 | Edinburgh Postnatal Depression Scale and at 3 and 10 months | Mother-child interactions (maternal caregiving) | MDS to maternal caregiving: b = –0.21, p<.05 |

| | | | | | |
|---|---|---|---|---|---|
| | | | and 12-item General Health Questionnaire at 3 months<br><br>Emotional and verbal responsiveness of mother, Provision of appropriate play materials, Organization of the physical and temporal environment, and opportunities for variety in daily stimulation subscales of the Home Observation for Measurement of the Environment, and Positive relationship and Detachment subscales of the Caregiver | | Maternal caregiving to child language: b = –0.27, p<.05 |

| | | | | | |
|---|---|---|---|---|---|
| | | | Interaction Scale at 10 and 36 months<br><br>Reynell Developmental Language Scale at 36 months | | |
| Zajicek-Farber 2010 USA | Cross-sectional | Mothers were on average 24.6 years (SD=5.5) and infants were 16 to 18 months old. N=198 | Edinburgh Postnatal Depression Scale<br><br>Self-reported engagement in literacy-oriented stimulating activities<br>MacArthur Communicative Development Inventories | Maternal parenting behaviours (stimulating activities) | MDS to stimulating activities: b= -0.39, p<.001<br><br>Stimulating activities to language development: 0.61, p <.001 |
| Piteo et al 2012 Australia | Longitudinal | Subjects were from the control arm of a randomized control trial on | Edinburgh Postnatal Depression Scale at 6 weeks and 6 months | Family stress (quality of home environment) | MDS to home environment: b= -0.35, p>.05 |

| | | | | | |
|---|---|---|---|---|---|
| | | full term and pre-term infants in 5 perinatal centers. N=360 | Home Screening Questionnaire at 18 months<br><br>Bayley Scales of Infant and Toddler Development at 18 months | | Home environment to cognitive scores: b=0.80, p<.01)<br><br>Home environment to language scores: b=1.04, p<.01 |
| Chen et al 2013 Taiwan | Cross-sectional | Mothers were 20-40 years old and children were 6-24 months old. N=60 | Edinburgh Postnatal Depression Scale<br><br>Infant Toddler-Home Observation for Measurement of the Environment | Family stress (quality of home environment) | MDS to home environment: b= -0.28, p<.05<br><br>Home environment to cognitive outcome: b=0.51, p<.001 |

| | | | | | |
|---|---|---|---|---|---|
| | | | Comprehensive Developmental Inventory for Infants and Toddlers screening test | | |
| Letourneau et al 2013 Canada | Longitudinal | Canadian National Longitudinal Survey of Children and Youth. N=10,033 | 12 items from the 20-item Center for Epidemiologic Studies-Depression Rating Scale at 0-1 years, 2-3 years, and 4-5 years<br><br>McMaster Family Assessment Device and Western Australian Child Health Survey at 0-1 years, 2-3 years, and 4-5 years<br><br>Peabody Picture Vocabulary Test-Revised at 4-5 years | Maternal parenting behaviours (parenting style)<br><br>Family stress (family functioning) | MDS to receptive vocabulary scores: OR= 3.03, p<.05<br><br>Parenting style to receptive vocabulary scores: OR=1.99, p<.05<br><br>Family functioning to receptive vocabulary scores: OR= 1.44, p>.05 |

[a]Some studies measured more than one child developmental outcome, however, only measures used to assess cognitive

development are reported here.

**4.2** ***Article 2***

**Maternal depressive symptoms and children's academic performance: Sex differences in the mediating role of school experiences**

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## Abstract

**Background –** Maternal depressive symptoms (MDS) are negatively associated with children's academic performance, with stronger effects sometimes reported in boys. However, few studies have tested the mechanisms of this association. We examined the mediating role of school engagement and peer victimization in this association and tested for sex differences.

**Methods** – Participants were 1173 families from a population-based longitudinal Canadian study. MDS were self-reported annually using the Centre for Epidemiologic Studies Depression Scale (child's ages: 5 months to 5 years). Data on mediators (peer victimization, cognitive, behavioural, and emotional school engagement) were reported annually from ages 6-10 by multiple informants including children, parents, and teachers using items from validated scales. Mathematics, reading, and writing exam scores at age 12 were obtained from standardized exams administered by Québec's Ministry of Higher Education and Teaching. Structural Equation Modelling was used to test mediation by school experiences in boys and girls.

**Results –** Exposure to MDS was negatively associated with mathematics, reading, and writing scores in girls and with mathematics only in boys. Cognitive and behavioural engagement significantly mediated the association between MDS and mathematics, reading, and writing scores in girls. There were no significant mediators for boys.

**Conclusions –** Prevention and intervention strategies aiming to improve school engagement might be beneficial for daughters of mothers experiencing depressive symptoms. Further research is needed to replicate these findings and to identify the mechanisms explaining this association in boys.

## Introduction

Early childhood is a period characterized by rapid growth and brain development. Children's experiences during this period provide the foundation for future life success, and failure to cultivate core (e.g., cognitive, social, emotional) skills impedes their ability to learn at later ages (Shonkoff et al., 2012). Exposure to maternal depressive symptoms (MDS) during this sensitive period is adversely associated with children's cognitive outcomes, including academic performance. Systematic reviews report small yet consistent negative effects of early MDS on later academic performance, with some studies reporting stronger effects in boys (Grace, Evindar, & Stewart, 2003; Liu et al., 2017; Sanger, Iles, Andrew, & Ramchandani, 2015). However, the mechanisms of this association remain unclear.

Bronfenbrenner (1979) posits that interactions between the home and school microsystems influence children's development. Experiences within the home microsystem can therefore have an impact on children's interactions with their peers and learning environment within the school microsystem, which subsequently influence children's outcomes. There is evidence that maternal characteristics (e.g., maternal cognitions, behaviours, and affect) mediate the association between MDS and cognitive development in early childhood (Ahun & Côté, 2019). Beyond early childhood, only a handful of studies have tested potential mediators of this association (Pearson et al., 2016; Psychogiou, Russell, & Owens, 2019; Yan & Dix, 2014), even though there is clear evidence that children exposed to MDS in early childhood continue to experience negative outcomes into middle childhood and adolescence (Sanger et al., 2015). The afore-mentioned studies identified child characteristics (i.e., social withdrawal, executive function, and mental health) as mediators of this association. However, as children grow older and become less dependent on their parents, it is important to understand how formative aspects of children's school

experiences – i.e., peer victimization and school engagement – may play a role in this association (Ladd, Ettekal, & Kochenderfer-Ladd, 2017; Yan, Schoppe-Sullivan, & Feng, 2019).

Children exposed to MDS in early childhood are more likely to have poorer academic outcomes in later childhood and adolescence compared to non-exposed children (Sanger et al., 2015). However, evidence regarding sex differences is mixed. Some studies report poorer performance in sons of mothers with depressive symptoms (Hay et al., 2001; Murray et al., 2010), others find that daughters have poorer academic outcomes (Paquin et al., 2020; Shen et al., 2016), while some find no sex differences (Ng-Knight, Shelton, Frederickson, McManus, & Rice, 2018). None of the studies that examined the mechanisms of this association beyond early childhood tested for sex differences (Pearson et al., 2016; Psychogiou et al., 2019; Yan & Dix, 2014). Given these mixed findings, it is not clear whether boys or girls are more sensitive to the negative effects of MDS. In the following paragraphs, we explore potential mechanisms in the school microsystem through which early exposure to MDS may influence children's later academic performance. By elucidating the mechanisms of this association, we hope to better understand the different ways in which MDS are associated with academic performance in boys and girls.

Peer victimization and school engagement are two core aspects of children's school microsystem (Ladd et al., 2017) that are associated both with MDS and children's academic performance (Claessens, Engel, & Curran, 2015; Côté et al., 2018; Nakamoto & Schwartz, 2010; Upadyaya & Salmela-Aro, 2013). Peer victimization refers to the experience of being bullied or aggressed repeatedly over time by one or more peers (Ladd & Kochenderfer-Ladd, 2002); while school engagement reflects students' active investment in their learning activities and is conceptualized as a three-dimensional construct consisting of cognitive (i.e., intellectual effort devoted to learning tasks), behavioural (i.e., constructive or cooperative engagement in classroom

activities), and emotional (i.e., feelings about peers, teachers, schoolwork) engagement (Fredricks, Blumenfeld, & Paris, 2004).

Exposure to MDS in early childhood is associated with peer victimization in later childhood (Côté et al., 2018; Tsypes & Gibb, 2015). Children exposed to MDS are more likely to experience interpersonal relationship difficulties, lower empathic response, and disrupted emotion regulation as they grow older (Galbally & Lewis, 2017; Tsypes & Gibb, 2015; Yap, Pilkington, Ryan, & Jorm, 2014). These difficulties may then set the stage for lower-quality interpersonal peer relationships which can consequently increase a child's risk of being socially excluded or victimized (Hamilton et al., 2016). Mothers experiencing depressive symptoms are also less likely to promote children's learning and cultivate children's academic aspirations (Augustine & Crosnoe, 2010). Parental involvement in their child's education – particularly in the early years – is instrumental in promoting children's academic success, and lack of involvement undermines children's academic engagement and performance both at school entry and throughout their academic careers (Pomerantz, Kim, & Cheung, 2012). Exposure to MDS in early childhood may therefore be associated with children's decreased engagement with their learning environment (e.g., lack of persistence in academic tasks and less eagerness to learn) (Claessens et al., 2015; Murray et al., 2006).

With respect to academic performance, children who are more invested in their education on all three dimensions (i.e., cognitive, behavioural, emotional) of school engagement have better concurrent and subsequent academic performance (Upadyaya & Salmela-Aro, 2013). Additionally, girls have been found to have higher levels of engagement than boys, which may explain why girls sometimes outperform boys academically (Pomerantz, Altermatt, & Saxon, 2002; Upadyaya & Salmela-Aro, 2013). Beyond school engagement, interpersonal relationships

play an important role in children's academic outcomes. A meta-analysis reported a small but significant negative correlation between the experience of peer victimization and concurrent and subsequent academic performance (Nakamoto & Schwartz, 2010). However, no sex differences were found.

In the present study, we examined the mediating role of school experiences in the association between MDS and academic performance in boys and girls. Specifically, we tested the mediating role of peer victimization and children's cognitive, behavioural, and emotional school engagement in middle childhood (6-10 years) in the association between early (5 months-5 years) exposure to MDS and children's academic performance at age 12. We hypothesized that exposure to MDS in early childhood would be negatively associated with cognitive, behavioural, and emotional engagement, but positively with peer victimization in older children. In turn, cognitive, behavioural, and emotional engagement would be positively associated with academic performance, whereas peer victimization would be negatively associated with performance. Due to evidence suggesting sex differences in the MDS-academic performance association, we tested mediation models separately by sex. We do not formulate any hypotheses regarding sex differences due to mixed findings in the literature.

## Methods

Participants were part of the Québec Longitudinal Study of Child Development, a cohort of 2,120 families with a 5-month-old infant born in 1997-1998 conducted by the *Institut de la Statistique du Québec* (ISQ; Québec Institute of Statistics) (Orri et al., 2020). Our analysis sample consisted of n=1173 participants with academic performance data. Respondents were parents, teachers, and target children. The research protocol was approved by the ISQ and the Sainte-Justine

Hospital Research Centre ethics committees, and informed consent was obtained at each data collection. An exhaustive list of items used is presented in the supplementary material (see Supplement 1 to 3, available online). Sample characteristics are also presented in the supplementary material (***Table S1***).

***MDS*** during the past week were self-reported by mothers when children were 5 months (Cronbach's alpha = 0.81), 1½ (0.82), 3½ (0.81), and 5 (0.82) years old using a short version of the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). The CES-D was used dimensionally, with response categories on each item ranging between 0 (none) to 3 (all the time). This validated short CES-D includes 12 questions from the original at each time of assessment (Poulin, Hand, & Boudreau, 2005). Mean scores were created at each age by averaging across items. These scores (standardized on a 0-10 scale) were used to compute the final exposure variable (Pearson's $r$=.35-.44, $p$<.0001)**.** Using the conventional cut-off from the original CES-D (16/60, which is equivalent to 2.67/10 in this data; Weissman, Sholomskas, Pottenger, Prusoff, & Locke, 1977), 11.5% of mothers in our sample had elevated levels of depressive symptoms.

***Academic performance***. Every Québec student must write *Ministère de l'Éducation et de l'Enseignement Supérieur* (Ministry of Higher Education and Teaching) exams at the end of grade 6 (age 12). The following evaluation criteria were used to assess competencies in each subject: mathematics – task comprehension, mobilizing concepts and processes, solution explanation, analysis and making informed choices, applying solutions, and justification; reading – extraction of pertinent explicit and implicit information, text interpretation, and pertinent reactions to literary and informational texts; and writing – relevance and adequacy of ideas, appropriate organization of the text, syntax and punctuation, vocabulary, and spelling. Scores are expressed in percentages.

Continuous scores from each exam – mathematics, reading, and writing – were examined as separate outcomes.

***Peer victimization*** was assessed using items from an adapted version of the self-report victimization scale (Ladd & Kochenderfer-Ladd, 2002). The mean of parent (6 years; 3 items), child (6, 7, 8, and 10 years; 3 items), and teacher (6, 7, 8, and 10 years; 3 items) reports of victimization frequency (e.g., name calling, physical aggression) were used to create a latent score using the correlated traits-correlated (methods-minus-one) approach (Papa, Litson, Lockhart, Chassin, & Geiser, 2015), as research suggests that multi-informant reports provide non-overlapping data on victimization and are better predictors of academic performance than single-informant reports (Ladd & Kochenderfer-Ladd, 2002; Nakamoto & Schwartz, 2010). The model showed a good fit to the data, RMSEA = .02, CFI = .99. Participants with higher scores were victimized by peers on a more frequent basis. Note that participants in this study attended co-educational day schools.

***Cognitive, behavioural, and emotional school engagement***. The study child's cognitive (6, 7, 8, 10 years; $r$=.49-.57, $p$<.0001; 10 items) and behavioural (6, 7, 8 years; $r$=.50-.67, $p$<.0001; 9 items) engagement were teacher-reported using items from the EDI (Janus & Offord, 2007). Cognitive engagement was assessed using items such as "challenges the teacher in a positive way", while behavioural engagement was conceptualized as the frequency with which children engaged in behaviours such as "works autonomously". Higher scores indicate more frequent cognitive and behavioural engagement behaviours, respectively. Emotional engagement (e.g., "I am proud to be studying at this school") was self-reported at ages 6,7, and 8 ($r$=.27-.39, $p$<.0001; 5 items) (Hill & Werner, 2006). Participants with higher scores were more emotionally engaged with their schools. All three measures were assessed on a scale of 0 to 10.

***Covariates.*** We searched previous literature for variables that could confound the associations between our exposure, mediator, and outcome variables (Augustine & Crosnoe, 2010; Claessens et al., 2015). We selected variables if they were correlated with MDS and any of the mediators or outcomes. Unless otherwise specified, all covariates were assessed at baseline (i.e., 5 months) according to epidemiological guidelines for modelling longitudinal data whereby – as much as possible – potential covariates are selected at baseline and not at subsequent timepoints (Greenland & Morgenstern, 2001; Pearce & Greenland, 2005).

The following variables were included as covariates: maternal verbal IQ assessed using the Peabody Picture Vocabulary Test (5 years; Dunn & Dunn, 1981), age (dichotomized as ≤21 or >21 years because becoming a mother before 21 years is a known risk factor for child outcomes in the Québec population; Tremblay et al., 2004), generalized anxiety symptoms assessed using a 10-item screening tool (based on 4th edition DSM criteria) for parental anxiety in large-scale longitudinal studies (4½ years; see Shapiro, Seguin, Muckle, Monnier, & Fraser, 2017 for further description), and youth antisocial behaviour assessed with five binary questions on conduct problems based on 4th edition DSM criteria (Zoccolillo, Paquette, & Tremblay, 2005), in-home observations of mother-child interactions (stimulation and verbalization) using the HOME (Caldwell & Bradley, 1985), mother-reported behavioural and depressive and anxiety symptoms (1.5 years) (Achenbach, 1991; Behar & Stringfield, 1974; Boyle et al., 1993), children's cognitive school readiness (5 years) as assessed by the Lollipop test (Chew, 1989), single-parent family, family dysfunction as assessed by the Family Dysfunction Scale (Byles, Byrne, Boyle, & Offord, 1988), and socioeconomic status (derived from parental education and occupational status and household income). A mean score of parent-reported peer victimization at 3½, 4½, and 5 years

was also included as a covariate to account for baseline peer victimization. Further information on the questionnaires and methods of data collection can be found online at the QLSCD website.

***Data Analyses***.

First, covariates were identified on the basis of their correlations with exposure, mediator, and outcome variables (***Table S2***). All the covariates listed above and reported in ***Table S2*** were retained for all subsequent models. We then used SEM to estimate the direct and indirect (via peer victimization and cognitive, behavioural, and emotional engagement) associations between MDS and children's academic performance. We adjusted for covariates in the association between MDS and potential mediators, and between potential mediators and each outcome. Mediation was tested via the significance of the indirect effect from the exposure variable via the mediators to the outcome (Holmbeck, 2002). The indirect effect is significant if the product of the coefficient of the pathway from MDS to the mediator and the coefficient of the pathway from the mediator to the outcome is significant (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). We tested whether there were any sex differences in these models by comparing the fit of a freely estimated model (i.e., all estimated parameters allowed to freely vary between sexes) with the fit of a model in which all estimated parameters were constrained to be equal across sexes (Kline, 2015).

SEM was performed with Mplus version 8.6 (Muthén & Muthén, 2019) using the robust maximum likelihood estimator. The R-Mediation package (Tofighi & MacKinnon, 2011) was used to build unbiased confidence intervals in R version 4.0.3 (R Core Team, 2019) for indirect effects because normal parametric tests would be biased due to the non-normal distribution of the indirect effect. Furthermore, differences in fit between the freely estimated and constrained models testing for sex differences were calculated by hand using the equation specified in Satorra and Bentler

(2010) given that the likelihood ratio test cannot be used for models estimated with robust maximum likelihood. Missing data in covariates were handled using the full information maximum likelihood. Descriptive statistics, correlations, and unadjusted regressions were obtained using SAS v 9.4 (SAS Institute Inc, 2013).

## Results

Eighty-four percent of children were White. The remaining 16% were of African (1%), Native American (3%), and other (12%; including Asian, Arab, Latinx) ethnic origins. Fifty-two percent of children were girls and only 5% of mothers were 21 years or younger at birth. On average, mothers had low scores of depressive symptoms (median=1.06 out of 10; ***Table S1***). However, the prevalence of elevated symptoms (11.5%) was comparable to the prevalence of sub-clinical maternal depression in high-income countries (8-13%; Howard et al., 2014; Lanes, Kuk, & Tamim, 2011). Girls had higher reading and writing scores than boys, but mathematics scores were not significantly different across sexes. Boys were victimized by peers more frequently and girls were more cognitively, behaviourally, and emotionally engaged in school (***Table 1***). Participants without government exam data (n=947) were more likely to be male, to come from a low socioeconomic status family, to live in a single-parent household, and to experience higher levels of family dysfunction compared to those in the analysis sample. They also had lower scores on a test of cognitive school readiness, received lower levels of verbalization and stimulation in mother-child interactions, and had mothers with higher levels of depressive symptoms and lower levels of verbal IQ (***Table S3***). Inverse probability weighting, in which weights represent the probability of being included in the analysis sample, were therefore used in all analyses (Seaman & White, 2013).

In unadjusted regression models, exposure to MDS was associated with lower mathematics (standardized  = -.11, $p$<.05), reading (= -.09,  $p$<.05), and writing (= -.20,  $p$<.05) exam scores in girls and with lower mathematics scores (= -.11,  $p$<.05) only in boys. MDS were negatively associated with cognitive ( = -.11, $p$<.05) and behavioural (= -.09,  $p$<.05) engagement in both sexes. MDS were only associated with emotional engagement (= -.10, $p$<.05) and peer victimization (= .10, $p$<.05) in girls. Higher levels of behavioural and cognitive engagement were associated with higher mathematics, reading, and writing exam scores, whereas emotional engagement was not associated with any academic outcomes (data not shown). There were no sex differences in these associations. On the other hand, peer victimization was negatively associated with mathematics (= -.18, $p$<.05) scores in both sexes and with, reading (= -.16, $p$<.05), and writing (= -.26, $p$<.05) scores in girls only.

Tests of differences in direct and indirect associations between boys and girls showed that mediation models where parameters were freely estimated for each sex were superior to models with constrained parameters across all outcomes (mathematics [$\chi^2_{235}$ = 690.1 , $p$ <.001], reading [$\chi^2_{235}$ = 671.6, $p$ <.001], writing [$\chi^2_{235}$ = 731.3, $p$ <.001]). The final models were therefore estimated for boys and girls separately. ***Figures 1A***, ***1B***, and ***1C*** illustrate the mediation models including covariates and mediators in the same model for mathematics, reading, and writing exam scores for both sexes. The total and simple direct and indirect effects of each adjusted model are reported in ***Table 2***. The unadjusted mediation models are presented in ***Figure S1*** and the corresponding effects in ***Table S4***.

In unadjusted models, cognitive and behavioural engagement mediated the association between MDS and girls' mathematics, reading, and writing scores. The only significant mediator for boys was cognitive engagement in the association with writing scores (***Figure S1*** and ***Table***

***S4***). After adjusting for covariates, there were no significant mediators in the association between MDS and academic performance in boys, although cognitive school engagement was positively associated with mathematics, reading, and writing scores. Girls exposed to higher levels of MDS had lower levels of cognitive and behavioural school engagement. These factors were in turn significantly associated with poorer performance on the mathematics exam (***Figure 1A***). Cognitive and behavioural engagement also significantly mediated the association between MDS and girls' reading (***Figure 1B***) and writing (***Figure 1C***) scores.

## Discussion

This is the first study to examine sex differences in the mediating role of school experiences in the association between early MDS and subsequent academic performance. In line with our hypotheses, we found that children's school experiences mediated the association between exposure to MDS in early childhood and academic performance in early adolescence. However, this association was only observed in girls. Specifically, cognitive and behavioural school engagement mediated the association between MDS and mathematics, reading, and writing exam scores. Emotional engagement and peer victimization were not significant mediators. None of the potential mediators explained the association in boys.

In line with Shen et al.'s findings (2016), exposure to early MDS was associated with subsequent lower mathematics, reading, and writing scores in girls and with lower mathematics scores in boys. Our findings of indirect effects via school engagement only in girls suggest that there may be sex-specific mediators of the association between maternal depression and children's cognitive outcomes. There is some prior evidence of sex-specific mediators, where researchers found that children's self-control and their perceptions of maternal warmth only mediated the

association between maternal depression and academic performance in girls (Ng-Knight et al., 2018). Understanding which modifiable factors play a role in the effect of maternal depression on boys' and girls' cognitive outcome can inform the development of interventions that can target sex-specific mediators.

Further research is needed to understand how exposure to MDS in early childhood is associated with the different dimensions of school engagement. One possible route is via negative maternal cognitions, behaviours, and affect (Goodman, 2020). Mothers with depressive symptoms are more likely to use coercive parenting practices and less likely to show sensitivity when engaging with their children (Murray et al., 2006). When asked to help their child solve a mathematics problem, mothers with elevated depressive symptoms used more directions and control, were less emotionally supportive, provided less information to help their child understand the problem, and showed little enthusiasm for problem solving (Murray et al., 2006). Unsupportive parenting also undermines a child's sense of autonomy and leads to decreased motivation and engagement in school (Pomerantz et al., 2012). In this context, children of mothers with depressive symptoms may be less likely to internalize parental values about the importance of academic success and may form less positive relationships with peers and teachers, which act as sources of cognitive-motivational and emotional support (Furrer & Skinner, 2003). However, this is only one potential mechanism. Exposure to MDS tends to co-occur with other early-life family risk factors (e.g., family dysfunction) which may explain the association between MDS and children's later academic outcomes (Ahun & Côté, 2019).

Our findings are in line with previous studies showing an association between exposure to early MDS and increased risk of peer victimization (Côté et al., 2018; Tsypes & Gibb, 2015), with the distinction that our findings were only significant in girls. Although the indirect effect from

MDS to academic performance via peer victimization was not significant in our study, peer victimization was significantly associated with girls' academic performance. Given the bi-directional association between academic performance and mental health (Panayiotou & Humphrey, 2018), it is plausible that part of the association between peer victimization and mental health is explained by poor academic performance, and vice versa. The finding that poor academic performance exacerbates internalizing symptoms in girls (Panayiotou & Humphrey, 2018) supports the hypothesis that girls tend to evaluate themselves more negatively than boys, which can lead to increased distress and internalizing symptoms (Pomerantz et al., 2002). Overall, these and previous data suggest that reducing peer victimization (e.g., through the use of school-based anti-bullying programs; Gaffney, Ttofi, & Farrington, 2019) may help mitigate the negative impact of MDS on child outcomes.

Our findings have important implications for research and practice. First, our research supports the recent US Preventive Services Task Force statement recommending clinicians to screen for depressive symptoms in the perinatal period and refer women to counseling (Curry et al., 2019). This can help improve maternal wellbeing (Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2015). Second, interventions targeting parenting behaviours in families where the mother has experienced depressive symptoms may have a positive influence on school engagement (Goodman & Garber, 2017), given that children's sense of relatedness to their parents (e.g., feeling accepted, special, and important) can help them form harmonious peer relationships and engage in classroom activities (Furrer & Skinner, 2003). However, since this is only one of many potential routes through which MDS influences school engagement, further research is needed to identify other avenues of intervention. Third, testing the impact of bullying prevention programs on the association between MDS and child outcomes can provide information about the putative role of

peer victimization (Côté et al., 2018). However, our results on the associations between MDS, peer victimization, and academic performance were only significant in girls. Further research is needed to improve understanding of the mechanisms of the association between exposure to early MDS and boys' academic performance. One potential avenue of exploration may be through behavioural problems, as boys are more likely to develop insecure attachment than girls and this may foster behavioural problems that may negatively influence academic performance (Grace et al., 2003; Panayiotou & Humphrey, 2018).

This study's strengths include repeated assessments of MDS over five years, thus enabling us to capture the persistence of symptoms over time; detailed multi-informant assessments of peer relations and school engagement across middle childhood (Nakamoto & Schwartz, 2010); and inclusion of a wide range of empirically based covariates in a robust statistical model, thereby providing confidence in the temporality and statistical significance of reported associations.

Nevertheless, we faced some limitations. First, children exposed to MDS were less likely to have outcome data, resulting in a loss of power for detecting associations. However, the detection of significant associations despite this suggests that its impact was limited. Furthermore, we conducted weight-adjusted analyses to address the potential bias resulting from lack of outcome data. Second, MDS were self-reported and not clinically assessed, therefore limiting our capacity to make inference to populations with clinically significant levels of depression. Nonetheless, we used a validated instrument for assessing MDS in population samples, where prevalence of clinically severe mental health problems is relatively low, but prevalence of sub-clinical symptoms is high. Third, even though the associations obtained were generally small, these effects are still relevant for large-scale interventions as small differences at a population level can greatly impact population health (Rose, 1985). Nevertheless, it is possible that we did not detect some associations

in this sample due to the relatively low scores of MDS. Fourth, we were unable to control for baseline school engagement because it was not assessed prior to age 6 in this sample. Finally, we chose to use mean score constructs because we were interested in examining their presentation over a specific period of time (e.g., average level of peer victimization in middle childhood). However, this limited our ability to comment on fluctuations in the constructs from one time point to another.

## Conclusion

The present study adds to the existing literature by showing that exposure to early MDS was negatively associated with girls' academic performance via its associations with cognitive and behavioural school engagement. Further research is needed to replicate these findings and to better elucidate the role of sex differences in the mechanisms of these associations.

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**Table 1**. Table of weight-adjusted mean scores of exposure, mediator, and outcome variables[a]

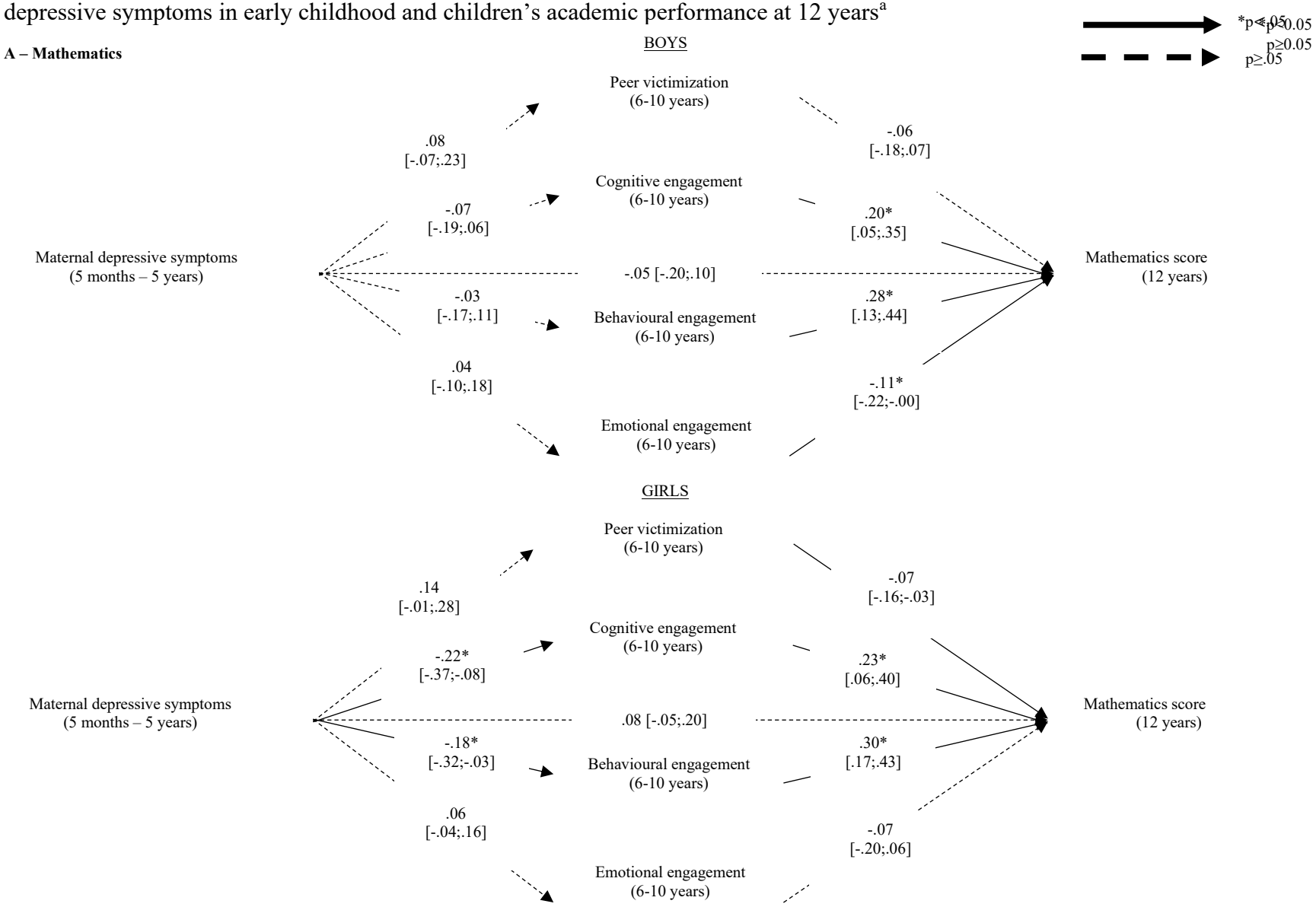
| | Entire sample (n=1173) | | Boys (n=559) | | Girls (n=614) | |
|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* |
| **Exposure** | | | | | | |
| Maternal depressive symptoms | 1.28 | .91 | 1.28 | .87 | 1.28 | .94 |
| **Outcomes** | | | | | | |
| Mathematics scores | 74.36 | 13.54 | 74.23 | 13.18 | 74.46 | 13.88 |
| Reading scores | 71.88 | 14.36 | 68.92* | 13.68 | 74.55* | 14.58 |
| Writing scores | 73.97 | 12.46 | 69.81* | 11.52 | 77.87* | 12.38 |
| **Mediators** | | | | | | |
| Peer Victimization[b] | -.00 | .07 | .02* | .07 | -.02* | .07 |
| Cognitive engagement | 6.84 | 1.25 | 6.49* | 1.26 | 7.17* | 1.18 |
| Behavioural engagement | 8.02 | 1.27 | 7.59* | 1.33 | 8.41* | 1.12 |
| Emotional engagement | 8.09 | 1.46 | 7.82* | 1.41 | 8.33* | 1.47 |

*Significant at $p<.05$

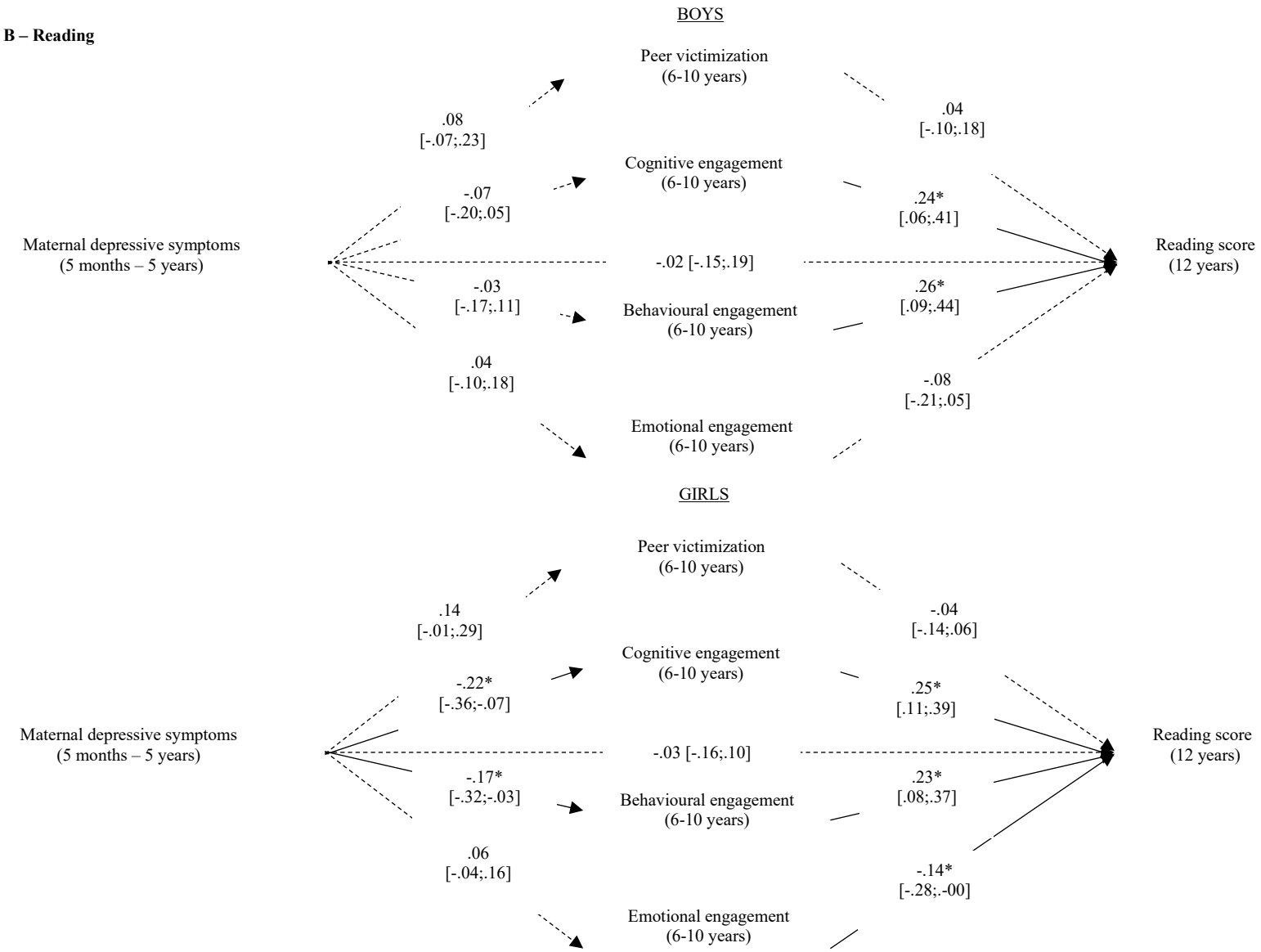
[a] Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2010), ©*Gouvernement du Québec* (Government of Québec), *Institut de la Statistique du Québec* (Québec Institute of Statistics)

[b] Latent variable of peer victimization created using parent, teacher, and child-reported peer victimization from 6-10 years

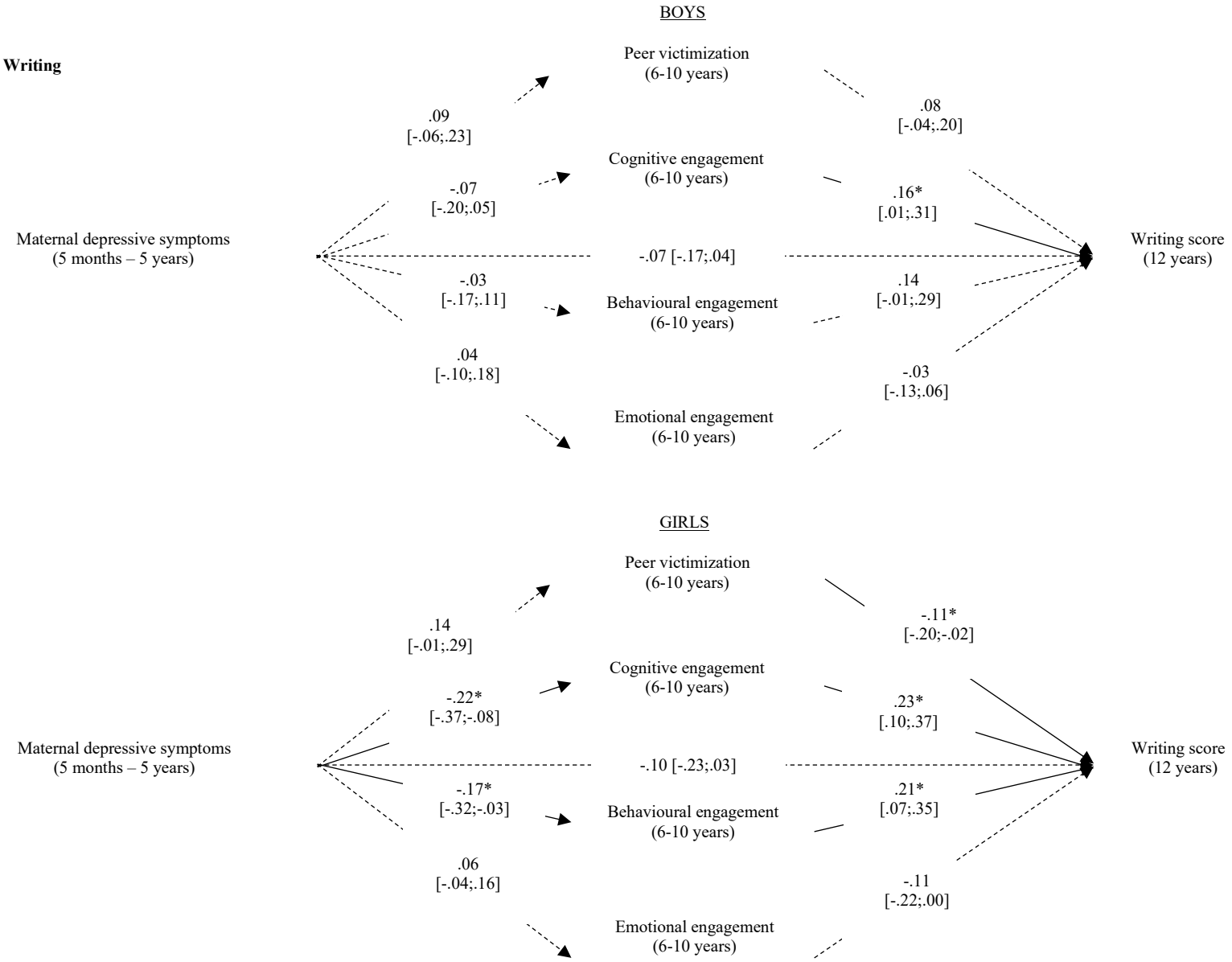
**Figure 1** Mediation models of the adjusted associations (standardized [95% confidence intervals]) between exposure to maternal depressive symptoms in early childhood and children's academic performance at 12 years[a]



**B – Reading**


BOYS
Peer victimization (6-10 years)
Cognitive engagement (6-10 years)
Behavioural engagement (6-10 years)
Emotional engagement (6-10 years)
Maternal depressive symptoms (5 months – 5 years)
.08 [-.07;.23]
-.07 [-.20;.05]
-.03 [-.17;.11]
.04 [-.10;.18]
-.02 [-.15;.19]
.04 [-.10;.18]
.24* [.06;.41]
.26* [.09;.44]
-.08 [-.21;.05]
Reading score (12 years)
GIRLS
Peer victimization (6-10 years)
Cognitive engagement (6-10 years)
Behavioural engagement (6-10 years)
Emotional engagement (6-10 years)
Maternal depressive symptoms (5 months – 5 years)
.14 [-.01;.29]
-.22* [-.36;-.07]
-.17* [-.32;-.03]
.06 [-.04;.16]
-.03 [-.16;.10]
-.04 [-.14;.06]
.25* [.11;.39]
.23* [.08;.37]
-.14* [-.28;.-00]
Reading score (12 years)

**C – Writing**




[a] Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2010), ©*Gouvernement du Québec* (Government of Québec), *Institut de la Statistique du Québec* (Québec Institute of Statistics)

**Table 2.** Indirect and direct effects (standardized [95% confidence intervals]) of maternal depressive symptoms on children's academic performance adjusted for covariates[a,b]

| | Boys | Girls |
|---|---|---|
| | Mathematics | |
| Total effect | -.08 [-.25;.09] | -.04 [-.17;.09] |
| Direct effect | -.05 [-.20;.10] | .08 [-.05;.20] |
| Indirect effect | | |
| via Peer victimization | .00 [-.01;.03] | -.01 [-.03;.00] |
| via Cognitive engagement | -.01 [-.05;.01] | -.05* [-.11;-.01] |
| via Behavioural engagement | -.01 [-.05;.03] | -.05* [-.11;-.01] |
| via Emotional engagement | -.00 [-.03;.01] | -.00 [-.02;.01] |
| | Reading | |
| Total effect | -.01 [-.18;.17] | -.14 [-.28;.01] |
| Direct effect | .02 [-.15;.19] | -.03 [-.16;.10] |
| Indirect effect | | |
| via Peer victimization | .00 [-.01;.02] | -.01 [-.03;.01] |
| via Cognitive engagement | -.02 [-.06;.01] | -.05* [-.11;-.01] |
| via Behavioural engagement | -.01 [-.05;.03] | -.04* [-.08;-.00] |
| via Emotional engagement | -.00 [-.02;.01] | -.01 [-.03;.01] |
| | Writing | |
| Total effect | -.08 [-.19;.04] | -.21* [-.36;-.06] |
| Direct effect | -.07 [-.17;.04] | -.10 [-.23;.03] |
| Indirect effect | | |
| via Peer victimization | .01 [-.03;.01] | -.02 [-.04;.00] |
| via Cognitive engagement | -.01 [-.04;.01] | -.05* [-.10;-.01] |
| via Behavioural engagement | -.00 [-.03;.02] | -.04* [-.08;-.00] |
| via Emotional engagement | -.00 [-.01;.01] | -.01 [-.02;.00] |

*p<05

[a] Socioeconomic status, mother-child interactions (stimulation and verbalization), family functioning, maternal age, anxiety, antisocial behaviour, and verbal IQ, and children's school readiness, depression and anxiety symptoms, hyperactivity, inattention, physical aggression, and peer victimization

[b] Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2010), ©*Gouvernement du Québec* (Government of Québec), *Institut de la Statistique du Québec* (Québec Institute of Statistics)

**Supplementary Material for *Article 2***

**Supplement 1** – EXPOSURE VARIABLE: Maternal depressive symptoms

Items assessing maternal depressive symptoms over the past 7 days (5 months – 5 years): short version of the Center for Epidemiologic Studies Depression scale (CES-D) – self-reported

The frequency of each symptom was rated on a scale ranging from 0-3: 0 – 'Rarely or none of the time (< 1 day)'; 1 – 'Some or a little of the time (1-2 days)'; 2 – 'Occasionally or a moderate amount of time (3-4 days)'; 3 – 'Most or all of the time (5-7 days)'.

1. I did not feel like eating: my appetite was poor
2. I felt that I could not shake off the blues even with help from my family or friends
3. I had trouble keeping my mind on what I was doing
4. I felt depressed
5. I felt that everything I did was an effort
6. I felt hopeful about the future
7. My sleep was restless
8. I was happy
9. I felt lonely
10. I enjoyed life
11. I had crying spells
12. I felt that people disliked me

Note. Total scores were converted to scores varying between 0 and 10. Mean scores over the 4 assessment periods were used in the analyses.

**Supplement 2** – OUTCOME VARIABLES: Offspring academic outcomes (math, reading, writing)

Every Québec student must write government examinations (created by the Ministry of Higher Education and Teaching) at the end of grade 6 (age 12 years) to be admissible to high school. The results of the tests were made accessible and corrected by the Québec Institute of Statistics. Using the terms and guidelines established by the Ministry, the Québec Institute of Statistics' centralized correction was supervised by 4 people and conducted by a team consisting mostly of retired teachers or new teaching graduates. Inter-judge reliability assessments were also conducted (Jalbert, 2011; Pairon 2011; Deschenes & Roberge, 2011). Reading examination corrections relied on 3 evaluation criteria: (1) extraction of pertinent explicit and implicit information (75% of grade), (2) text interpretation (8% of grade), and (3) pertinent reactions to literary and informational texts (17% of grade). Each response was judged as being satisfactory, acceptable, or unsatisfactory (3, 2, or 0 points, respectively) and summed to a total of 36 points. Writing examination correction relied on 5 evaluation criteria: (1) relevance and adequacy of ideas, (2) appropriate organization of the text, (3) syntax and punctuation, (4) vocabulary, and (5) spelling. Each criterion was rated on an A-to-E scale according to the Ministry of Education, Recreation and Sports (MERS) evaluation grid, where A = 20 points, B = 16 points, C = 12 points, D = 8 points, and E = 4 points. An overall score of 100 can then be calculated by adding the points obtained in each test. Finally, mathematic examination correction relied on 2 skills. The mathematic problem-solving questions (30%) relied on 3 evaluation criteria: (1) task comprehension, (2) mobilizing concepts and processes, and (3) solution explanation. The mathematical concept and process reasoning (70%) depended on 3 evaluation criteria: (1) analyze and make informed choices, (2) apply solution, and (3) justify. Each evaluation criterion was rated on an A-to-E scale outlined in the Ministry of Education's evaluation grid. The grades in each academic performance examination ranged as follows: reading comprehension (6– 100), writing (32–100), and mathematics (22–100). The scores are percentages.

References

Deschesnes, J., Roberge, A. Rapport de la session de correction de l'épreuve obligatoire de mathématique. L'Esperance et ses secrets. In : *Rapport présenté* à *l'équipe de l'ÉLDEQ de l'Institut de la statistique du Québec, Montréal;* July 26 2011; Québec, Canada; unpublished document

Jalbert, P. Correction de l'épreuve obligatoire d'écriture ministérielle 2010. Lecture au pilote maritime Gary Provencher. Report of l'ÉLDEQ à ISQ; July 4 2011; Montréal, Canada; unpublished document

Pairon, S. Correction du volet lecture de l'épreuve ministérielle. En amont et en aval. Report of l'ÉLDEQ à l'ISQ; June 21 2011; Montréal, Canada; unpublished document

**Supplement 3** – MEDIATOR VARIABLES: Peer victimization, cognitive, behavioural, and emotional school engagement

Items assessing peer victimization (6 – 10 years) – child-reported
The frequency of each perceived victimization behaviour was rated on a scale ranging from never (coded as 0) to 'Once or twice' (coded as 1) to 'more often' (coded as 2).
"Has it ever occurred that a child from your school…
1. Has called you names or said mean things to you?
2. Has pushed, hit, or kicked you?
3. Has laughed at you?

Items assessing peer victimization over the last 12 months (6 years) – mother and father-reported
The frequency of each perceived victimization behaviour was rated on a scale ranging from 1-3: 1 – 'Never or not true'; 2 – 'Sometimes or somewhat true'; 3 – 'Often or very true'.
"How often would you say that [INSERT NAME OF TARGET CHILD] …
1. Has been called names by other children?
2. Was hit or pushed by other children?
3. Has been laughed at by other children

Items assessing peer victimization over the last 6 months (6 – 10 years) – teacher-reported
The frequency of each perceived victimization behaviour was rated on a scale ranging from 1-3: 1 – 'Never or not true'; 2 – 'Sometimes or somewhat true'; 3 – 'Often or very true'. "In your opinion, [INSERT NAME OF TARGET CHILD] …
1. Has been called names by other children?
2. Was hit or pushed by other children?
3. Has been laughed at by other children

Items assessing cognitive school engagement over the past 12 months (6 years) – teacher-reported
The frequency of each behaviour was rated on a scale ranging from 1-5: 1 – 'Never'; 2 – 'Rarely'; 3 – 'Sometimes'; 4 – 'Often'; 5 – 'Always'.
1. Is curious about the world
2. Is willing to play with a new toy
3. Is willing to play a new game
4. Shows a keen interest in playing with or reading a new book

Items assessing cognitive school engagement over the past 12 months (7 – 10 years) – teacher-reported
The frequency of each behaviour was rated on a scale ranging from 1-5: 1 – 'Never'; 2 – 'Rarely'; 3 – 'Sometimes'; 4 – 'Often'; 5 – 'Always'.
1. Challenges the teacher in a positive way
2. Shows creativity
3. Is capable of resolving problems
4. Puts a lot of effort into work

5. Participates in class
6. Asks questions when he/she does not understand

Items assessing behavioural school engagement over the past 12 months (6 – 10 years) – teacher-reported

The frequency of each behaviour was rated on a scale ranging from 1-5: 1 – 'Never'; 2 – 'Rarely'; 3 – 'Sometimes'; 4 – 'Often'; 5 – 'Always'.

1. Listens attentively
2. Follows instructions
3. Finishes assignments on time
4. Works autonomously
5. Works cleanly and carefully

**The following items were only included in the attitude towards learning score at age 6 years**

6. Is capable of resolving daily problems on his/her own
7. Is capable of following instructions with only one step
8. Is capable of following class routines without being reminded
9. Is capable of adapting to changes in the schedule

Items assessing emotional school engagement over the past 12 months (6 – 10 years) – child-reported

Responses to each item were rated on a scale ranging from 1-5: 1-'Strongly disagree'; 2-'Disagree'; 3-'Uncertain'; 4-'Agree'; 5-'Strongly agree'.

1. I am proud to be studying at this school
2. I am happy to be studying at this school
3. I feel safe at my school
4. Most mornings, I feel like going to school
5. I like my school

**Table S1**. Sample characteristics[a]

| | Analysis sample n=1173[b] | Range | Child's age at assessment |
|---|---|---|---|
| Participant | | | |
| *Boys, %* | 47.7 | 0/1 | 5 months |
| *White, %* | 84.0 | 0/1 | 5 months |
| *Lollipop Test Score, median (IQR)* | 60.00 (7.0) | 11-69 | 5 years |
| *Aggression, median (IQR)* | .83 (1.7) | 0-19 | 1.5 years |
| *Depressive and anxiety symptoms, median (IQR)* | .00 (1.0) | 0-10 | 1.5 years |
| *Hyperactivity, mean (SD)* | 3.46 (2.1) | 0-10 | 1.5 years |
| *Inattention, median (IQR)* | 1.67 (3.3) | 0-10 | 1.5 years |
| *Peer victimization, median (IQR)* | 1.11 (1.4) | 0-10 | 3.5-5 years |
| Mother | | | |
| *≤ 21 years at child's birth, %* | 5.5 | 0/1 | 5 months |
| *Depressive symptoms, median (IQR)* | 1.06 (1.3) | 0-10 | 5 months-5 years |
| *Anxiety, median (IQR)* | 0.88 (1.4) | 0-8 | 4 years |
| *Youth antisocial behaviour, median (IQR)* | 1.00 (1.0) | 0-5 | 5 months |
| *IQ, median (IQR)* | 8.57 (0.7) | 4-10 | 5 months |
| *Stimulation, mean (SD)* | 4.83 (2.4) | 0-10 | 5 months |
| *Verbalization, mean (SD)* | 6.76 (1.6) | 0-10 | 5 months |
| Family | | | |
| *Socioeconomic status, mean (SD)* | .13 (1.0) | -3-3 | 5 months |
| *Family dysfunction, median (IQR)* | 1.39 (1.9) | 0-10 | 5 months |
| *Single-parent family, %* | 5.6 | 0/1 | 5 months |

[a] Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2010), ©*Gouvernement du Québec*, *Institut de la Statistique du Québec*

[b] Means and standard deviations are reported for normally distributed continuous variables and medians and inter-quartile ranges are reported for non-normally distributed continuous variables.

**Table S2**. Weight-adjusted Pearson correlation matrix for study variables, n=1173[a]

**A. Boys, n=559**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| 1. Maternal depressive symptoms (5mo – 5y) | | | | | | | | |
| ***Offspring outcomes (12y)*** | | | | | | | | |
| 2. Math | -.12* | | | | | | | |
| 3. Reading | -.03 | .61* | | | | | | |
| 4. Writing | -.08 | .45* | .48* | | | | | |
| ***Potential mediators (6-10y)*** | | | | | | | | |
| 5. Peer victimization | .08 | -.16* | -.07 | -.03 | | | | |
| 6. Cognitive engagement | -.12* | .43* | .42* | .41* | -.21* | | | |
| 7. Behavioural engagement | -.12* | .48* | .41* | .36* | -.32* | .74* | | |
| 8. Emotional engagement | -.02 | -.02 | .03 | .08 | -.12 | .16* | .22* | |
| ***Covariates (5mo-5y)*** | | | | | | | | |
| 9. Lollipop test score | -.02 | .23* | .11* | .35* | -.04 | .35* | .32* | .05 |
| 1. Mother <21 at birth | -.03[b] | -.31[b]* | -.32[b]* | -.34[b]* | -.10[b] | -.22[b]* | -.19[b]* | .22[b]* |
| 11. Maternal anxiety | .40* | -.03 | .04 | .05 | -.02 | -.00 | -.04 | -.05 |
| 12. Maternal youth antisocial behaviour | .16* | -.01 | -.04 | -.14* | -.04 | -.16* | -.15* | -.08 |
| 13. Maternal IQ | -.05 | .07 | .07 | .06 | -.10 | .10* | .03 | -.04 |
| 14. Mother-child interactions (stimulation) | -.19* | .13* | .15* | .07 | .01 | .12* | .14* | .03 |
| 15. Mother-child interactions (verbalization) | -.13* | .02 | .08 | .09* | -.03 | .11* | .07 | .13* |
| 16. Family socioeconomic status | -.23* | .28* | .24* | .44* | .06 | .25* | .25* | .13* |
| 17. Family dysfunction | .37* | .01 | -.03 | .05 | .07 | -.04 | -.04 | -.10* |
| 18. Single-parent family | .24[b]* | -.31[b]* | -.29[b]* | -.28[b]* | -.04[b] | -.23[b]* | -.29[b]* | .11[b] |
| 19. Aggression | .14* | -.02 | .05 | -.02 | -.01 | -.10* | -.08 | -.00 |
| 2. DAS[c] | .20* | .03 | .03 | .10* | -.06 | .02 | -.00 | .01 |
| 21. Hyperactivity | .19* | .00 | -.01 | -.07 | -.03 | -.06 | -.07 | .07 |
| 22. Inattention | .14* | .03 | -.07 | -.08 | -.05 | -.03 | -.03 | -.02 |
| 23. Peer victimization | .24* | -.05 | -.01 | .01 | .15* | -.10* | -.12* | .01 |

**B. Girls, n=614**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| 1. Maternal depressive symptoms (5mo – 5y) | | | | | | | | |
| ***Offspring outcomes (12y)*** | | | | | | | | |
| 2. Math | -.11* | | | | | | | |
| 3. Reading | -.13* | .58* | | | | | | |
| 4. Writing | -.18* | .57* | .60* | | | | | |
| ***Potential mediators (6-10y)*** | | | | | | | | |
| 5. Peer victimization | .10* | -.21* | -.16* | -.26* | | | | |
| 6. Cognitive engagement | -.25* | .49* | .44* | .48* | -.19* | | | |
| 7. Behavioural engagement | -.17* | .52* | .45* | .49* | -.29* | .74* | | |
| 8. Emotional engagement | .06 | .00 | -.11* | .05 | -.07 | .14* | .04 | |
| ***Covariates (5mo-5y)*** | | | | | | | | |
| 9. Lollipop test score | .10* | .05 | .01 | .25* | -.09 | .17* | .10* | .58* |
| 1. Mother <21y at birth | .21[b]* | -.19[b]* | -.16[b]* | -.13[b] | .05[b] | -.16[b]* | -.19[b]* | .06[b] |
| 11. Maternal anxiety | .45* | -.07 | -.09* | -.14* | .03 | -.15* | -.11* | -.11* |
| 12. Maternal youth antisocial behaviour | .16* | -.09* | -.04 | -.04 | .02 | -.09* | -.12* | .09* |
| 13. Maternal IQ | -.12* | .14* | .25* | .21* | -.06 | .14* | .06 | .05 |
| 14. Mother-child interactions (stimulation) | -.04 | .09* | .12* | .17* | -.02 | .08 | .11* | .06 |
| 15. Mother-child interactions (verbalization) | -.01 | .06 | .13* | .14* | .05 | .09* | .07 | .11* |
| 16. Family socioeconomic status | -.22* | .33* | .33* | .37* | -.11* | .31* | .25* | .08 |
| 17. Family dysfunction | .30* | -.12* | -.01 | -.08 | .02 | -.07 | -.02 | -.15* |
| 18. Single-parent family | -.32[b]* | -.26[b]* | -.27[b]* | -.22[b]* | -.03[b] | -.18[b]* | -.14[b] | .08[b] |
| 19. Aggression | -.02 | -.06 | -.05 | -.11* | .05 | -.01 | -.02 | .05 |
| 2. DAS[c] | .27* | .07 | .05 | .08 | -.17* | -.02 | .09* | -.10* |
| 21. Hyperactivity | .12* | .05 | .08 | -.05 | -.00 | .02 | .04 | -.14* |
| 22. Inattention | .07 | .08 | .06 | .06 | -.04 | -.01 | .06 | -.21* |
| 23. Peer victimization | .21* | -.16* | -.09* | -.09* | -.13* | -.21* | -.13* | -.05 |

[a] Polyserial correlations. Note that weights cannot be applied to polyserial correlations in SAS 9.4, therefore these correlations are from the unweighted sample

[b] Depressive and anxiety symptoms

[c] Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2010), ©*Gouvernement du Québec*, *Institut de la Statistique du Québec*. *Significant at p<.05

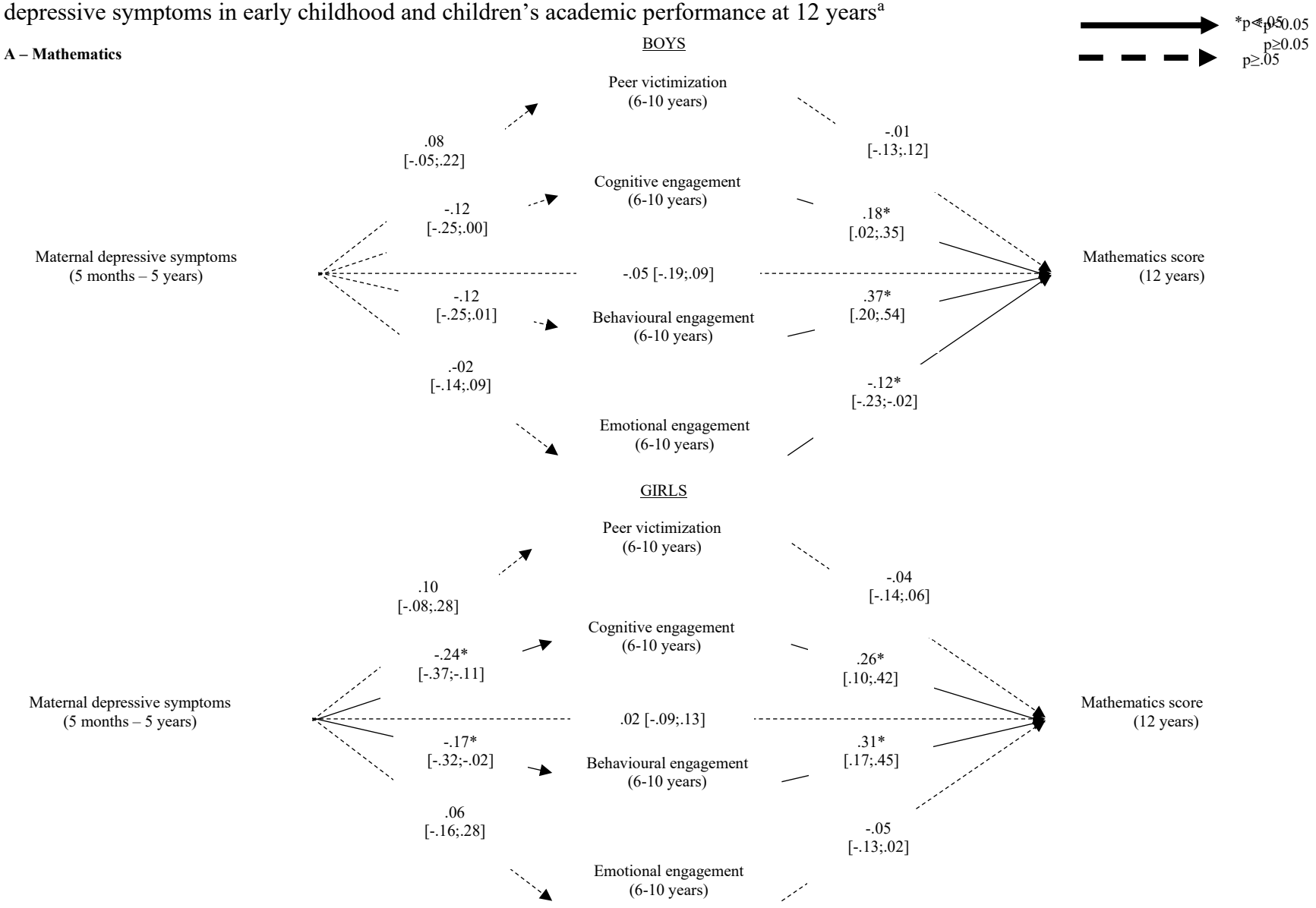
**Table S3**. Comparison of baseline sample characteristics between analysis sample (n=1173) and those without government exam scores (n=947)[a]

| | Analysis sample n=1173 | Participants without exam data n=947 | p-value |
|---|---|---|---|
| Participant | | | |
| *Boys, %* | 47.7 | 55.0 | .001 |
| *Lollipop Test Score, median (IQR)* | 60.00 (7.0) | 57.00 (11.5) | <.0001 |
| *Aggression, median (IQR)* | 0.83 (1.7) | 0.83 (1.7) | .755 |
| *Depressive and anxiety symptoms, median (IQR)* | 0.00 (1.0) | 0.00 (1.0) | .089 |
| *Hyperactivity, mean (SD)* | 3.46 (2.1) | 3.50 (2.2) | .684 |
| *Inattention, median (IQR)* | 1.67 (3.3) | 1.67 (3.3) | .376 |
| *Peer victimization, median (IQR)* | 1.11 (1.4) | 1.11 (1.4) | .112 |
| Mother | | | |
| *<21 years at child's birth, %* | 5.5 | 6.0 | .575 |
| *Depressive symptoms, median (IQR)* | 1.06 (1.3) | 1.16 (1.5) | .005 |
| *Anxiety, median (IQR)* | 0.88 (1.4) | 0.88 (1.6) | .747 |
| *Youth antisocial behaviour, median (IQR)* | 1.00 (1.0) | 1.00 (1.0) | .290 |
| *IQ, median (IQR)* | 8.57 (0.7) | 7.86 (1.4) | <.0001 |
| *Stimulation, mean (SD)* | 4.83 (2.4) | 4.59 (2.3) | .032 |
| *Verbalization, mean (SD)* | 6.76 (1.6) | 6.54 (1.7) | .004 |
| Family | | | |
| *Socioeconomic status, mean (SD)* | 0.13 (1.0) | -0.16 (1.0) | <.0001 |
| *Family dysfunction, median (IQR)* | 1.39 (1.9) | 1.39 (2.2) | .025 |
| *Single-parent family, %* | 5.6 | 11.2 | <.0001 |

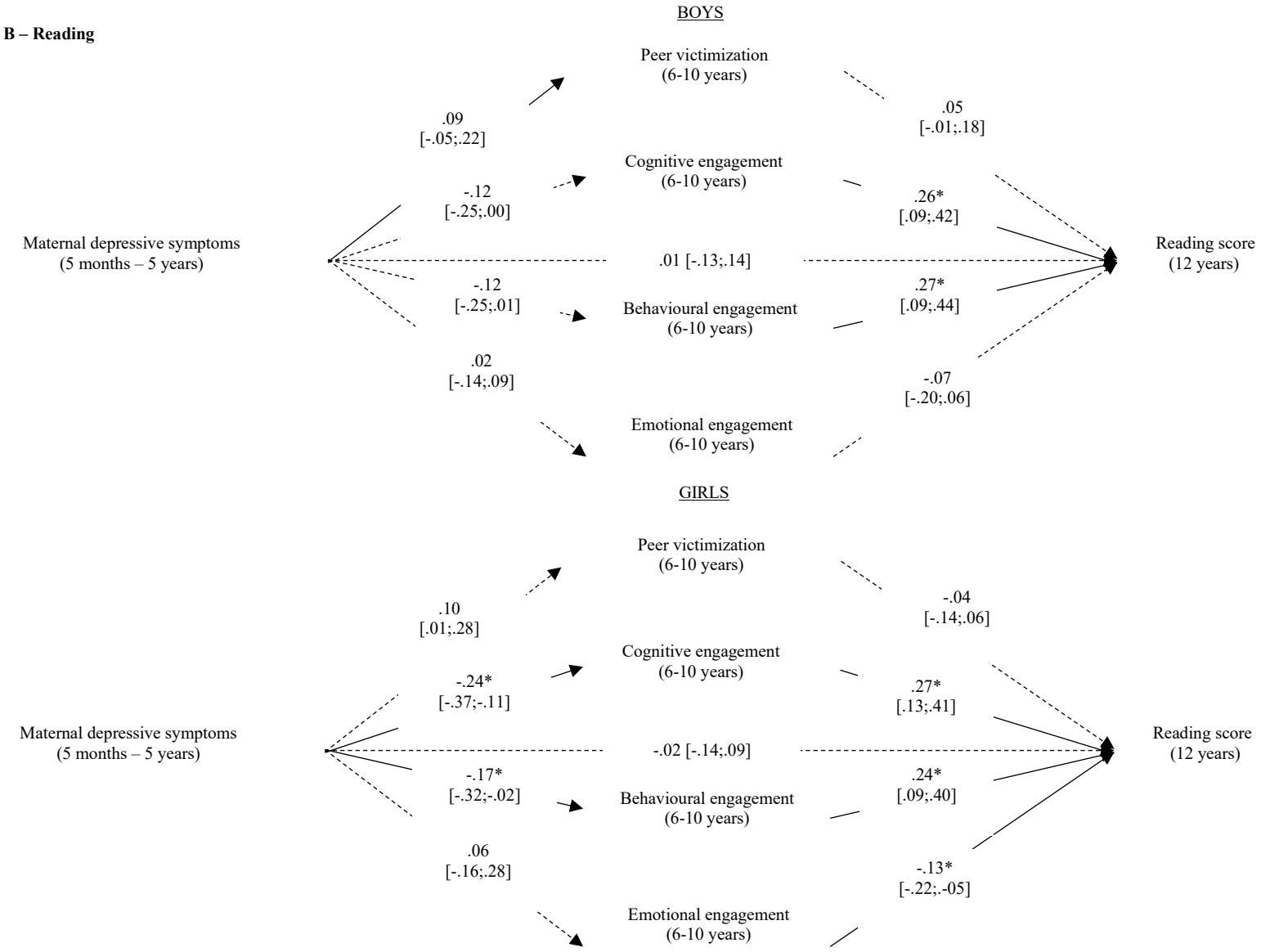
Categorical variables were compared using chi-square tests and t-tests were used for continuous variables.

[a] Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2010), ©*Gouvernement du Québec*, *Institut de la Statistique du Québec*

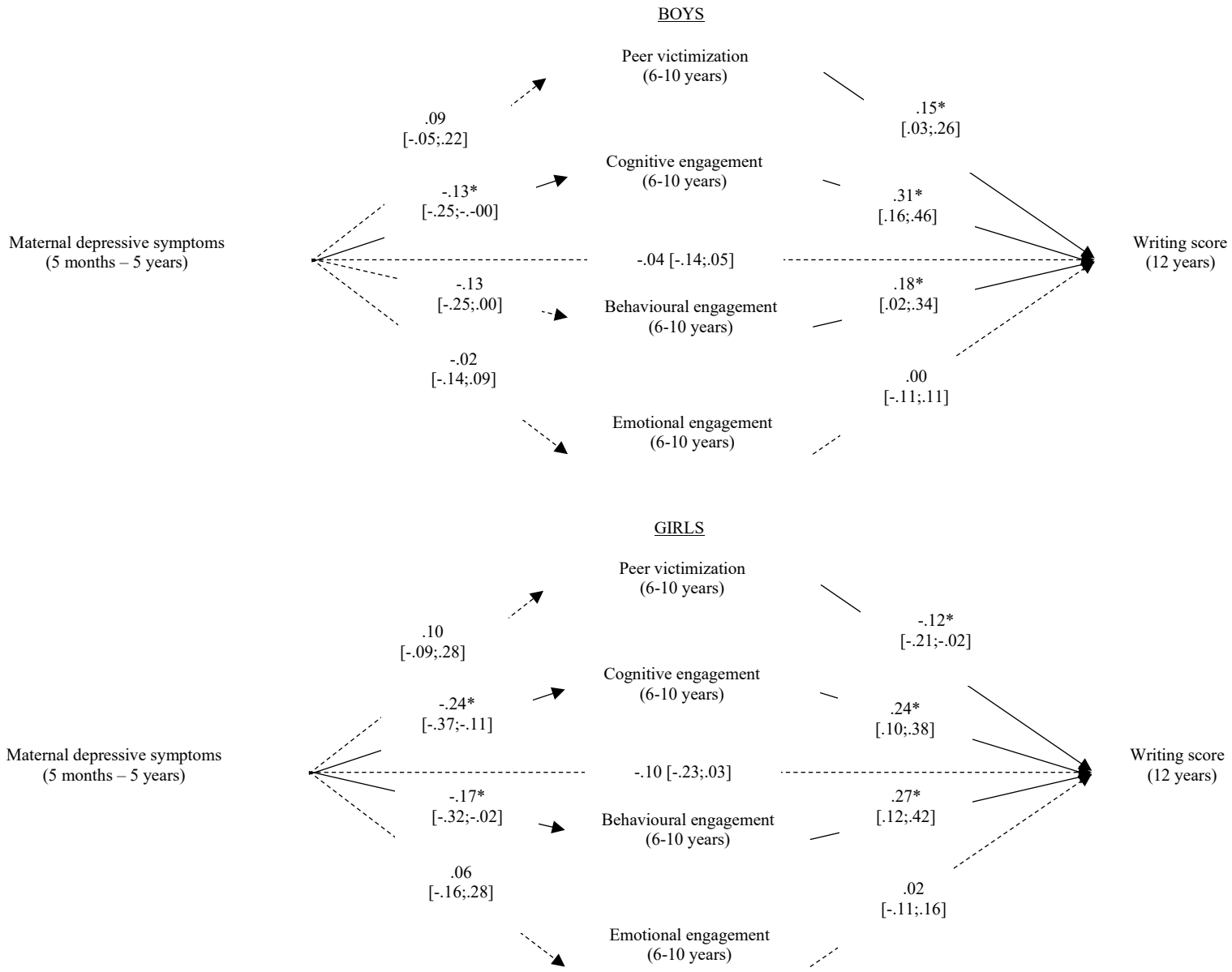
**Figure S1** Mediation models of the unadjusted associations (standardized [95% confidence intervals]) between exposure to maternal depressive symptoms in early childhood and children's academic performance at 12 years[a]



**B – Reading**


BOYS
Peer victimization (6-10 years)
Cognitive engagement (6-10 years)
Behavioural engagement (6-10 years)
Emotional engagement (6-10 years)
Maternal depressive symptoms (5 months – 5 years)
.09 [-.05;.22]
-.12 [-.25;.00]
-.12 [-.25;.01]
.02 [-.14;.09]
.01 [-.13;.14]
.05 [-.01;.18]
.26* [.09;.42]
.27* [.09;.44]
-.07 [-.20;.06]
Reading score (12 years)
GIRLS
Peer victimization (6-10 years)
Cognitive engagement (6-10 years)
Behavioural engagement (6-10 years)
Emotional engagement (6-10 years)
Maternal depressive symptoms (5 months – 5 years)
.10 [.01;.28]
-.24* [-.37;-.11]
-.17* [-.32;-.02]
.06 [-.16;.28]
-.02 [-.14;.09]
-.04 [-.14;.06]
.27* [.13;.41]
.24* [.09;.40]
-.13* [-.22;-.05]
Reading score (12 years)

**C – Writing**




[a] Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2010), ©*Gouvernement du Québec* (Government of Québec), *Institut de la Statistique du Québec* (Québec Institute of Statistics)

**Table S4.** Unadjusted indirect and direct effects (standardized [95% confidence intervals]) of maternal depressive symptoms on children's academic performance[b]

| | Boys | Girls |
|---|---|---|
| | Mathematics | |
| Total effect | -.11 [-.27;.05] | -.10 [-.22;.01] |
| Direct effect | -.05 [-.18;.09] | .02 [-.08;.14] |
| Indirect effect | | |
| via Peer victimization | -.00 [-.03;.04] | -.00 [-.02;.01] |
| via Cognitive engagement | -.02 [-.06;.00] | -.06* [-.12;-.02] |
| via Behavioural engagement | -.05 [-.11;.00] | -.05* [-.11;-.01] |
| via Emotional engagement | .00 [-.01;.02] | -.00 [-.02;.01] |
| | Reading | |
| Total effect | -.05 [-.20;.10] | -.14* [-.26;-.02] |
| Direct effect | .01 [-.13;.14] | -.01 [-.13;.10] |
| Indirect effect | | |
| via Peer victimization | .00 [-.04;.04] | -.00 [-.02;.01] |
| via Cognitive engagement | -.03 [-.08;.00] | -.06* [-.12;-.02] |
| via Behavioural engagement | -.03 [-.08;.00] | -.04* [-.09;-.00] |
| via Emotional engagement | .00 [-.01;.02] | -.01 [-.04;.02] |
| | Writing | |
| Total effect | -.09 [-.21;.03] | -.19* [-.34;-.04] |
| Direct effect | -.01 [-.16;.04] | -.01 [-.03;.01] |
| Indirect effect | | |
| via Peer victimization | .01 [-.01;.04] | -.01 [-.04;.01] |
| via Cognitive engagement | -.04* [-.09;.-00] | -.06* [-.11;-.02] |
| via Behavioural engagement | -.02 [-.06;.00] | -.05* [-.10;-.00] |
| via Emotional engagement | .00 [-.01;.01] | -.00 [-.02;.03] |

*p<.05

[b]Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2010), ©*Gouvernement du Québec* (Government of Québec), *Institut de la Statistique du Québec* (Québec Institute of Statistics)

## 4.3 *Article 3*

### Maternal depressive symptoms and children's cognitive school readiness: The role of gene-environment mechanisms

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## Abstract

**Background:** Maternal depressive symptoms are a robust risk factor for poor cognitive outcomes in children, yet the role of gene-environment interplay in this association is not well understood. The objective of this study was to evaluate gene-environment interaction in the association between maternal depressive symptoms and children's cognitive school readiness.

**Methods:** Data come from a population-based birth cohort of 538 twin pairs. Maternal depressive symptoms were self-reported (Centre for Epidemiologic Studies Depression Scale) when children were aged 6 and 18 months (a mean score was used). Children's cognitive school readiness was assessed using the Lollipop test when children were 5 years. Analyses were conducted with structural equation modelling.

**Results**: Maternal depressive symptoms were correlated with children's cognitive school readiness ($r$ = –0.10). Shared environmental factors explained most of the variance in children's cognitive school readiness (52%). The remaining variance was accounted for by genetic (30%) and nonshared environmental factors (18%). As the level of maternal depressive symptoms increased, the relative contribution of nonshared environmental factors to the variance in children's cognitive school readiness increased (0.14 [95% CI: 0.04 to 0.24]) whereas the relative contribution of genetic factors decreased (–0.28 [–0.64 to 0.08]).

**Conclusions**: In contexts of elevated maternal depressive symptoms, environmental – and potentially modifiable – factors may be especially important for shaping children's cognitive outcomes. This suggests that interventions to improve the early childhood environment of children exposed to maternal depressive symptoms may improve their cognitive outcomes.



**Keywords**: maternal depressive symptoms; cognitive development; gene-environment interaction

## Introduction

Evidence suggests that children's cognitive development is influenced both by genetic and environmental factors, in an additive or interactive fashion (Tucker-Drob, Briley, & Harden, 2013). Maternal depressive symptoms are one aspect of the family environment negatively associated with children's cognitive development in early childhood, with numerous studies showing a small yet consistent direct association between elevated maternal depressive symptoms and lower levels of children's cognitive outcomes (see (Ahun & Côté, 2019; Goodman, Simon, Shamblaw, & Kim, 2020; Liu et al., 2017; Power, van IJzendoorn, Lewis, Chen, & Galbally, 2021; Rogers et al., 2020) for reviews). However, these studies did not account for the contribution of genetic factors to children's cognitive development. It is also unclear whether maternal depressive symptoms interact with genetic factors in predicting children's cognitive outcomes. The aim of this study was to examine such potential gene-environment interaction in the association between maternal depressive symptoms and children's cognitive outcomes.

This study focused on cognitive school readiness as a measure of cognitive development. Cognitive school readiness involves the cognitive and language skills that reflect a child's ability to function successfully in school contexts and is a strong predictor of academic performance (Carpentier et al., 2021; Davies, Janus, Duku, & Gaskin, 2016; La Paro & Pianta, 2000). Genetically informed studies on cognitive school readiness in early childhood have shown that genetic factors explain 0-19% of its variance while environmental factors – especially those shared between family members – explain 34-76% (Lemelin, 2007; Rhemtulla & Tucker-Drob, 2012; Tucker-Drob & Bates, 2016). In other words, the variance in children's cognitive school readiness is largely due to shared environmental contributions that make twins similar to each other, as opposed to nonshared environments that are unique to each twin (Turkheimer & Waldron, 2000).

However, these estimates do not reflect potential interactive contributions of environmental and genetic factors on cognitive school readiness.

To date, genetically informed studies have mostly focused on socioeconomic status as an aspect of the shared environment that may interact with genetic contributions to children's cognitive school readiness. Such a gene-environment interaction would be indicated, for instance, when the expression of a genetic disposition for a given trait varies depending on environmental conditions (Price & Jaffee, 2008). In a sample of 4-year-olds, Rhemtulla and Tucker-Drob (2012) found that genetic factors explained a smaller proportion of variance in the cognitive school readiness of children from low socioeconomic status families compared to children in high socioeconomic status families. The finding that genetic contributions to cognitive school readiness may be suppressed by adverse environments has also been replicated with other cognitive outcomes such as intelligence and academic achievement (Tucker-Drob & Bates, 2016; Tucker-Drob et al., 2013).

The interaction between socioeconomic status and children's genetic dispositions to the development of cognitive school readiness may be explained by Bronfenbrenner and Ceci's (1994) bioecological model. This model proposes that high-quality reciprocal interactions between children and individuals in their immediate environments (referred to as proximal processes) are necessary for the actualization of their individual genetic potentials for healthy development (Bronfenbrenner & Ceci, 1994; Rhemtulla & Tucker-Drob, 2012). Environments that do not promote the necessary cognitive stimulation may override genetic contributions to cognitive school readiness and thus hamper optimal cognitive development even for children with high genetic endowment. This suppression process of gene-environment interaction was shown in the aforementioned studies, as genetic factors explained less of the variance in children's cognitive

school readiness in environments of low socioeconomic status (Rhemtulla & Tucker-Drob, 2012; Tucker-Drob & Bates, 2016; Tucker-Drob et al., 2013).

It is unknown, however, whether other aspects of children's shared environment – such as maternal depressive symptoms – interact with genetic contributions to children's cognitive outcomes in a similar way. Studies show that mothers experiencing depressive symptoms are less likely to use complex language when communicating with their child and to engage in cognitively stimulating behaviours in mother-child interactions (Dix & Meunier, 2009; Goodman et al., 2020). Furthermore, there is evidence that these maternal behaviours explain part of the association between maternal depressive symptoms and children's cognitive outcomes (Ahun & Côté, 2019; Goodman et al., 2020). It is therefore plausible that – as outlined in the bioecological model – genetic contributions to children's cognitive school readiness would decrease in contexts of elevated maternal depressive symptoms. The aim of this study was to examine whether such a suppression process of gene-environment interaction is observed.

## Methods

### *Participants*

Data were drawn from the Québec Newborn Twin Study, an ongoing prospective longitudinal follow-up of a birth cohort of twins born between 1995 and 1998 in the greater Montréal area (Boivin et al., 2013; Boivin et al., 2019). The initial sample included 662 twin pairs who were assessed at age 6 months and followed-up on an annual basis up to age 6 and every 1-2 years thereafter. Parents' consent was obtained before each data collection. Zygosity was initially assessed via questionnaire (Hill Goldsmith, 1991) and ascertained with a 96% correspondence through genotyping (Forget-Dubois et al., 2003). The majority of families were Caucasian (89%)

and the remaining 11% were of African (2%), Asian (3%), Native American (0.2%), and other (5.8%; including Asian, Arab, Latinx, and bi/multi-ethnic) ethnic origins. The ethics boards of the St-Justine Hospital Research Centre approved all procedures. The average attrition rate for this cohort in the first decade of data collection was approximately 3% per year. Participants were included in the study sample if they had data on maternal depressive symptoms when children were 6 or 18 months old and data on children's cognitive school readiness at age 5 years. The study sample after attrition was 538 twin pairs (81% retention), which is comparable to that of other longitudinal birth cohorts (Fraser et al., 2013; Orri et al., 2020). Participants in the analysis sample did not differ significantly from those excluded (n = 124) on any demographic criteria (i.e., maternal education, family income, single-parent family, ethnicity, and child's sex).

***Measures***

*Maternal depressive symptoms* were self-reported when children were 6 and 18 months old using a short (12-item) version of the Centre for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). The short CES-D is a reliable and psychometrically sound measure of non-clinical depression (Poulin, Hand, & Boudreau, 2005), assessing the occurrence and severity of depressive symptoms during the previous week (e.g., "I felt alone", "I felt depressed", "Everything I did was an effort"). Response categories range between 1 (never) to 4 (all the time), with total possible scores ranging from 12 to 48. A mean score of maternal depressive symptoms was created by averaging the scores at 6 (Cronbach's $\alpha$ = 0.82) and 18 ($\alpha$ = 0.82) months, as these scores were strongly correlated with each other ($r$ = 0.48; *Mean* = 17.57, *SD* = 4.8, *range* = 12–48, *skewness* = 1.30 [standard error = 0.11], *kurtosis* = 1.69 [standard error = 0.21]). Using the conventional cut-off from the original CES-D (16/60, which corresponds to 12.8/48 in these data; (Weissman,

Sholomskas, Pottenger, Prusoff, & Locke, 1977)), the prevalence of elevated depressive symptoms in the study sample was 18.1%, which is similar to the global prevalence of sub-clinical symptoms (15-25%; Gelaye et al., 2016; Howard et al., 2014).

*Children's cognitive school readiness* was assessed with the Lollipop Test, a well-validated multidimensional measure of cognitive school readiness (Chew, 1989). Trained research assistants administered four subtests (identification of colors and shapes and copying shapes; picture description, position, and spatial recognition; identification of numbers and counting; identification of letters and writing) when children were aged 5 years. A total score (with a maximum of 69) was calculated from the sum of the four subtests ($\alpha$ = 0.73; *Mean* = 42.63, *SD* = 13.3, *range* = 1–69, *skewness* = –0.29 [standard error = 0.11], *kurtosis* = –0.45 [standard error = 0.23]).

***Data analyses***

All analyses were conducted using structural equation modelling in Mplus 8.6 (Muthén & Muthén, 2019). Alpha levels were set to 0.05. As the pattern of missingness varied across measures, the Full Information Maximum Likelihood approach – which permitted the use of all available data – was employed. There were no missing data for maternal depressive symptoms but 13% of the sample did not have data on children's cognitive school readiness. According to Little's missing completely at random test, data on children's cognitive school readiness were not missing completely at random ($\chi^2$ = 9.86, df = 2, $p$ < 0.01). There were no differences in maternal depressive symptoms between participants with and without cognitive school readiness data ($p$ = 0.168). The Mplus Automation package (Hallquist & Wiley, 2018) in R was used to prepare the data. Descriptive statistics and correlations were obtained using the Statistical Package for the

Social Sciences version 25 (IBM Corporation, 2017). Maternal depressive symptoms were positively skewed, so a logarithmic transformation was applied and findings based on the transformed data are reported.

Analyses were conducted in two steps. First, a full univariate ACE twin model was specified to estimate genetic and environmental contributions to children's cognitive school readiness. This model is based on a comparison of the covariance between monozygotic (MZ) and dizygotic (DZ) twins for a given measure, knowing that MZ twins share 100% of their segregating genes whereas, on average, DZ twins share approximately 50%. The model partitions the variance of a given measure between additive genetic (A), shared environmental (C), and nonshared environmental (E) sources. The extent to which MZ twins are more similar than DZ twins on a given variable reflects additive genetic factors (A). The shared environment (C) augments the similarity between twins regardless of zygosity, whereas the nonshared environment (E) makes twins of a pair more different and encompasses measurement error (Turkheimer & Waldron, 2000).

Second, a non-additive twin model was specified to estimate the gene-environment interaction (Price & Jaffee, 2008). In this model, children's cognitive school readiness loaded on the latent sources of variance A, C, and E with coefficients *a*, *c*, and *e* representing the respective factor loadings (***Figure 1***). To test the hypothesized gene-environment interaction, an interaction term between maternal depressive symptoms and the genetic contribution to children's cognitive school readiness was added (denoted by coefficient $b_{ma}$). The potential moderating role of maternal depressive symptoms on the shared and nonshared environmental contributions to children's cognitive school readiness were also estimated (denoted by coefficients $b_{mc}$ and $b_{me}$, respectively). Adding these additional moderations was important to avoid a potentially biased (e.g., inflated)

$b_{ma}$ estimate (Price & Jaffee, 2008). The model also included an estimate of the residual direct contribution of maternal depressive symptoms to children's cognitive school readiness (denoted by coefficient *b*) and an estimate of the correlation between maternal depressive symptoms and genetic contributions to children's cognitive school readiness (denoted by coefficient $r_{ma}$). Adding this latter coefficient was important to control for potential gene-environment correlation when estimating gene-environment interaction (Price & Jaffee, 2008).

## Results

The mean score of maternal depressive symptoms aggregated over 6 and 18 months showed a small but significant negative correlation with children's cognitive school readiness at age 5 years ($r = –0.10$, $p = .005$). Intraclass correlations in regard to children's cognitive school readiness were slightly higher in MZ (*intraclass correlation* = 0.89, $p < 0.001$) than DZ pairs twins (0.79, $p < 0.001$).

The univariate ACE model showed that genetic factors (A) accounted for 30% of the variance in children's cognitive school readiness, shared environmental factors (C) accounted for 52% of the variance, and the remaining 18% were accounted for by nonshared environmental factors (E). Nested models restricting the variance components to AE, CE, and E did not fit the data better than the full ACE model (***Table 1***). The full ACE model was therefore used in the subsequent analysis. In the non-additive twin model, neither the remaining direct association of maternal depressive symptoms with children's cognitive school readiness (*b* = –0.27 [95% CI –0.62 to 0.08]) nor the correlation between maternal depressive symptoms and the genetic contribution to children's cognitive school readiness (*rGE* = 0.42 [95% CI –0.23 to 1.00]) were

significant. The interactions between maternal depressive symptoms and the genetic or shared environmental contributions to children's cognitive school readiness also failed to reach statistical significance (*GxE* = –0.28 [95% CI –0.64 to 0.08] and $b_{mc}$ = 0.01 [95% CI –0.15 to 0.18]). However, there was a significant interaction between maternal depressive symptoms and nonshared environmental contributions to children's cognitive school readiness ($b_{me}$ = 0.14 [95% CI 0.04 to 0.24]).

***Figure 2*** depicts the relative variance components (A, C, and E) of children's cognitive school readiness as a function of maternal depressive symptoms. As can be seen, as the level of maternal depressive symptoms increased, the relative contribution of nonshared environmental factors on children's cognitive school readiness increased somewhat whereas the relative contribution of genetic factors slightly decreased. The contribution of shared environmental factors to children's cognitive school readiness did not change as a function of maternal depressive symptoms.

## Discussion

The goal of this study was to test whether maternal depressive symptoms moderate the genetic-environmental etiology of children's cognitive school readiness. In line with previous studies, we found that environmental factors – particularly shared factors that augment the similarity between twins regardless of zygosity – explained the largest portion of the variance in children's cognitive school readiness (Lemelin, 2007; Rhemtulla & Tucker-Drob, 2012). We also replicated meta-analytic findings of a longitudinal negative correlation between maternal depressive symptoms and children's cognitive outcome (Liu et al., 2017; Power et al., 2021; Rogers et al., 2020).

Maternal depressive symptoms also significantly moderated the (nonshared) environmental – but not the genetic – variance components of children's cognitive school readiness. The interaction pattern was concordant with a suppression process of gene-environment interaction. Specifically, environmental contributions to children's cognitive school readiness at age 5 years slightly increased (and genetic contributions decreased) at higher levels of maternal depressive symptoms, assessed when twins were 6 and 18 months old. This is in line with findings from previous studies that examined gene-environment interaction in the association between children's cognitive outcomes and other aspects of the family environment, notably socioeconomic status (Rhemtulla & Tucker-Drob, 2012; Tucker-Drob & Bates, 2016; Tucker-Drob et al., 2013). Although it is worth noting that these studies found a significant gene-environment interaction and a larger moderation of environmental contributions to children's cognitive school readiness by socioeconomic status than we did with maternal depressive symptoms. Overall, findings from prior research and the present study are consistent with the bioecological model's proposition that exposure to early adversity may play a role in the contributions of genetic and environmental factors to children's cognitive school readiness (Bronfenbrenner & Ceci, 1994).

Unique environmental factors explained more of the variance in children's cognitive school readiness at higher levels of maternal depressive symptoms. Prior research on the mechanisms of the association between maternal depressive symptoms and children's cognitive outcomes can help clarify what these environmental factors could be. Goodman & Gotlib's (1999) Developmental Model for Understanding Mechanisms of Transmission hypothesizes that the timing and course of maternal depression, child's sex, and paternal characteristics (i.e., mental health, parenting behaviours) may moderate the association between maternal depressive symptoms and children's cognitive outcomes. In the context of the present study, paternal parenting behaviours – which

have been shown to be nonshared environmental factors (Klahr & Burt, 2014) – may be one aspect of the environment that could explain more of the variance in children's cognitive outcomes in the presence of elevated maternal depressive symptoms. In this regard, there are two competing hypotheses concerning the interaction between maternal depressive symptoms and paternal parenting behaviours. The *spillover hypothesis* posits that maternal depression can negatively influence fathers' well-being and thus lead to decreased paternal involvement with their child (Goodman, Lusby, Thompson, Newport, & Stowe, 2014). Alternatively, the *compensatory/buffering hypothesis* suggests that fathers may try to compensate for – or buffer – depression in their partner by becoming more involved in caring and providing for their child (Goodman et al., 2014).

There is empirical evidence for both hypotheses, with some studies finding that higher levels of maternal depression are associated with higher levels of paternal involvement in childcare (i.e., *compensatory/buffering hypothesis*; (Sejourne, Vaslot, Beaumé, Goutaudier, & Chabrol, 2012)) and others finding that higher levels of maternal depression are associated with lower levels of paternal involvement (i.e., *spillover hypothesis*; (Maselko et al., 2019)). Indeed, one study found evidence of both hypotheses, depending on developmental timing: maternal depression was associated with greater paternal involvement in the first 6 months after birth, but was associated with lower paternal involvement in the second half of the first year of life (Goodman et al., 2014). This suggests that fathers may be able to compensate for/buffer maternal depression up to a point, but that paternal involvement is likely lower when maternal depression is chronic (Goodman et al., 2014; Newkirk, 2018). Considering this, the results of the present study suggest that further research is needed to determine whether targeting paternal parenting behaviours in families where the mother is experiencing depressive symptoms may help improve children's cognitive outcomes.

Further research is also needed to explore the interaction between maternal depressive symptoms and paternal parenting behaviours, as well as how this interaction is associated with children's cognitive outcomes.

### *Strengths and Limitations*

The present study had many strengths including its longitudinal time span over 4½ years and the use of independent assessments of maternal depressive symptoms and children's cognitive school readiness, thereby minimizing shared method variance. However, some limitations should be considered. The correlation between maternal depressive symptoms and children's cognitive school readiness was modest, most likely due to the longitudinal nature of this study. Furthermore, the sample was ethnically homogenous, with close to 90% of participants being of European origin. Additional studies are needed with more diverse samples in different cultural contexts to increase the generalizability of these findings.

## Conclusion

Despite its limitations, the present study suggests that the relative contributions of genetic and environmental factors to children's cognitive school readiness vary depending on exposure to maternal depressive symptoms in early childhood. These findings support both Bronfenbrenner and Ceci's bioecological model and empirical evidence on the contribution of children's environmental context on the extent to which genetic factors explain the variance in their cognitive outcomes (Bronfenbrenner & Ceci, 1994; Tucker-Drob et al., 2013). This is relevant for public health as it indicates that interventions to improve children's early childhood environments can limit the potentially detrimental association of adverse events such as exposure to maternal depressive symptoms with children's cognitive outcomes. Further research is needed to replicate

these findings and to identify modifiable environmental factors in the early childhood environment that may offset the potential negative association between maternal depression and children's cognitive outcomes.

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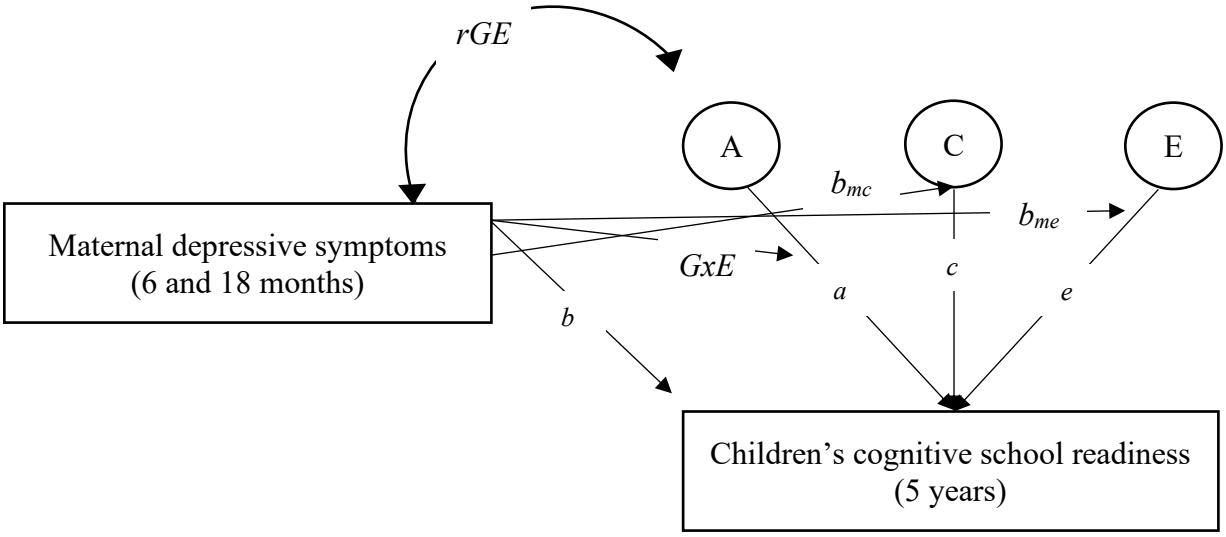


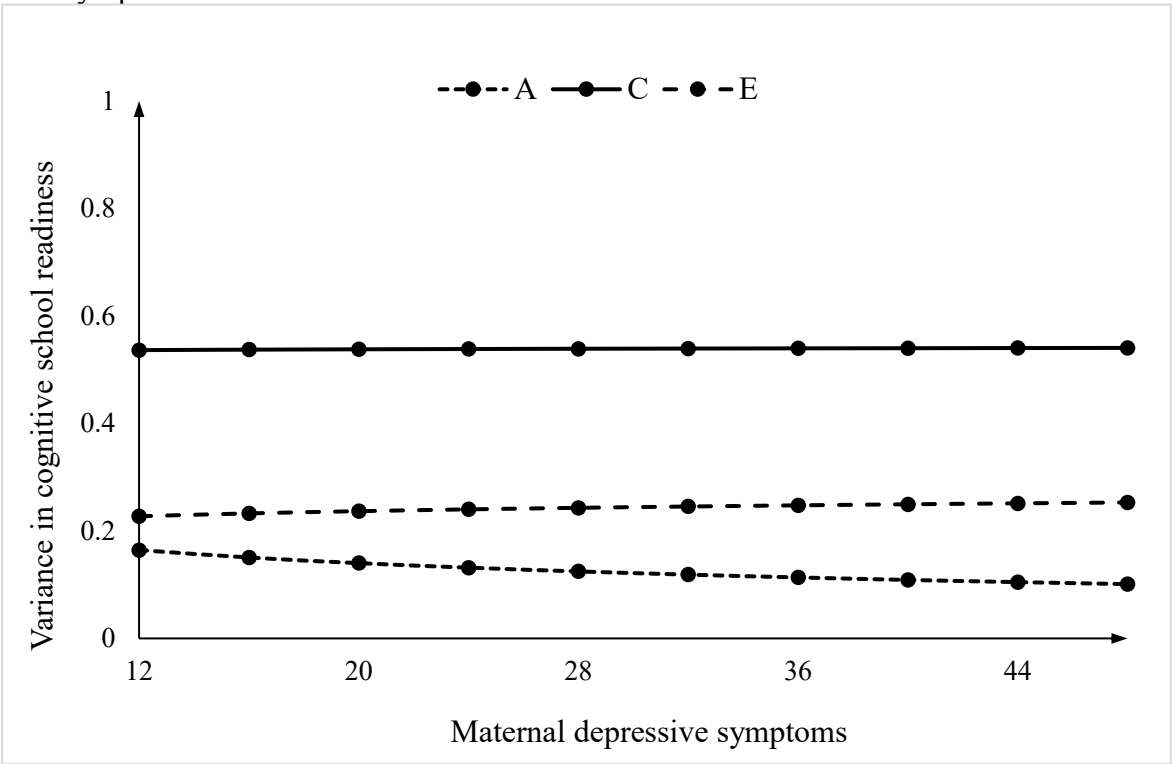

**Figure 1.** Path diagram showing observed variables (square boxes), latent variables (circles), regression paths (single-head arrows), and correlations (double-headed arrows). *A, C,* and *E* reflect the proportion of variance in children's cognitive school readiness explained by additive genetics, shared environment, and nonshared environment, respectively. *a* = additive genetic path parameter; *c* = shared environment path parameter; *e* = nonshared environment path parameter; *GxE* = linear moderation of genetic contribution to children's cognitive school readiness by maternal depressive symptoms; $b_{mc}$ = linear moderation of shared environment contribution to children's cognitive school readiness by maternal depressive symptoms; $b_{me}$ = linear moderation of nonshared environment contribution to children's cognitive school readiness by maternal depressive symptoms; $r_{ma}$ = correlation between maternal depressive symptoms and genetic contribution to children's cognitive school readiness; *b* = residual direct contribution of maternal depressive symptoms to children's cognitive school readiness.

**Table 1.** Univariate model of proportion of variance in children's cognitive school readiness explained by genetic (A), shared environment (C), and nonshared environment (E) factors, with 95% confidence intervals

| | *a* | *c* | *e* | Δ-2LL | AIC | BIC |
|---|---|---|---|---|---|---|
| **ACE** | **0.29 (.17-.43)** | **0.52 (.40-.64)** | **0.18 (.14-.22)** | | **2255.0** | **2258.8** |
| AE | 0.82 (.79-.86) | 0.00 | 0.18 (.14-.21) | 38.58* | 2291.5 | 2294.4 |
| CE | 0.00 | 0.73 (.69-.77) | 0.27 (.23-.31) | 19.44* | 2272.4 | 2275.3 |
| E | 0.00 | 0.00 | 1.00 (1.00-1.00) | 365.18* | 2616.1 | 2618.1 |

*a* = additive genetic path parameter; *c* = shared environment path parameter; *e* = nonshared environment path parameter; Δ-2LL = difference in twice the negative loglikelihood between the full model and the model that is tested; AIC, Akaike's Information Criterion; BIC, sample-size adjusted Bayesian Information Criterion. The best-fitting model is in bold.
*$p < 0.05$

**Figure 2.** Moderation of the contribution of genetic and environmental factors to children's cognitive school readiness by maternal depressive symptoms



## 4.4 *Article 4*

**Sex differences in the association between maternal depression and child and adolescent cognitive development: A systematic review and meta-analysis**

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**Authors' contributions.** M.N. Ahun developed the study concept, conducted the literature review, performed the data analysis, and prepared the first draft of the manuscript under the supervision of S.M. Côté and G. Gariépy. C. Gapare helped conduct the literature review. All authors contributed to the study design and interpretation of results and provided critical feedback on drafts of the manuscript.

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## Abstract

**Background.** Maternal depression is negatively associated with cognitive development across childhood and adolescence, with mixed evidence on whether this association differs in boys and girls. Herein, we performed a systematic review and meta-analysis of sex-specific estimates of the association between maternal depression and offspring cognitive outcomes.

**Method.** Seven databases (PubMed, EMBASE, PsycINFO, ERIC, CINAHL, Scopus, ProQuest) were searched for studies examining the longitudinal association between maternal depression and offspring (up to 18 years) cognitive outcomes. Studies were screened and included based on predetermined criteria by two independent reviewers (Cohen's $\kappa$=0.76). We used random-effects models to conduct a meta-analysis and used meta-regression for subgroup analyses. The PROSPERO record for the study is CRD42020161001.

**Results.** Twelve studies met inclusion criteria. Maternal depression was associated with poorer cognitive outcomes in boys (*Hedges' g* = –0.36 [95% CI: –0.60 to –0.11]), but not in girls (–0.17 [–0.41 to 0.07]). The association in boys varied as a function of the measure of depression used ($b$ = –0.70, $p$ = 0.005): when maternal depression was assessed via a diagnostic interview, boys (–0.84 [–1.23 to –0.44]) had poorer cognitive outcomes than when a rating scale was used (–0.16 [–0.36 to 0.04]).

**Conclusions.** This review and meta-analysis indicate that maternal depression is only significantly associated with cognitive outcomes in boys. Understanding the role of sex differences in the underlying mechanisms of this association can inform the development of targeted interventions to mitigate the negative effects of maternal depression on offspring cognitive outcomes.

## Introduction

Maternal depression consists of persistent sad mood or loss of pleasure accompanied by cognitive and somatic symptoms that are severe and persist over time during pregnancy and postnatally (American Psychiatric Association, 2013). Both clinical (assessed via diagnostic interview; 11-13%) and sub-clinical (assessed via rating scale; 15-25%) levels of maternal depression are prevalent in the general population (Gelaye, Rondon, Araya, & Williams, 2016; Howard et al., 2014). Studies report consistent associations of clinical and sub-clinical maternal depression with poor offspring outcomes across childhood and adolescence (Stein et al., 2014). This includes cognitive developmental outcomes, which consist of age-related increases in language, intellectual, academic, and executive functioning capabilities that are affected by genetic, social, and psychological factors that are sensitive to broader contextual determinants (Walker et al., 2011). Over the past two decades, researchers have systematically investigated the role of maternal depression as a psychological factor associated with offspring's cognitive outcomes (Grace, Evindar, & Stewart, 2003; Liu et al., 2017; Rogers et al., 2020; Sanger, Iles, Andrew, & Ramchandani, 2015), with some studies suggesting that these associations are stronger in boys (Grace et al., 2003; Sanger et al., 2015). However, there is still no clear indication of the role of sex differences in this association. Herein we present findings from the first meta-analysis of the differences in the association between maternal depression and cognitive outcomes in boys and girls.

Using both theory and empirical evidence to examine whether there are sex differences in the association between maternal depression and offspring outcomes is relevant for the design, implementation, and evaluation of interventions that aim to mitigate the negative effects of maternal depression. From a theoretical perspective, biological and developmental factors can

contribute to variations in how boys and girls react to maternal depression (Kraemer, 2000). For example, it is possible that the maturational advantage held by girls in cognitive skills (e.g., language, reading) in early childhood might protect from the negative impact of (postnatal) maternal depression (Galsworthy, Dionne, Dale, & Plomin, 2000; Grace et al., 2003; Logan & Johnston, 2010; Sohr-Preston & Scaramella, 2006). This suggests that boys may be more vulnerable to the effect of maternal depression and that they may therefore experience poorer cognitive outcomes compared to girls. Another factor possibly contributing to sex differences is male foetuses' increased vulnerability to antenatal maternal stress (i.e., anxiety, depression, elevated stress levels) and its neurodevelopmental consequences (Bale & Epperson, 2015; DiPietro & Voegtline, 2017; O'Donnell & Meaney, 2017; Sandman, Glynn, & Davis, 2013). However, the specific pathways through which exposure to antenatal depression may increase boys' risk for poorer cognitive outcomes are not clear. Although children exposed to antenatal depression are more likely to be born prematurely or with low birthweight – both of which are more prevalent in boys (DiPietro & Voegtline, 2017) – and these conditions are subsequently associated with poorer cognitive outcomes, there is no clear evidence that prematurity or low birthweight mediate the association between maternal depression and offspring cognitive outcomes (Dadi, Miller, Bisetegn, & Mwanri, 2020; Gelaye et al., 2016; Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2015; O'Donnell & Meaney, 2017).

From an empirical perspective, there is mixed evidence of sex differences in the association between maternal depression and offspring cognitive outcomes. Grace et al. (2003) provided the first narrative synthesis of sex differences in this association and concluded that overall, sons of depressed mothers had lower scores on standardized measures of cognitive outcomes than daughters of depressed mothers. In a systematic review focusing on cognitive outcomes in

adolescents, Sanger et al. (2015) again found evidence of a stronger association between maternal depression and cognitive outcomes in boys, however some studies found no evidence of sex differences in this association (e.g., Galler et al., 2004). Recent publications do not provide a clear indication of whether boys truly are more vulnerable than girls, with some studies reporting a stronger association in girls (e.g., Ahun et al., 2020) and others reporting no sex differences (e.g., Ng-Knight, Shelton, Frederickson, McManus, & Rice, 2018). Although there have been two recent meta-analyses of the association between maternal depression and cognitive outcomes across childhood and adolescence (Liu et al., 2017; Rogers et al., 2020), neither has advanced our understanding of sex differences in this association.

The objectives of the present study were to systematically review the literature on longitudinal associations between maternal depression and offspring (up to age 18 years) cognitive outcomes and to provide the first meta-analysis of sex-specific estimates of this association.

## Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for standard reporting (PRISMA [Table S1]; Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). The protocol for this review was preregistered on the PROSPERO international prospective register of systematic reviews (registration number CRD42020161001). The only deviation we made from this protocol was the addition of a new subgroup in the meta-regression analyses as specified below.

***Search strategy***

Studies included in this meta-analysis were identified using both electronic and manual searches. We searched for relevant studies on maternal depression and offspring cognitive outcomes across seven electronic databases (PubMed MEDLINE, Embase, ERIC, PsycINFO, CINAHL, Scopus, and ProQuest Dissertations and Theses Online) from inception to January 2020. Search terms included the concepts of maternal depression *([(postnatal or postpartum or perinatal or peri-natal or antenatal or maternal or mother) AND (depression or depressive symptoms)] OR major depression OR minor depression)* and cognitive development *(child development OR cognition OR [cognitive or language or verbal or intelligence or academic or reading or writing or development or learning])*. The search concepts were combined with the Boolean operator "and". The specific search equations used in each database can be found in Table S2. Follow-up manual searches were conducted from the reference lists of systematic reviews, meta-analyses, and theses retrieved from the electronic search (Ebeid, 2018; Grace et al., 2003; Liu et al., 2017; Sanger et al., 2015).

***Study inclusion criteria***

A study was considered eligible for inclusion if it: (i) provided sex-specific estimates of the quantitative association between clinical or sub-clinical maternal depression and offspring cognitive outcomes in a longitudinal study; (ii) was published in a peer-reviewed journal in English or French; (iii) assessed maternal depression during pregnancy or any time after birth; (iv) assessed cognitive outcomes in offspring 18 years old or younger; (v) did not use data from a case study or randomized controlled trial (to avoid bias introduced by the potential impact of the trial on the association of interest); and (vi) had a population-based sample of children and mothers in that

context. If the study population was described as a specific subset of children/adolescents (e.g., born prematurely) or mothers (e.g., recruited because they had a medical condition or were taking medication, alcohol, or other drugs), the study was excluded.

### *Study selection*

The article selection process consisted of three steps. First, MNA and CG independently screened the titles and abstracts of the 9145 articles (after removal of duplicates) identified through electronic and manual searches. Studies deemed by both reviewers to not fulfill the inclusion criteria were excluded. Second, the remaining studies were independently read in full by the two reviewers and selected for inclusion in the analysis if identified as relevant by both reviewers. There was substantial agreement between reviewers (Cohen's $\kappa = 0.76$) (Viera & Garrett, 2005). Disagreements were resolved in team discussions with GG and SMC. Third, data from each selected study were abstracted onto a standardized form independently by the two reviewers, including authors, year of publication, country where the study was conducted, study population, sample size, study design, exposure and outcome measures, age of the child/adolescent at exposure and outcome assessments, and sex-specific estimates.

### *Study quality assessment*

We extracted the necessary information to assess risk of bias using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, which was designed to examine study quality according to Cochrane collaboration criteria (National Heart Lung and Blood Institute: National Institutes of Health, 2014). The tool includes items assessing the clarity of the research question and the study design (i.e., definition of sample,

reporting of attrition), the use of valid exposure and outcome measures, and whether key potential confounding variables were included in analyses (Table S3). Each item is scored as yes, no, or not reported. To assess publication bias, we regressed studies' effect estimates onto their standard errors using Egger's linear regression test and a funnel plot (Borenstein, Hedges, Higgins, & Rothstein, 2011). A significant result of the test suggests that the plot is asymmetric, and bias is present, while a non-significant result suggests minimal bias.

***Meta-analysis***

Data were analyzed from September to November 2020 using the *metafor* version 2.0 (Viechtbauer, 2010) and *robumeta* version 2.0 (Fisher, Tipton, & Zhipeng, 2017) packages in R version 4.0.3 (R Core Team, 2019). The *robumeta* package uses a robust variance meta-analysis approach that accounts for multiple effects from the same sample (Hedges, Tipton, & Johnson, 2010). All studies reported offspring cognitive outcomes as continuous variables using a variety of measures. We used maternal depression as our exposure to capture studies using either a rating scale or a diagnostic interview to assess depression. If a study assessed depression at several time points, we used the mean of children/adolescents' age at those time points. When a study used more than one measure to assess depression or cognitive outcomes, we gave priority to the measure that was more commonly used (i.e., more frequently cited) in the literature. If a study used both a rating scale and a diagnostic interview to assess depression, the association with the diagnostic interview measure was used.

We converted sex-specific estimates of the association between maternal depression and cognitive outcomes to a common bias-corrected metric of *Hedges' g* (Borenstein et al., 2011; Lüdecke, 2019 ; Table S4), which represents the difference between two group means (cognitive

scores for daughters and sons of mothers with high versus low/no depression or higher versus lower levels of depression) divided by the pooled standard deviation (Cohen, 1988; Hedges, 1981). This metric uses a weighted pooled standard deviation to provide an effect size estimate that is not biased by small samples. Where studies did not provide all the relevant data to convert sex-specific estimates into *Hedges' g*, we reached out to authors to provide said data. Out of seven authors contacted, three provided data. We examined the crude effect of maternal depression on offspring cognitive outcomes using *Hedges' g* and used guidelines to interpret effect sizes that are meaningful, where 0.10 is small, 0.20 is medium, 0.30 is large, and greater than 0.40 is very large (Funder & Ozer, 2019). We used standard meta-analytical methods to estimate the summary effect sizes using the inverse variance approach and robust variance random-effects models.

Heterogeneity was assessed by calculating the $I^2$ index (Table S4). We also conducted subgroup analyses by comparing sex-specific estimates across the following categorical variables: time of exposure to maternal depression (exposure during pregnancy versus after birth), method of measuring maternal depression (rating scale versus diagnostic interview), child age at cognitive outcome assessment (childhood [birth to 10 years] versus adolescence [11 to 18 years]), and length of time between assessments of exposure and outcome (short [≤1 year] versus long [>1 year]). All subgroups except the length of time between exposure and outcome were prespecified in the registered protocol. Meta-regressions were conducted to determine whether the sex-specific associations between maternal depression and offspring cognitive outcomes varied within these subgroups. Two-sided $p < .05$ indicated significance based on the regression of sex-specific meta-analytic estimates onto each of these subgroups. We ran sensitivity analyses to determine whether an outlier study (Ng-Knight et al., 2018) affected reported estimates. Results were similar with and without this study, so the former are henceforth reported.

## Results

### *Study characteristics and quality*

Of the 9145 articles assessed for eligibility, we screened the full text of 167 (***Figure 1***). In total, 12 articles from 8 unique datasets met eligibility criteria and were included in the meta-analysis (***Table 1***). Studies were conducted in six countries: six in the UK (Hay et al., 2001; Hay, Pawlby, Waters, & Sharp, 2008; Murray et al., 2010; Murray, Hipwell, Hooper, Stein, & Cooper, 1996; Ng-Knight et al., 2018; Sharp et al., 1995), two in Canada (Ahun et al., 2020; Paquin et al., 2020), and one each in Australia (Cornish et al., 2005), the USA (Davies & Windle, 1997), South Africa (Donald et al., 2019), and Finland (Nolvi et al., 2018).

According to the quality assessment, most articles used a range of robust study design features (***Table S5***). All studies clearly stated their research objectives, allowed sufficient time between the assessment of exposure and outcome (defined as 4 months; Liu et al., 2017), and used valid and reliable measures. However, studies varied as to whether maternal depression was assessed continuously or categorically. The most notable risks of bias related to a lack of information on statistical power to determine sample size (only one study provided this information; Murray et al., 2010) and sample selection and attrition. Five studies reported dropout rates greater than 20%, suggesting a risk of selective sampling bias (e.g., greater loss to follow-up of mothers with higher levels of depression). Another key risk of bias was the lack of sex-specific estimates of the adjusted associations between maternal depression and cognitive outcomes. Although most studies included covariates in their analyses, only two (Ahun et al., 2020; Ng-Knight et al., 2018) reported separate adjusted associations for boys and girls. Results should therefore be interpreted within the context of these limitations. With respect to publication bias,

the funnel plot was roughly symmetric with non-significant *p-values* from the Egger's linear regression test ($p = 0.176$), indicating minimal publication bias (***Figure S1***).

***Meta-analysis and meta-regression results***

The meta-analysis of crude estimates from the 12 studies showed a statistically significant association between maternal depression and cognitive outcomes in boys and a non-significant association in girls (***Figures 2 and 3***). This indicates that on average, boys exposed to elevated levels of maternal depression had a –0.36 standardized mean difference on assessments of cognitive outcomes compared to boys who were exposed to lower levels. The overall difference between boys' and girls' estimates was not significant ($b = 0.25$, $p = 0.145$). There was significant heterogeneity in the estimates in both boys and girls across studies.

Subgroup analyses (***Tables S6 to S9***) revealed that maternal depression as assessed by a diagnostic interview was more strongly associated with boys' cognitive outcomes ($n = 6$ studies; *Hedges' g* = –0.84 [95% CI: –1.23 to –0.44]) than that assessed via rating scales ($n = 6$ studies; –0.16 [–0.36 to 0.04]). Furthermore, boys exposed postnatally to maternal depression ($n = 10$ studies; –0.40 [–0.73 to –0.08]) had poorer cognitive outcomes than those exposed antenatally ($n = 2$ studies; –0.25 [–1.58 to 1.07]) and boys whose cognitive outcomes were assessed more than 12 months after assessment of maternal depression ($n = 8$ studies; –0.52 [–0.91 to –0.13]) had poorer cognitive outcomes compared to those with a shorter amount of time between maternal depression and cognitive assessments ($n = 4$ studies; –0.16 [–0.65 to 0.33]). Meta-regression analyses showed that only the difference between boys whose mothers were assessed via diagnostic interview versus those whose mothers were assessed via rating scale was significant ($b = –0.70$, $p = 0.005$).

Subgroup analyses in girls revealed that maternal depression remained non-significantly associated with cognitive outcomes across all but one subgroups. Maternal depression was only associated with girls' cognitive outcomes when there was more than 12 months between assessments of maternal depression and cognitive outcomes ($n$ = 8 studies;–0.17 [–0.27 to –0.08]). However, meta-regression analyses revealed that this estimate was not significantly different ($b$ = 0.07, $p$ = 0.890) from that of girls with a shorter amount of time between assessments ($n$ = 4 studies; –0.24 [–1.22 to 0.74]).

## Discussion

This is the first meta-analysis of sex-specific estimates of the association between maternal depression and offspring cognitive outcomes. Results from 12 articles showed consistent evidence of moderate-to-large associations in boys. This association varied as a function of the measure of maternal depression used, whereby effect sizes were stronger for boys whose mothers were assessed via diagnostic interview. The meta-analytic effect of maternal depression on cognitive outcomes in girls was not significant, although subgroup analyses revealed that the effect was significant for girls whose cognitive outcomes were assessed 12 months after assessment of maternal depression. Our findings of sex differences in the association between maternal depression and offspring cognitive outcomes align with consistent findings of sex differences in various child outcomes in response to antenatal maternal stress, although the direction of this difference varies by child outcome (Bale & Epperson, 2015; DiPietro & Voegtline, 2017; Kraemer, 2000; Sandman et al., 2013).

Our results replicate meta-analytic findings of a significant association between maternal depression and cognitive outcomes across childhood and adolescence and support narrative review

findings of stronger associations in boys compared to girls (Grace et al., 2003; Liu et al., 2017; Rogers et al., 2020; Sanger et al., 2015). A novel finding in this meta-analysis was that the method of assessing maternal depression (diagnostic interview versus rating scale) moderated the association between maternal depression and cognitive outcomes in boys. This moderation may be explained by antenatal exposure to clinical maternal depression since clinical depression is more likely to persist over time (i.e., from the antenatal to the postnatal period; Heron et al., 2004; Underwood et al., 2016) and the hypothesized mechanisms through which maternal depression may confer greater risk to boys' cognitive outcomes occur during pregnancy (e.g., premature birth, low birth weight; Dadi et al., 2020; Gelaye et al., 2016; Linsell et al., 2015; O'Donnell & Meaney, 2017). However, it was not possible to test this hypothesis in the meta-analysis because all the studies that used a diagnostic interview to assess maternal depression were conducted in the postnatal period.

That we only found a significant overall association in boys is in line with the notion that girls' maturational advantage in cognitive skills (e.g., reading) in early childhood may protect from the negative effect of (postnatal) maternal depression (Grace et al., 2003; Sohr-Preston & Scaramella, 2006). However, given the small number of studies which assessed antenatal depression ($n$ = 2 in both ours and Liu et al.'s meta-analyses), it is possible that both studies were under-powered to provide reliable estimates. Rogers et al. (2020) found a slightly stronger association between postnatal (versus antenatal) maternal depression and cognitive outcomes but did not test for sex differences. The small number of studies that have examined sex differences in the effects of antenatal and postnatal maternal depression suggest that for some child outcomes (e.g., internalizing symptoms), girls are more vulnerable to variations in the exposure to maternal

depression (i.e., low antenatal depression and high postnatal depression or vice versa) than boys (Braithwaite, Pickles, Wright, Sharp, & Hill, 2020; Sandman et al., 2013).

Additional subgroup analyses revealed that for both boys and girls, the amount of time between assessments of maternal depression and cognitive outcomes was important. Specifically, maternal depression was associated with cognitive outcomes when there was a longer amount of time between their assessments (i.e., more than 12 months). Liu et al. (2017) also found a significant association between maternal depression and cognitive outcomes when there was a longer amount of time between assessments (defined as 4 months or more). One potential explanation for this may be that a longer amount of time between assessments reflects more chronic exposure to maternal depression. There is evidence that the chronicity, rather than the timing, of exposure to maternal depression is associated with poorer cognitive outcomes (Ahun et al., 2017; Netsi et al., 2018; Sohr-Preston & Scaramella, 2006). For example, Ahun et al. (2017) found that children chronically exposed to maternal depression from birth to age 5 years scored lower on a measure of verbal abilities compared to children exposed earlier (i.e., before age 3) or later (i.e., between 3 and 5 years) in the postnatal period. However, neither Ahun et al. (2017) nor Netsi et al. (2018) tested for sex differences. Only one study in the meta-analysis considered the chronicity of maternal depression and they found that chronically exposed children had worse cognitive outcomes but found no sex differences (Cornish et al., 2005). It is therefore not clear whether boys are also more vulnerable to chronic exposure to maternal depression compared to girls.

The association between maternal depression and cognitive outcomes did not vary as a function of whether cognitive outcomes were assessed in childhood versus adolescence in boys or girls. The only other meta-analysis of the association between maternal depression and cognitive

outcomes across childhood and adolescence also failed to find a significant variation in this association by child's age at the time of cognitive assessment (Rogers et al., 2020). However, both meta-analyses had relatively low power to detect moderation, so results should be interpreted cautiously. Previous research does suggest that the small-to-moderate yet consistent association between maternal depression and cognitive outcomes persists into adolescence, so it is important to consider the effects of maternal depression across developmental periods (Sanger et al., 2015). Furthermore, as discussed earlier, it is likely that the chronicity of exposure to maternal depression, rather than the child's age at cognitive assessment, is important in understanding how the effects of maternal depression on cognitive outcomes persist into adolescence (Ahun et al., 2017; Netsi et al., 2018; Sohr-Preston & Scaramella, 2006).

To translate the findings of this meta-analysis into public health interventions, we need to understand whether sex differences exist in the underlying mechanisms of the association between maternal depression and offspring cognitive outcomes. Studies examining underlying mechanisms are needed to identify modifiable mediators which can be targeted in interventions to mitigate the negative effects of maternal depression. For instance, maternal depression was associated with academic performance in both boys and girls, but school engagement only mediated the association between exposure and outcome in girls (Ahun et al., 2020). In another study, children's self-control and their perceptions of maternal warmth only mediated the association in girls (Ng-Knight et al., 2018). These findings suggest that the association between maternal depression and girls' cognitive outcomes is explained by an indirect effect. They also suggest that the maturational advantage held by girls in cognitive skills may protect from the direct – but not the indirect – effect of maternal depression. Another key mechanism of this association is maternal parenting, whereby maternal depression negatively influences maternal sensitivity and mother-child interactions

which are consequently associated with poorer cognitive outcomes (Ahun & Côté, 2019; Goodman, Simon, Shamblaw, & Kim, 2020). However, there is mixed evidence on the moderating role of sex in these pathways.

Prevention and treatment interventions for mothers at risk of experiencing depression and for those experiencing depression are also important public health interventions for mitigating the negative effect of maternal depression on child outcomes (Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2015; Goodman, Cullum, Dimidjian, River, & Kim, 2018; Letourneau, Dennis, Cosic, & Linder, 2017; O'Connor, Senger, Henninger, Coppola, & Gaynes, 2019; Rahman et al., 2018; Tsivos, Calam, Sanders, & Wittkowski, 2015). However, there is currently little evidence that such interventions lead to improved child outcomes. Of the handful of prevention and treatment interventions that have assessed impacts on children's cognitive outcomes (Cicchetti, Rogosch, & Toth, 2000; Clark, Tluczek, & Wenzel, 2003; Cooper, De Pascalis, Woolgar, Romaniuk, & Murray, 2015; Hayden et al., 2012; Kersten-Alvarez, Hosman, Riksen-Walraven, Van Doesum, & Hoefnagels, 2010; N. Letourneau et al., 2011; Makrides et al., 2010; Maselko et al., 2015; Milgrom et al., 2015; Murray, Cooper, Wilson, & Romaniuk, 2003; Verduyn, Barrowclough, Roberts, Tarrier, & Harrington, 2003), few have found a significant impact.

Cicchetti et al. (2000) found no sex differences in the positive impact of the intervention on cognitive outcomes whereas Milgrom et al. (2015) did not test for sex differences. One study found no overall effect of the intervention, however, girls in the intervention group had better post-intervention cognitive outcomes compared to their male counterparts (Cooper et al., 2015). These results indicate that there is no clear evidence of the moderating role of child's sex in the impact of treatment and prevention interventions for maternal depression on offspring cognitive outcomes. Recent evidence suggests that for prevention and treatment interventions to

significantly improve child outcomes, they need to be combined with parenting interventions that enhance mothers' overall parenting skills, including specific skills (e.g., cognitive stimulation) that can help improve children's cognitive outcomes (Goodman & Garber, 2017; Goodman et al., 2020).

### *Recommendations for future research*

Our findings highlight important avenues for future research on the role of sex differences in the association between maternal depression and offspring cognitive outcomes. Given the lack of evidence that treating or preventing maternal depression alone leads to subsequent improvements in children's cognitive outcomes, further research is needed on the effectiveness of interventions that jointly treat or prevent maternal depression and focus on improving parenting skills (Goodman & Garber, 2017; Goodman et al., 2020). Additionally, examining the moderating role of sex on intervention impacts can inform researchers and clinicians as to whether such interventions meet the particular needs of boys and girls. For example, moderation analyses of a parenting intervention only found significant improvements in boys' behavioural outcomes, suggesting that the intervention may need to be modified to address behavioural problems in girls (Gardner, Hutchings, Bywater, & Whitaker, 2010). Further research is also needed to clarify the role of sex differences in mediators of the association between maternal depression and offspring cognitive outcomes. Such work could lead to the development of public health interventions that target the sex-specific modifiable factors through which maternal depression influences offspring cognitive outcomes and thus address the particular needs of boys and girls. Furthermore, given the lack of studies reporting sex-specific associations adjusted for covariates, future studies should use a consistent set of covariates to facilitate the interpretation of pooled adjusted associations in meta-

analyses (Hutchinson et al., 2015). Finally, an exploration of whether maternal depression influences girls' and boys' cognitive outcomes differently in more ethnically and economically diverse samples is needed. The majority of studies in this meta-analysis included participants who were White and had high levels of socioeconomic status, our results are therefore primarily applicable to families from Western, educated, industrialized, rich, and democratic societies (Henrich, Heine, & Norenzayan, 2010).

### *Limitations*

This meta-analysis was limited by the modest number of studies fulfilling eligibility criteria. We therefore had little power for subgroup analyses and our results should thus be interpreted cautiously. Furthermore, due to a lack of reporting on sex differences in the adjusted association between maternal depression and offspring cognitive outcomes, we were unable to account for the role of covariates in our meta-analysis. Although we restricted the meta-analysis to longitudinal studies and hence were able to establish temporality in reported associations, we cannot comment on the causality of these associations due to the observational nature of included studies. Nevertheless, it is worth noting that maternal depression remained significantly associated with offspring cognitive outcomes after accounting for important covariates such as maternal anxiety and level of education. Furthermore, in the two studies that reported adjusted sex-specific associations (Ahun et al., 2020; Ng-Knight et al., 2018), sex differences remained after adjusting for covariates. It is therefore likely that our findings would hold after accounting for covariates. Our meta-analysis also highlights important limitations in the extant literature on maternal depression and offspring's cognitive outcomes which have already been discussed.

## Conclusion

The results of this meta-analysis underscore the importance of examining the differential impact of maternal depression on boys' and girls' cognitive outcomes. To translate these findings into public health interventions, further research is needed to better understand the modifiable mediators of this association in boys and girls and to examine the differential impact of integrated interventions that aim both to prevent or treat maternal depression and improve parenting skills on boys' and girls' cognitive outcomes.

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**Figure 1.** PRISMA flow diagram of selection procedure. The reasons to exclude initially identified articles to reach *n*=167 were: (1) the study was not relevant to our research questions; (2) the study was a systematic review or meta-analysis, (3) study participants were beyond age range or not from a population-based sample, and (4) study outcomes did not focus on cognitive development.

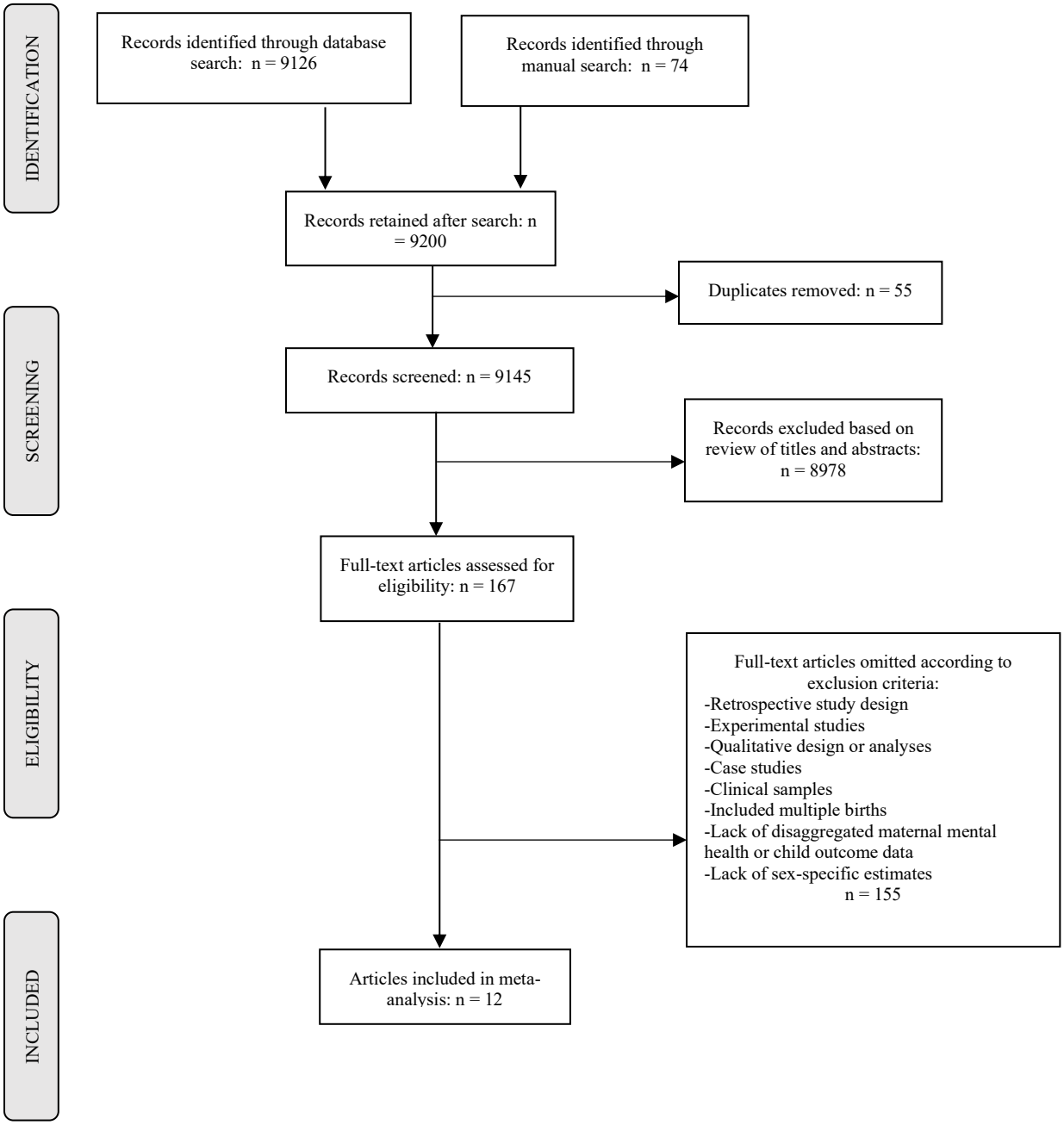


**Table 1.** Characteristics of studies included in meta-analysis of sex-specific associations between maternal depression and child and adolescent cognitive outcomes

| Citation | Cohort/sample | Sample size (B,G) | Country | Race, ethnicity | Overall sample SES | Method of measuring maternal depression | Time of exposure to maternal depression | Child cognitive outcome measure | Age category [c] | Time between exposure and outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Ahun et al., 2020 | Québec Longitudinal Study of Child Development | 1173 (B=559, G=614) | Canada | 84% White, 3% Native American; 1% African, 12% other | High SES (mean score above centered value of SES index) | RS, CES-D | Postnatal | Academic performance, Maths | Adolescent | 9 years 4 months |
| Cornish et al., 2005 | Community sample | 112 (B=58, G=56) | Australia | 93% White, 7% other | High SES (50% have college or university degree) | DI, CIDI | Postnatal | Bayley, MDI | Child | 4 months |
| Davies et al., 1997 | Community sample | 443 (B=204, G=239) | USA | 97% White, 3% other | High SES (50% >USD$40,000 per year) | RS, CES-D | Postnatal | Academic performance, GPA | Adolescent | 1 year |
| Donald et al., 2019 | Drakenstein Child Health Study | 734 (B=380, G=354) | South Africa | Not reported | Low SES (61% >USD$100 per month) | RS, EPDS | Antenatal | Bayley, MDI | Child | 2 years |
| Hay et al., 2001 | Community sample [a] | 132 (B=62, G=70) | UK | 78% White, 1.5% African, 0.5% Asian, 20% other | Low SES (89% working class) | DI, CIS | Postnatal | WISC, composite | Adolescent | 10 years 9 months |
| Hay et al., 2008 | Community sample [a] | 121 (B=55, G=66) | UK | 78% White, 22% other | Low SES (88% working class) | DI, CIS | Postnatal | WASI, composite | Adolescent | 16 years |
| Murray et al., 1996 | Community sample [b] | 94 (B=47, G=47) | UK | Not reported | High SES (65% middle-upper class) | DI, SPI | Postnatal | MSCA, composite | Child | 4 years 9 months |
| Murray et al., 2010 | Community sample [b] | 89 (B=43, G=46) | UK | Not reported | High SES (64% middle-upper class) | DI, SPI | Postnatal | Academic performance, GCSE | Adolescent | 10 years 4 months |
| Ng-Knight et al., 2018 | Community sample | 578 (B=312, G=266) | UK | 60% White, 40% minority (non-White) ethnicity | High SES (16% socioeconomic deprivation) | RS, HADS-D | Postnatal | Academic performance, Maths, English, Science | Adolescent | 1 year |
| Nolvi et el., 2018 | FinnBrain Birth Cohort Study | 214 (B=114, | Finland | Not reported | High SES (74% university or polytechnics degree) | RS, EPDS | Antenatal | Executive Function, | Child | 8 months |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | G=100) | | | | | | delayed response task | | |
| Paquin et al., 2020 | Québec Longitudinal Study of Child Development | 1137 (B=541, G=596) | Canada | Not reported | High SES (80.1% sufficient income) | RS, CES-D | Postnatal | Lollipop, composite | Child | 3 years 7 months |
| Sharp et al., 1995 | Community sample [a] | 135 (B=60, G=75) | UK | Not reported | Not reported | DI, CIS | Postnatal | MSCA, composite | Child | 3 years 6 months |

*Notes*. [a] These studies used data from the same community sample in south London. [b] These studies used data from the same community sample in Cambridge. [c] Child defined as birth to 10 years and adolescent as 11 to 18 years.

B,G = number of boys (B) and girls (G) in sample; DI = diagnostic interview; CES-D = Centre for Epidemiological Studies – Depression Scale; CIDI = Composite International Diagnostic Interview; CIS = Clinical Interview Schedule; EPDS = Edinburgh Postnatal Depression Scale; GCSE = General Certificate of Secondary Education; GPA = grade point average; HADS-D = depression subscale of Hospital Anxiety and Depression Scale; MDI = mental development index; MSCA = McCarthy Scales of Children's Abilities; RS = rating scale; SES = socioeconomic status; SPI = Standardized Psychiatric Interview; UK = United Kingdom; USA = United States of America; WASI = Wechsler Abbreviated Scale of Intelligence; WISC = Weschler Intelligence Scale for Children-III.

**Figure 2.** Association between maternal depression and cognitive outcomes in boys

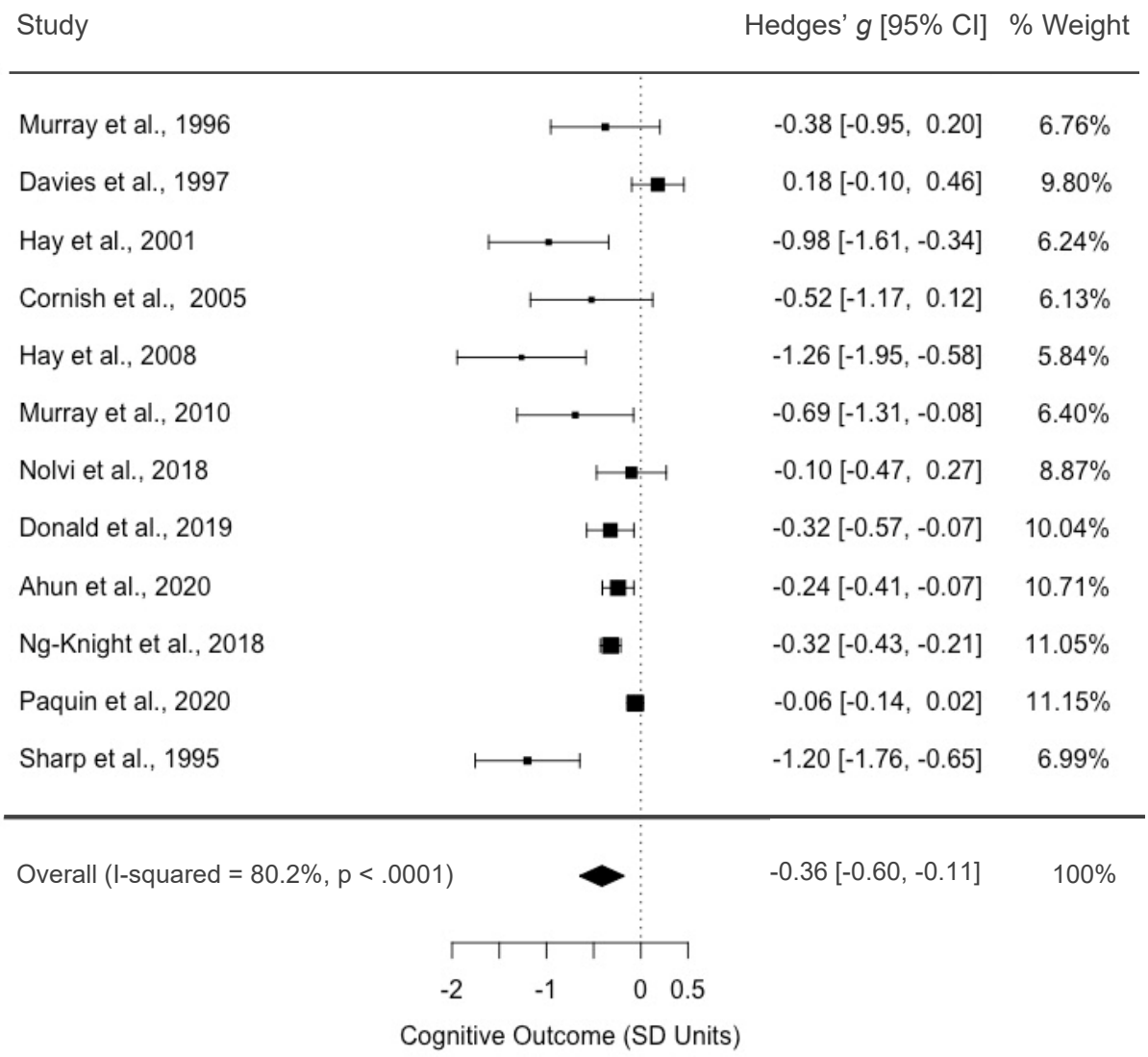
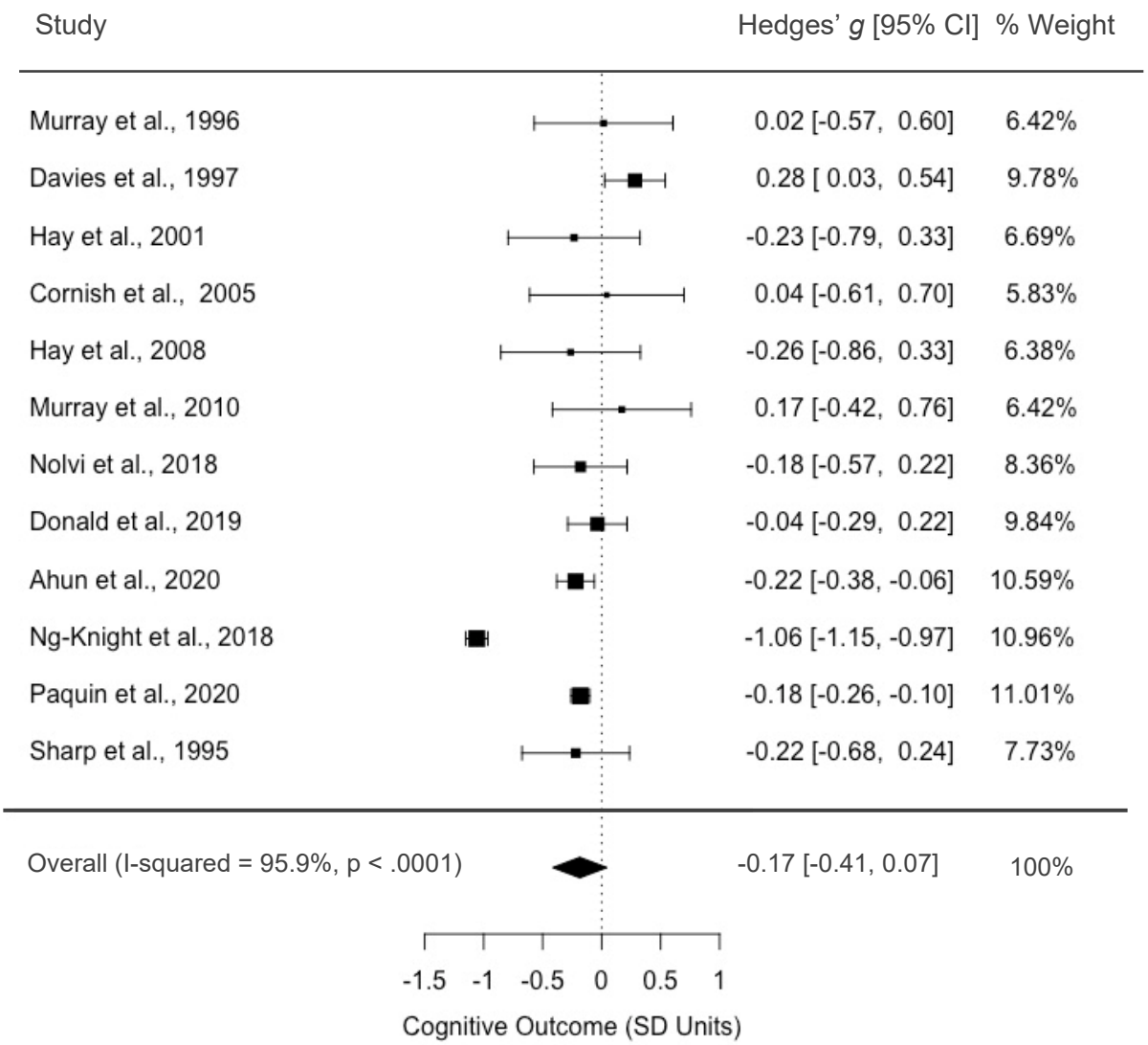


**Figure 3.** Association between maternal depression and cognitive outcomes in girls



**Supplementary Material for *Article* 4**

**Table S1.** PRISMA Checklist[1]

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background, objectives, data sources, study eligibility criteria, participants, and interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number | 3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known | 4-6 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS) | 6 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale | 7-8 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched | 7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated | 7, Table S2 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, including in systematic review, and if applicable, included in the meta-analysis) | 7-8 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators | 7-8 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made | 7-9 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis | 8-9 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means) | 9-10 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis | 9-10 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies) | 8-9 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified | 9-10 |

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusion at each stage, ideally with a flow diagram | 8;11; Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide citations | 11; Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12) | 11-12; Table S5 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: a) simple summary data for each intervention group, b) effect estimates and confidence intervals, ideally with a forest plot | 10-11; Figures 2 and 3 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency | 12-13; Figures 2 and 3; Tables S6 to S9 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see item 15) | 11-12 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]) | 12-13 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome, consider their relevance to key groups (e.g., healthcare providers, users, and policymakers) | 13-19 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias) | 18-19 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research | 17-18 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data), role of funders for the systematic review | 2 |

[1] From *Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine, 6(7), e1000097. doi:https://doi.org/10.1371/journal.pmed.1000097*

**Table S2.** Search equations

| Database | Search equation |
|---|---|
| PubMed MEDLINE | (((postnatal OR postpartum OR perinatal OR peri-natal OR antenatal) ADJ3 (depress*)) OR ((matern* OR mother* OR mothers/) AND (depress* OR depression/ OR major depression/ OR minor depression/)) OR exp portpartum depression) AND (cognitive development OR exp child development/ OR exp cognition/ OR cogniti* or language* or verbal or intelligen* or academic* or read* or writing or development or learning) |
| Embase | [[((depress* adj3 (post natal or postnatal or postpartum or post partum or perinatal or peri-natal or antenatal)).ab,kw,ti.) OR (exp minor depression/ or exp perinatal depression/ or exp postnatal depression/ or exp major depression/ or exp antenatal depression/ or exp depression/)] AND [(exp mother/) OR ((mother* or matern*).ab,kw,ti.)]] AND [(exp cognition/) OR (exp child development/) OR (exp language development/ or exp language/) OR (exp intelligence test/ or exp intelligence quotient/ or exp intelligence/) OR ((cognit* or language* or verbal or memory or intelligen* or academic* or read* or writing or development).ab,kw,ti.)] |
| ERIC | ((MAINSUBJECT.EXACT.EXPLODE("Depression (Psychology)") OR (ab(depress* NEAR/3 post natal OR postnatal OR postpartum OR post partum OR perinatal OR peri-natal OR antenatal) OR if(depress* NEAR/3 post natal OR postnatal OR postpartum OR post partum OR perinatal OR peri-natal OR antenatal) OR ti(depress* NEAR/3 post natal OR postnatal OR postpartum OR post partum OR perinatal OR peri-natal OR antenatal))) AND ((ab(mother* OR matern*) OR if(mother* OR matern*) OR ti(mother* OR matern*)) OR MAINSUBJECT.EXACT.EXPLODE("Mothers"))) AND (MAINSUBJECT.EXACT.EXPLODE("Cognitive Development") OR MAINSUBJECT.EXACT.EXPLODE("Child Development") OR (MAINSUBJECT.EXACT.EXPLODE("Child Language") OR MAINSUBJECT.EXACT.EXPLODE("Language")) OR MAINSUBJECT.EXACT.EXPLODE("Intelligence") OR (ab(cognit* OR language* OR verbal OR memory OR intelligen* OR academic* OR read* OR writing OR development) OR ti(cognit* OR language* OR verbal OR memory OR intelligen* OR academic* OR read* OR writing OR development) OR if(cognit* OR language* OR verbal OR memory OR intelligen* OR academic* OR read* OR writing OR development))) |
| PsycINFO | ((((((**MeSH**: (depression))))) *OR* ((((**abstract**: (depress* NEAR/3 post natal))) *OR* ((**abstract**: (postnatal))) *OR* ((**abstract**: (postpartum))) *OR* ((**abstract**: (post partum))) *OR* ((**abstract**: (perinatal))) *OR* ((**abstract**: (peri-natal))) *OR* ((**abstract**: (antenatal)))) *OR* (((**Keywords**: (depress* NEAR/3 post natal))) *OR* ((**Keywords**: (postnatal))) *OR* ((**Keywords**: (postpartum))) *OR* ((**Keywords**: (post partum))) *OR* ((**Keywords**: (perinatal))) *OR* ((**Keywords**: (peri-natal))) *OR* ((**Keywords**: (antenatal)))) *OR* (((**title**: (depress* NEAR/3 post natal))) *OR* ((**title**: (postnatal))) *OR* ((**title**: (postpartum))) *OR* ((**title**: (post partum))) *OR* ((**title**: (perinatal))) *OR* ((**title**: (peri-natal))) *OR* ((**title**: (antenatal)))))) *AND* (((((**abstract**: (mother*))) *OR* ((**abstract**: (matern*)))) *OR* (((**Keywords**: (mother*))) *OR* ((**Keywords**: (matern*)))) *OR* (((**title**: (mother*))) *OR* ((**title**: (matern*))))) *OR* ((((**MeSH**: (mother))))))) *AND* ((((**abstract**: (cognit*)) *OR* (**abstract**: (language*)) *OR* (**abstract**: (verbal)) *OR* (**abstract**: (memory)) *OR* (**abstract**: (intelligen*)) *OR* (**abstract**: (academic*)) *OR* (**abstract**: (read*)) *OR* (**abstract**: (writing)) *OR* (**abstract**: (development))) *OR* ((**Keywords**: (cognit*)) *OR* (**Keywords**: (language*)) *OR* (**Keywords**: (verbal)) *OR* (**Keywords**: (memory)) *OR* (**Keywords**: (intelligen*)) *OR* (**Keywords**: (academic*)) *OR* (**Keywords**: (read*)) *OR* (**Keywords**: (writing)) *OR* (**Keywords**: (development))) *OR* ((**title**: (cognit*)) *OR* (**title**: (language*)) *OR* (**title**: (verbal)) *OR* (**title**: (memory)) *OR* (**title**: (intelligen*)) *OR* (**title**: (academic*)) *OR* (**title**: (read*)) *OR* (**title**: (writing)) *OR* (**title**: (development)))) *OR* (((**MeSH**: (intelligence)))) *OR* (((**MeSH**: (language)))) *OR* (((**MeSH**: (child development)))) *OR* (((**MeSH**: (cognition))))) |

| | |
|---|---|
| CINAHL | ((MH "Depression+") OR (MH "Depression, Postpartum") OR (AB ( depress* N3 post natal or postnatal or postpartum or post partum or perinatal or peri-natal or antenatal ) OR TI ( depress* N3 post natal or postnatal or postpartum or post partum or perinatal or peri-natal or antenatal ))) AND ( (AB ( mother* or matern* ) OR TI ( mother* or matern*) OR (MH "Mothers+")) AND ((MH "Cognition+") OR (MH "Child Development") OR (MH "Language+") OR (MH "Language Development") OR (MH "Intelligence+") OR (AB ( cognit* or language* or verbal or memory or intelligen* or academic* or read* or writing or development ) OR TI ( cognit* or language* or verbal or memory or intelligen* or academic* or read* or writing or development ) )) |
| Scopus | (((KEY (depression)) OR (TITLE-ABS-KEY (depress* W/3 post AND natal OR postnatal OR postpartum OR post AND partum OR perinatal OR peri-natal OR antenatal))) AND ((TITLE-ABS-KEY (matern* OR mother*)) OR (KEY(mother)))) AND ((KEY (cognition)) OR (KEY (child AND development)) OR (KEY(language)) OR (KEY (intelligence)) OR (TITLE-ABS-KEY (cognit* OR language* OR verbal OR memory OR intelligen* OR academic* OR read* OR writing OR development))) AND (LIMIT-TO (EXACTKEYWORD, “Depression”) OR LIMIT-TO (EXACTKEYWORD, “Mother”) OR LIMIT-TO (EXACYKEYWORD, “Cognition”) OR LIMIT-TO (EXACTKEYWORD, “Child Development”) OR LIMIT-TO (EXACTKEYWORD, “Cognitive Development”) OR LIMIT-TO (EXACTKEYWORD, “Language Development”) OR LIMIT-TO (EXACTKEYWORD, “Intelligence”)) |
| ProQuest | ((su(depression) OR (ab(depress* NEAR/3 post natal OR postnatal OR postpartum OR post partum OR perinatal OR peri-natal OR antenatal) OR ti(depress* NEAR/3 post natal OR postnatal OR postpartum OR post partum OR perinatal OR peri-natal OR antenatal))) AND ((ab(mother* OR matern*) OR ti(mother* OR matern*)) OR su(mother))) AND (su(cognition) OR su(child development) OR su(language) OR su(intelligence) OR (ab(cognit* OR language* OR verbal OR memory OR intelligen* OR academic* OR read* OR writing OR development) OR ti(cognit* OR language* OR verbal OR memory OR intelligen* OR academic* OR read* OR writing OR development))) |

**Table S3.** Study quality assessment criteria[1]

| Item | Title | Criteria |
|---|---|---|
| 1 | Clear research question | Was research question/objective clearly stated? |
| 2 | Defined sample | Was study population (who, when, where) clearly specified and defined? |
| 3 | Participation rate >50% | Was participation rate of eligible persons at least 50%? |
| 4 | Selection criteria noted | Were all the subjects selected from the same/similar populations (including the same time period)? Were inclusion/exclusion criteria for being in the study prespecified and applied uniformly? |
| 5 | Power calculation | Was a sample size justification, power description, or variance and effect estimates provided? |
| 6 | Exposure measured prior to outcome | For the analyses in this paper, was the exposure of interest measured prior to the outcome being measured? |
| 7 | Timeframe sufficient | Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? Sufficient timeframe was defined as ≥ 4 months[2] |
| 8 | Continuous exposure variables | For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? |
| 9 | Valid exposure measure | Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? |
| 10 | Times | Was the exposure assessed more than once over time? |
| 11 | Valid outcome measure | Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? |
| 12 | Blinding | Were the outcome assessors blinded to the exposure status of participants? |
| 13 | Attrition ≤ 20% | Was loss to follow-up after baseline 20% or less? |
| 14 | Confound variables | Were key potential confounding variables measured and adjusted statistically for their impact on the association between exposure and outcome in girls and boys separately? |

[1]Adapted from National Heart Lung and Blood Institute: National Institutes of Health. (2014). Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Retrieved from https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools and Rogers, A., Obst, S., Teague, S.J., Rossen, L., Spry, E.A., Macdonald, J.A., Sunderland, M., Olsson, C.A., Youssef, G., & Hutchinson, D. (2020). Association between maternal perinatal depression and anxiety and child and adolescent development: a meta-analysis. *JAMA Pediatrics*. DOI: https://doi.org/10.1001/jamapediatrics.2020.2910

[2] Liu, Y., Kaaya, S., Chai, J., McCoy, D. C., Surkan, P. J., Black, M. M., . . . Smith-Fawzi, M. C. (2017). Maternal depressive symptoms and early childhood cognitive development: a meta-analysis. *Psychological Medicine, 47*(4), 680-689. doi:https://doi.org/10.1017/s003329171600283x

**Table S4.** Meta-analysis and conversion of estimates to Hedges' *g* effect sizes formulae

| Estimate | Formula |
|---|---|
| **Meta-analysis estimates** | |
| Hedges' *g* | $\mathbf{1} - \left[\frac{3}{4(n_1+n_2-2)-1}\right] x \left[\frac{\overline{X}_1-\overline{X}_2}{\sqrt{\frac{(n_1-1)S_1^2+(n_2-1)S_2^2}{n_1+n_2-2}}}\right]$ |
| $I^2$ | $\left[\frac{Q-df}{Q}\right] x\ 100\%$ |
| **Conversion of estimates to Hedges' g** | |
| Pearson correlation | Effect sizes were manually calculated from each study using formulae retrieved from the book "Introduction to meta-analysis"[1]: $\mathbf{1} - \left[\frac{3}{4(n_1+n_2-2)-1}\right] x \left[\frac{2r}{\sqrt{1-r^2}}\right]$ |
| Regression coefficient | The *esc*[2] R package was used to convert regression coefficients into Hedges' *g* effect sizes based on formulae from the book "Practical meta-analysis"[3]: $\mathbf{1} - \left[\frac{3}{4(n_1+n_2-2)-1}\right] x \left[\frac{b}{\sqrt{\frac{(n_1-1)S_1^2+(n_2-1)S_2^2}{n_1+n_2-2}}}\right]$ |

[1] Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. (2011). Chapter 7: Converting among effect sizes. In: *Introduction to meta-analysis.* United Kingdom: John Wiley & Sons.

[2] Wilson, D.B. (2016) Formulas Used by the "Practical Meta-Analysis Effect Size Calculator". Unpublished manuscript: George Mason University

[3] Lipsey, M.W. & Wilson, D.B. (2001). *Practical meta-analysis*. Thousand Oaks, California: Sage Publications

**Table S5.** Quality assessment of included studies

| Citation | Clear research question | Defined sample | Participation rate >50% | Selection criteria noted | Power calculation | Exposure measured prior to outcome | Timeframe sufficient | Continuous exposure variable | Valid exposure measure | Times | Valid outcome measure | Blinding | Attrition ≤ 20% | Confounding |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ahun et al., 2020 | Y | Y | Y* | Y* | N | Y | Y | Y | Y | Y | Y | NR | N | Y |
| Cornish et al., 2005 | Y | N | Y | Y | N | Y | Y | N | Y | Y | Y | Y | Y | N |
| Davies et al., 1997 | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | N | NR | Y | N |
| Donald et al., 2019 | Y | Y | NR | Y | N | Y | Y | Y | Y | N | Y | Y | N | N |
| Hay et al., 2001 | Y | Y* | Y | NR | N | Y | Y | N | Y | N | Y | Y | Y | N |
| Hay et al., 2008 | Y | Y | Y | NR | N | Y | Y | N | Y | Y | Y | NR | Y | N |
| Murray et al., 1996 | Y | Y | Y | Y | N | Y | Y | N | Y | Y | Y | Y | Y | N |
| Murray et al., 2010 | Y | Y | Y* | Y | Y | Y | Y | N | Y | Y | Y | NR | Y | N |
| Ng-Knight et al., 2018 | Y | Y | N | N | N | Y | Y | Y | Y | Y | Y | NR | N | Y |
| Nolvi et el., 2018 | Y | N | Y | Y | N | Y | Y | Y | Y | Y | Y | NR | N | N |
| Paquin et al., 2020 | Y | Y | NR | NR | N | Y | Y | Y | Y | Y | Y | NR | N | N |
| Sharp et al., 1995 | Y | Y | Y | NR | N | Y | Y | N | Y | Y | Y | NR | Y | N |

*Notes*. Asterisk indicates that this criterion is noted in the cohort profile paper of the given study. N = no, NR = not reported, Y = yes.

**Figure S1**. Funnel plot of publication bias

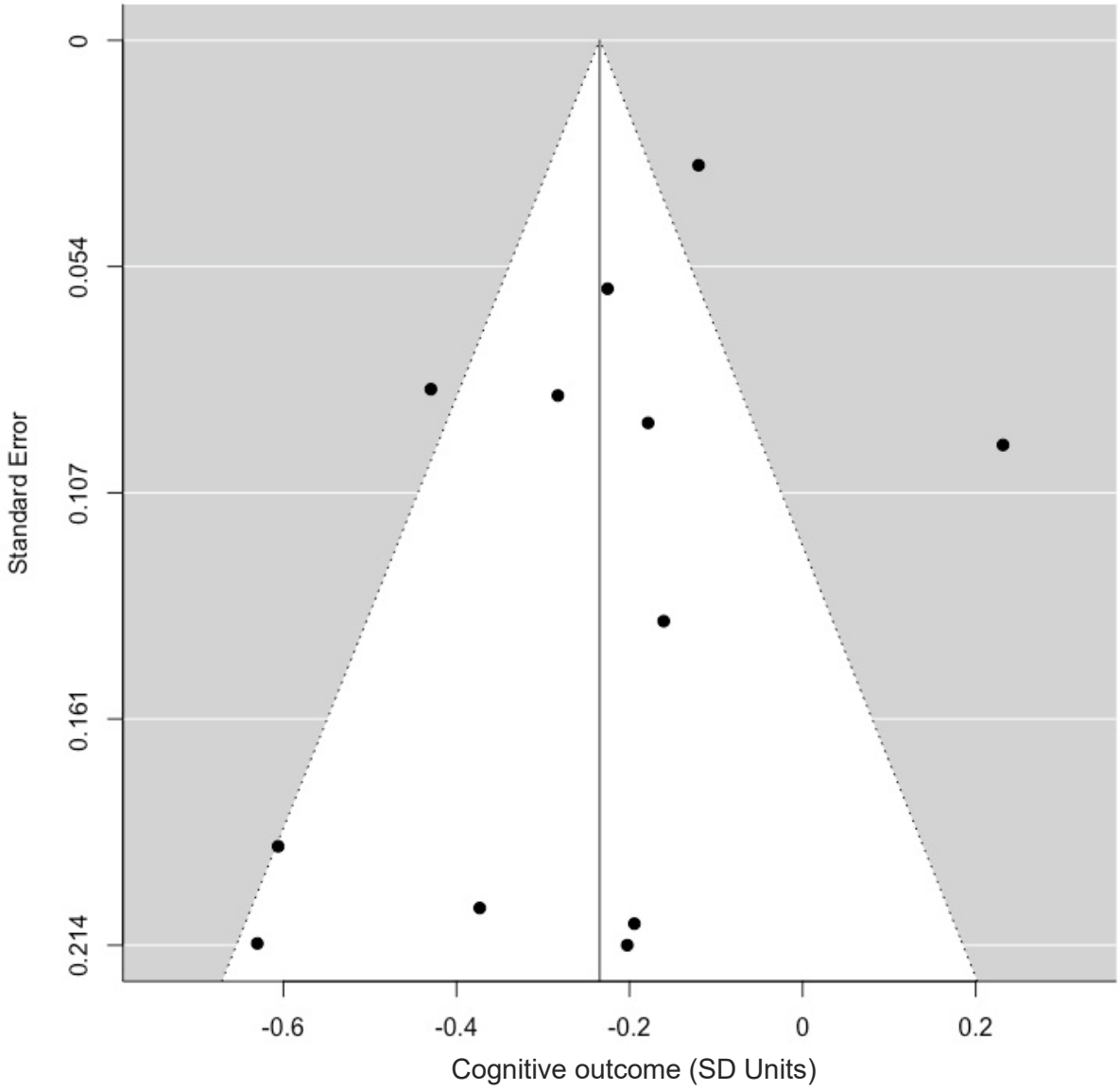


**Table S6**. Meta-regression analysis of effect sizes by time of exposure to maternal depression

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Boys*** | | | | | | | |
| | k | Hedges' *g* (95% CI) | $I^2$ | b | SE | t | p |
| Ante | 2 | -0.25 (-1.58 to 1.07) | 0% | -0.24 | 0.11 | 2.17 | 0.137 |
| Post | 10 | -0.40 (-0.73 to -0.08) | 83% | | | | |
| ***Girls*** | | | | | | | |
| Ante | 2 | -0.08 (-0.90 to 0.75) | 0% | -0.13 | 0.22 | -0.59 | 0.862 |
| Post | 10 | -0.19 (-0.48 to 0.11) | 96% | | | | |

*Notes*. *b* represents the difference in meta-analytic effect sizes between the early (0) and late (1) groups; *95% CI* represents the 95% confidence interval of the effect size; *k* represents the number of effect sizes. Ante = maternal depression assessed during pregnancy; Post = maternal depression assessed after child's birth

**Table S7**. Meta-regression analysis of effect sizes by method of measuring maternal depression

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Boys*** | | | | | | | |
| | k | Hedges' *g* (95% CI) | $I^2$ | b | SE | t | p |
| RS | 6 | -0.16 (-0.36 to 0.04) | 78% | -0.70 | 0.14 | -4.94 | 0.005 |
| DI | 6 | -0.84 (-1.23 to -0.44) | 28% | | | | |
| ***Girls*** | | | | | | | |
| RS | 6 | -0.24 (-0.72 to 0.24) | 98% | 0.17 | 0.20 | 0.85 | 0.445 |
| DI | 6 | -0.10 (-0.29 to 0.09) | 0% | | | | |

*Notes*. *b* represents the difference in meta-analytic effect sizes between the early (0) and late (1) groups; *95% CI* represents the 95% confidence interval of the effect size; *k* represents the number of effect sizes. DI = diagnostic interview; RS = rating scale.

**Table S8**. Meta-regression analysis of effect sizes by child age category at cognitive assessment

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Boys*** | | | | | | | |
| | k | Hedges' *g* (95% CI) | $I^2$ | b | SE | t | p |
| Child | 6 | -0.36 (-0.77 to 0.05) | 77% | 0.21 | 0.13 | 1.54 | 0.201 |
| Adolescent | 6 | -0.40 (-0.89 to 0.09) | 81% | | | | |
| ***Girls*** | | | | | | | |
| Child | 6 | -0.16 (-0.44 to 0.11) | 0% | 0.09 | 0.18 | 0.50 | 0.640 |
| Adolescent | 6 | -0.23 (-0.77 to 0.30) | 97% | | | | |

*Notes*. *b* represents the difference in meta-analytic effect sizes between the early (0) and late (1) groups; *95% CI* represents the 95% confidence interval of the effect size; *k* represents the number of effect sizes. Adolescent = defined as 11 to 18 years; Child = defined as birth to 10 years.

**Table S9**. Meta-regression analysis of effect sizes by length of time between assessments of maternal depression and cognitive outcome

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Boys*** | | | | | | | |
| | k | Hedges' *g* (95% CI) | $I^2$ | b | SE | t | p |
| Short | 4 | -0.16 (-0.65 to 0.33) | 76% | -0.18 | 0.13 | -1.37 | 0.245 |
| Long | 8 | -0.52 (-0.91 to -0.13) | 83% | | | | |
| ***Girls*** | | | | | | | |
| Short | 4 | -0.24 (-1.22 to 0.74) | 97% | 0.07 | 0.29 | 0.26 | 0.890 |
| Long | 8 | -0.17 (-0.27 to -0.08) | 0% | | | | |

*Notes*. *b* represents the difference in meta-analytic effect sizes between the early (0) and late (1) groups; *95% CI* represents the 95% confidence interval of the effect size; Long = defined as more than 12 months; Short = defined as 12 months or less.

# Chapter 5. Discussion

This chapter provides a broad summary of the results of the present dissertation and a discussion of its implications for public health and health promotion. It consists of five parts: (1) a summary of the major findings of each of the four articles; (2) a reflection on the general strengths and limitations of the dissertation (more detailed discussions on *Article*-specific strengths and limitations can be found in Chapter 4); (3) an outline of the scientific contributions of this research; (4) a discussion of the public health and health promotion implications of findings; (5) a discussion of emerging issues and future research on early childhood development; and (6) a conclusion.

## 5.1 Summary of results

### *5.1.1 Article 1* – A review of the mediators of the association between maternal depression and cognitive development in early childhood

The objective of this article was to provide a general understanding of the evidence on the potential mediators of the association between maternal depression and cognitive development as outlined in Goodman & Gotlib (1999). My co-author and I identified seven studies that tested two of the potential mediators (negative maternal cognitions, behaviours, and affect and a stressful family environment) (Chen et al., 2013; Kiernan & Huerta, 2008; Letourneau et al., 2013; Milgrom, Westley, & Gemmill, 2004; Piteo, Yelland, & Makrides, 2012; Stein et al., 2008; Zajicek-Farber, 2010). No studies examined innate dysfunctional neuroregulatory mechanisms as potential mediators of this association. Five studies used a measure of maternal cognitions, behaviours, and affect (e.g., maternal responsiveness, maternal parenting styles) and three examined a stressful family environment (e.g., family dysfunction, quality of home environment) as a mediator, with one study assessing both mediators (Letourneau et al., 2013). Of the seven studies included in the review, six found an indirect association between maternal depression and

children's cognitive outcomes via negative maternal cognitions, behaviours, and affect (Chen et al., 2013; Kiernan & Huerta 2008; Letourneau et al., 2013; Milgrom et al., 2004; Stein et al., 2008; Zajicek-Farber 2010).

This review reveals three important aspects of the current state of evidence on the role of mediators in the association between maternal depression and children's cognitive development. First, studies showed that mothers experiencing depression were less likely to engage in responsive and stimulating interactions with their children and that these characteristics were in turn associated with children's lower scores on standardized measures of cognitive skills (Kiernan & Huerta 2008; Stein et al., 2008). Second, the studies that examined stressful family environments as a mediator found that low quality home environments mediated the association between maternal depression and children's cognitive outcomes (Chen et al., 2013; Letourneau et al., 2013; Piteo et al., 2012). However, the use of a cross-sectional study design makes it difficult to determine the directionality of reported associations (Maxwell et al., 2011). Third and lastly, no studies examined the role of dysfunctional neuroregulatory mechanisms in the association between maternal depression and children's cognitive outcomes. Overall, our review identifies maternal parenting practices as modifiable factors which interventions could potentially target to improve the wellbeing of children exposed to maternal depression. This review also highlights gaps in our understanding of the role that stressful family environments and neuroregulatory mechanisms play in explaining the impact of maternal depression on children's cognitive outcomes.

### 5.1.2 *Article 2* – Maternal depression and academic performance: the role of school experiences and sex differences

Building on our findings from *Article 1*, I wanted to explore how factors outside the home microsystem influenced the association between maternal depression and children's cognitive outcomes. My co-authors and I focused on specific aspects of the school microsystem – where children spend increasing amounts of time as they grow older – and whether associations between these aspects (i.e., school engagement and peer victimization), maternal depression, and academic performance differed between boys and girls. We found that although exposure to maternal depression in early childhood was negatively associated with lower academic performance at 12 years in both boys and girls, there were no indirect associations via school engagement and peer victimization (assessed between child's ages 6 and 10 years) in boys. Indirect associations were only observed in girls, whereby the cognitive and behavioural dimensions of school engagement mediated the association between maternal depression and academic performance in mathematics, reading, and writing.

Further research is needed to better understand how the different dimensions of school engagement mediate this association and why it is only important for girls. It is likely that the negative impact of maternal depression on maternal cognitions, behaviours, and affect limits a mother's ability to engage in their child's learning and foster their academic motivation and engagement (Claessens et al., 2015; Goodman et al., 2020; Murray et al., 2006). Maternal depression's association with an increased risk of exposure to a stressful family environment may also explain how it leads to decreased school engagement in children. However, evidence of the potential moderating role of child's sex in this association is unclear (Goodman et al., 2020). Further research is also needed to understand which factors mediate the association between

maternal depression and academic performance in boys. Finally, it is worth noting that although the prevalence of maternal depression in this sample (11.5%) was lower than the global prevalence (15-25%), it falls within the range of reported rates of maternal depression in Canadian women (8.5-13.9%; Daoud et al., 2019; Lanes et al., 2011). Furthermore, that we found significant associations with children's cognitive outcomes in the presence of this relatively low prevalence further underscores how sub-clinical depressive symptoms can still influence child outcomes (Dix & Meunier 2009; Lovejoy et al., 2000; Meaney 2018; Moore Simas et al., 2019; Sohr-Preston & Scaramella 2006).

### *5.1.3 Article 3* – Maternal depression and children's cognitive school readiness: The role of gene-environment mechanisms

In *Article 3*, I addressed the lack of studies examining the role of genetics in the association between maternal depression and children's cognitive outcomes by testing the role of GxE. Using an advanced twin model estimated with SEM, my co-authors and I found that maternal depression moderated the extent to which genetic and environmental factors contributed to children's cognitive school readiness. This finding aligns with Bronfenbrenner & Ceci's (1994) *Bioecological Model of Development* and previous empirical studies showing that genetic contributions to children's cognitive school readiness are supressed – while environmental contributions are increased – in high adversity family environments (Rhemtulla & Tucker-Drob, 2012; Tucker-Drob & Bates, 2016; Tucker-Drob et al., 2011; Tucker-Drob et al., 2013; Turkheimer et al., 2003).

Our results suggest that interventions to improve the early childhood environment in the context of elevated maternal depression symptoms may have an impact on children's cognitive

school readiness. This is in line with recent reflections on how integrating components to improve parenting behaviours into interventions that aim to treat or prevent maternal depression can lead to positive impacts on child outcomes (Galbally & Lewis 2017; Goodman & Garber 2017; Howard & Khalifeh, 2020). These reflections are further discussed in section 5.4.

### *5.1.4 Article 4* – A meta-analysis of sex-specific associations between maternal depression and cognitive outcomes

*Article 4* provides the first quantitative summary of the association between maternal depression and cognitive outcomes across childhood and adolescence in boys and girls. Using data from 12 studies, my co-authors and I found a significant negative association between maternal depression and cognitive outcomes in boys and a non-significant association in girls. Our findings support Goodman & Gotlib's (1999) hypothesis that child's sex moderates the direct effect of maternal depression on children's cognitive outcomes. We extended this hypothesis by examining whether the moderating role of sex varied as a function of the timing of exposure to maternal depression, the method of assessment of maternal depression, child's age at cognitive outcome assessment, and the length of time between assessments of maternal depression and offspring cognitive outcome. We found that in boys, the method of assessment of maternal depression moderated the association between maternal depression and cognitive outcomes, such that boys exposed to maternal depression as assessed by a diagnostic interview (i.e., clinical depression) had poorer outcomes than boys exposed to maternal self-reports of depressive symptoms (i.e., sub-clinical depression). It is likely that boys exposed to clinical maternal depression were exposed antenatally, and that this may have increased the risk of poor cognitive outcomes via premature birth or low birth weight (Dadi et al., 2020; Gelaye et al., 2016; Linsell et al., 2015; O'Donnell &

Meaney 2017). Further research exploring these potential mediators is needed to test this hypothesis. None of the other meta-analytic moderators were significant in either boys or girls. However, this may be due to the relatively small number of studies reviewed and hence a lack of power to detect moderating effects.

Our findings contribute to the literature by showing that across studies in different WEIRD (i.e., Western, Educated, Industrialized, Rich, and Democratic; Henrich, Heine, & Norenzayan, 2010) countries, boys are systematically more vulnerable to the direct effects of maternal depression. When interpreted in the context of our findings of sex-specific mediators in *Article 2*, this research shows that although boys may be more vulnerable to the direct effect of maternal depression on children's cognitive outcomes, girls may be vulnerable to the indirect effects of maternal depression via mediating factors such as cognitive and behavioural school engagement. Overall, the results of *Articles 2* and *4* suggest that not only do we need to account for sex differences in the direct effect of maternal depression on children's cognitive outcomes, but we also need to consider how sex may moderate the indirect effects of maternal depression.

## 5.2 Strengths and limitations

### 5.2.1 General strengths

This dissertation has several strengths pertaining to the longitudinal design of the QLSCD and QNTS and the analytical strategy, which made use of robust statistical modelling of longitudinal data and quantitative and qualitative review methods to examine mediators and moderators of the association between maternal depression and children's cognitive outcomes. I discuss these two sets of strengths below.

***Strengths of the QLSCD and QNTS design***

A great strength of both the QLSCD and the QNTS is the broad range of measures collected prospectively, enabling my co-authors and I to establish temporality to rule out one or the other causal direction in estimated associations and to limit recall bias. Furthermore, both cohorts include large samples from the general population (n = 2120 and n = 662 families in QLSCD and QNTS, respectively), and the nature of the QNTS allows for the estimation of important gene-environment mechanisms. Secondly, both cohorts rely on high quality data of repeated measures collected at multiple time points across multiple developmental periods (early childhood in QNTS; early childhood to adolescence in QLSCD). This enabled us to assess repeated exposure to maternal depression in early childhood – thereby capturing the persistence of symptoms over time – and how it influenced potential mediators and cognitive outcomes in subsequent developmental periods. Thirdly, data were collected from multiple informants (i.e., parents, teachers, children) using reliable and well-validated scales (e.g., CES-D). Furthermore, trained research assistants also administered standardized tests (e.g., Lollipop test). The use of multi-informant reports, as well as a combination of reported and observed data, minimized shared method variance. Fourthly, the broad range of measures across both the QLSCD and the QNTS enabled us to assess different dimensions of cognitive outcomes, including cognitive school readiness and academic performance. Finally, the breadth of measures in the QLSCD enabled us to control for several confounders described in the literature, thus enabling us to examine the association between maternal depression and children's cognitive outcomes over and above the influence of other risk factors for poor cognitive outcomes (e.g., low socioeconomic status).

***Strength of our analytical strategy***

The present work was further strengthened by the use of statistical techniques to analyze longitudinal QLSCD and QNTS data in *Articles 2* and *3*, respectively. Both studies used SEM, a robust statistical technique that allows for the simultaneous testing of multiple pathways through which a given exposure may influence an outcome (Hayes 2017). This method enabled us to account for baseline confounders in longitudinal mediation models, thereby strengthening confidence in the temporality and statistical significance of reported associations. It also enabled us to show that the effect of maternal depression on cognitive outcomes persists from childhood into adolescence. Furthermore, we were able to test the moderating role of sex in all estimated associations (e.g., maternal depression and academic performance; maternal depression and school engagement; school engagement and academic performance). Finally, the use of SEM enabled us to run an advanced twin model that jointly estimates GxE and gene-environment correlation, thereby ensuring that GxE is not overestimated as it is in classic twin models that do not account for gene-environment correlation (Price & Jaffee 2008).

Another important strength of the analytical strategy was the focus on knowledge synthesis in *Articles 1* and *4* by qualitatively and quantitatively reviewing evidence on what we know and what we do not know about moderators and mediators of the association between maternal depression and children's cognitive outcomes (Khoury et al., 2010). The first review (*Article 1*) focused on summarizing evidence on potential mediators in the early childhood period, a sensitive period of development, while the second review (*Article 4*) adopted a broader scope – including studies that assessed cognitive outcomes across childhood and adolescence – and provided a quantitative summary of the overall association between maternal depression and cognitive

outcomes in boys and girls separately. The use of meta-analysis enabled us to further test for moderation of the sex-specific effects by running meta-regression models. We were therefore able to answer the question of whether the moderation of the maternal depression-cognitive outcome association by child's sex was further moderated by other factors including the method of assessment of maternal depression, the timing of exposure to maternal depression, child's age at cognitive outcome assessment, and the length of time between assessments of exposure to maternal depression and cognitive outcomes. Overall, these reviews and meta-analysis provide recent summaries of the literature and can inform the development of evidence-based recommendations for practice and future research.

### 5.2.2 General limitations

Despite the considerable strengths of this dissertation, there are important limitations that must be noted. Some of these limitations stem from the design and nature of the data in the QLSCD and the QNTS, while others arise from the analytical strategy.

First, sample attrition across the 12 years of QLSCD data used in *Article 1* decreased the representativeness of the sample and thus, the generalizability of the findings to the Québec population. As described in Chapter 3 (section 3.4), participants in the analysis sample (n = 1173) were significantly different from participants lost to follow-up (n = 947). I therefore used inverse probability weighting – where weights represent the probability of being included in the analysis sample – to reduce bias due to differential attrition in all analyses (Seaman & White 2013). This method minimizes attrition-related bias but does not fully correct for the bias of unobserved variables related to attrition since weights can only be created from observed variables.

Second, although the large sample of the QNTS enabled us to estimate both GxE and gene-environment correlation, heterogeneity in the zygosity and sexual make-up of the twin pairs (i.e., MZ male, MZ female, DZ male, DZ female, DZ male-female) meant that we did not have enough twin pairs in each group to test for the moderating role of sex in estimated associations. This is a general limitation of the broader literature on genetic and environmental contributions to cognitive school readiness, including studies that have examined the GxE of socioeconomic status and genetic contributions to cognitive school readiness (Lemelin, 2007; Rhemtulla & Tucker-Drob, 2012; Tucker-Drob & Bates, 2016; Tucker-Drob et al., 2013; Tucker-Drob, Rhemtulla, Harden, Turkheimer, & Fask, 2011). Moving forward, studies with larger sample sizes should explore whether the associations found in *Article 3* (with maternal depression) and previous studies (with socioeconomic status) differs in boys and girls.

Third, despite the inclusion of key confounders through statistical adjustment in *Article 2*, the capacity to make causal inferences is limited. Since maternal depression co-occurs with other risk factors that also have a negative impact on children's cognitive outcomes (e.g., low socioeconomic status; see section 2.2.1 in Chapter 2), these findings do not fully encapsulate how different aspects of the early childhood environment influence children's cognitive outcomes. Nevertheless, adjusting for these other risk factors in the analysis enabled us to report the association of maternal depression with children's cognitive outcomes independently from key confounders. It is also possible that unmeasured confounders might explain the observed associations – although the use of a genetically informed cohort in *Article 3* enabled us to strengthen inference by accounting for genetic factors. This limitation also applies to the reviewed studies in *Articles 1* and *4*, as they used observational data to estimate the associations between maternal depression and children's cognitive outcomes. Furthermore, because studies did not

report the adjusted associations of maternal depression and cognitive outcomes in girls and boys separately, we were only able to meta-analyze crude associations. Therefore, although the findings do support and build on the hypothesized processes through which maternal depression is associated with children's cognitive development (i.e., Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission*), experimental designs are needed to formally establish causality (Glass et al., 2013).

### 5.3 Scientific contributions

The four articles included in this dissertation contribute to the scientific understanding of early childhood development by exploring the mechanisms of the longitudinal association between maternal depression and children's cognitive outcomes. These findings shed light on the processes that explain why (i.e., mediators) and for whom (i.e., moderators) maternal depression has an effect on children's cognitive development by addressing the following questions:

(1) To what extent does the current literature on maternal depression and children's cognitive development support the proposed mediators in Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission*?

(2) Which factors in the school environment mediate the association between maternal depression and offspring academic performance? Do these mediational pathways differ in boys and girls?

(3) What is the role of gene-environment mechanisms in the association between maternal depression and children's cognitive school readiness?

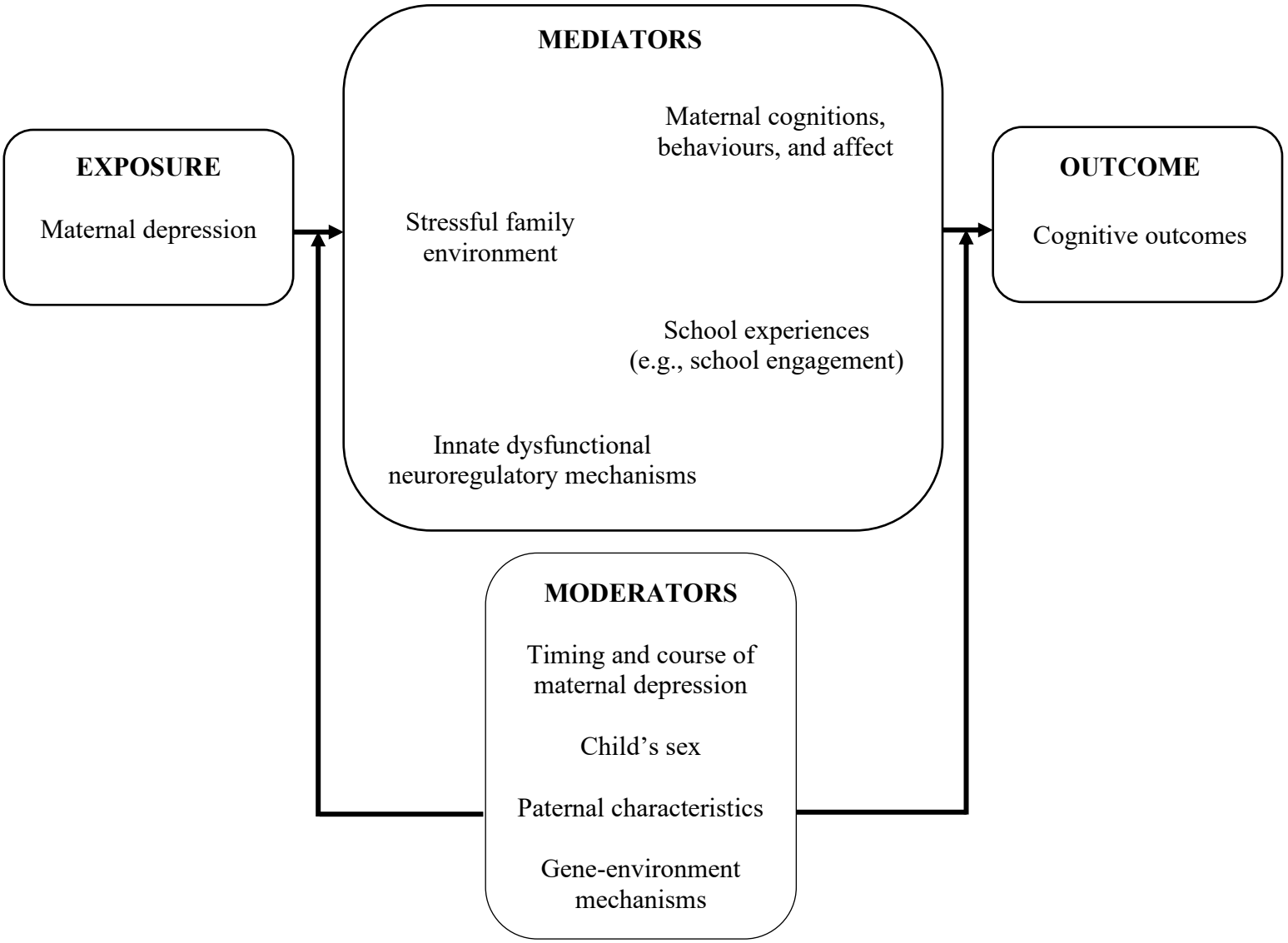
(4) To what extent does the current literature support Goodman & Gotlib's (1999) hypothesis that child's sex moderates the association between maternal depression and children's cognitive outcomes?

Findings from *Articles 1* to *4* answer these questions and address gaps in the existing literature by showing that: (1) only a handful of studies have examined Goodman & Gotlib's (1999) model in relation to children's cognitive outcomes, and most of them have identified negative maternal cognitions, behaviours, and affect as a significant mediator of the association between maternal depression and cognitive outcomes; (2) although maternal depression is longitudinally associated with academic performance in both boys and girls, school engagement only mediates the association in girls; (3) maternal depression moderates genetic and environmental contributions to children's cognitive school readiness; and (4) the current literature suggests that child's sex does moderate the association between maternal depression and cognitive outcomes, with boys at higher risk. Furthermore, these findings build on my Master's research which showed that the timing and course of (postnatal) maternal depression moderated the association between maternal depression and children's cognitive outcomes, whereby children exposed chronically were at greatest risk (Ahun et al., 2017). Overall, these findings suggest that addressing maternal cognitions, behaviours, and affect can help mitigate the negative effect of maternal depression on children's cognitive outcomes. They also suggest that boys and children chronically exposed to maternal depression may benefit more from interventions targeting maternal depression, and that for girls, addressing the impact of maternal depression on their school engagement may lead to improved cognitive outcomes. These findings scientifically contribute to theoretical and empirical understandings of the association between maternal depression and children's cognitive development.

From a theoretical perspective, our findings extend Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission* in three important ways. First, the results of *Article 3* suggest that the role of gene-environment mechanisms in the association between maternal depression and children's cognitive outcomes is better conceptualized as a moderator rather than a mediator. In other words, although heritability of genes that increase children's risk for mental health problems may mediate the association between maternal depression and child psychopathology, there is a moderation of genetic – and environmental – factors in the association between maternal depression and children's cognitive outcomes. Second, by exploring children's school experiences as potential mediators of the association between maternal depression and cognitive outcomes in *Article 2*, we extend Goodman & Gotlib's (1999) model to consider how factors outside of the family environment may explain the mechanisms of this association. Specifically, given that the home and school microsystems influence each other, it is possible that negative maternal cognitions, behaviours, and affect or a stressful family environment had an impact on school engagement, which subsequently influenced academic performance (Bronfenbrenner 1979; Nutbeam 1998). However, as we did not directly test whether there was an indirect effect of maternal depression on school engagement via these mediators, further studies are needed to test this serial mediation hypothesis. Third and lastly, our findings support Goodman's (2020) extension of the *Developmental Model for Understanding Mechanisms of Transmission* to embrace the notion of multiple mechanisms. Findings from *Articles 2* and *4* suggest that in addition to moderating the direct effect of maternal depression on children's cognitive outcomes, child's sex can also moderate the indirect effect of maternal depression on children's cognitive outcomes via the proposed mediators. It is also possible that the other moderators in the model (e.g., paternal characteristics) may also moderate the indirect

effects of maternal depression on children's cognitive outcomes. ***Figure 10*** illustrates the ways in which the studies in this dissertation extend Goodman & Gotlib's (1999) model. This extended framework can be used to guide future research on the mechanisms through which maternal depression influences children's cognitive outcomes.

**Figure 10.** An extension of Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission*



From an empirical perspective, our findings contribute to the advancement of knowledge regarding effective ways to provide healthy environments for children exposed to maternal depression and thus has important implications for public health and health promotion (Lund et al., 2018; National Scientific Council on the Developing Child, 2020; WHO Commission on Social Determinants of Health & World Health Organization, 2008; Richter et al., 2017). By using robust longitudinal methods to examine how the settings (or microsystems) within which children are embedded influences their health, this dissertation sheds light on the complex genetic and environmental processes that impact population health over time (Jaffee & Price, 2007; Khoury et al., 2011). For example, our analysis of school experiences as mediators of the association between maternal depression and academic performance in *Article 2* supports the realistic conceptualization of the home and school microsystems as open and dynamic spaces that interact with and influence each other (Bronfenbrenner 1979; Nutbeam 1998; Lund et al., 2018). We found that the impact of maternal depression on mediating factors is not only limited to the home, but that it also influences how children interact with their learning environment, particularly their school engagement.

These results support the use of interventions that empower mothers and children to improve their personal skills in parenting and learning, respectively, as outlined in strategy four of the Ottawa Charter on health promotion (Kickbusch 2003; World Health Organization 1986). This identification of key mediators that interventions can target to improve cognitive outcomes in children exposed to maternal depression is particularly important given the minimal impact of maternal depression interventions on children's cognitive outcomes (Goodman et al., 2018; Letourneau et al., 2017; O'Connor et al., 2019; Rahman et al., 2018; Tsivos et al., 2015). Furthermore, our findings are in line with the emergent understanding of the importance of addressing maternal parenting skills in interventions to prevent or treat maternal depression to have

significant impacts on child outcomes (Galbally & Lewis, 2017; Goodman, 2007; Goodman, 2020; Goodman & Garber, 2017; Howard & Khalifeh, 2020; Rahman et al., 2018; Rayce, Rasmussen, Væver, & Pontoppidan, 2020).

In addition to these scientific contributions, the present dissertation – particularly *Articles 1* and *4* – supports knowledge translation by providing summaries of what we know and what we do not know about why (i.e., mediators) and for whom (i.e., moderators) maternal depression has an effect on children's cognitive development (Khoury et al., 2010). The results of *Article 4* suggest that maternal depression does not influence boys and girls in the same way. We should therefore consider these sex differences in the design, implementation, and evaluation of interventions. For example, moderation analyses of a parenting intervention only found significant improvements in boys' behavioural outcomes, suggesting that the intervention may need to be modified to address behavioural problems in girls (Gardner, Hutchings, Bywater, & Whitaker, 2010). Findings from *Article 2* further underscore these sex differences, showing that school engagement is a significant mediator for girls but not for boys. Trying to improve children's investments in their learning activities may therefore help to mitigate the negative effects of maternal depression on academic performance in girls but perhaps not in boys. To better translate these findings into practice, further research is needed to examine not only sex differences in the impact of maternal depression, but also whether different mediators explain its impact on cognitive outcomes in boys and girls. Furthermore, findings from *Article 1* show that there is still a lot we do not know about the role of a stressful family environment and innate dysfunctional neuroregulatory mechanisms as mediators of the association between maternal depression and children's cognitive outcomes.

## 5.4 Public health and health promotion implications

The findings of this dissertation elucidate promising avenues for promoting children's healthy cognitive development. However, to better promote change at a population level, this information must be combined with findings from other empirical work on the social determinants of children's cognitive development to identify the best public health and health promotion interventions to improve child outcomes and contribute to the wellbeing of the overall family unit. Below, I reflect on some of these interventions, their practical implications, and how they should be prioritized to reach different subgroups within the population.

### *Addressing the social determinants of children's cognitive development*

As discussed in Chapter 2 (section 2.1), in addition to maternal depression, there are various factors within the home and school microsystems which can hinder or promote healthy cognitive development (Black et al., 2017; Bronfenbrenner, 1979; Grantham-McGregor et al., 2007; National Scientific Council on the Developing Child, 2020; Nutbeam, 1998; Walker et al., 2007, 2011). Thus, interventions that focus on improving the different settings within which children and their families are embedded – rather than focusing on maternal behaviour change alone – are also needed to promote children's healthy cognitive development. For example, there is ample evidence that the use of early childhood care and education services (i.e., childcare) is associated with significant improvements in various cognitive outcomes including reading, vocabulary, intelligence, school readiness, and academic performance across childhood and adolescence (see Burger, 2010; Melhuish et al., 2015 for reviews). Furthermore, some studies show that children from families with a low socioeconomic status – another factor associated with cognitive development – who attend childcare have better cognitive outcomes than their peers

from higher socioeconomic strata (Burger, 2010; Melhuish et al., 2015). This evidence suggests that investing in early childhood care and education – for example via the implementation of subsidies to make services more affordable or the training of the work force to ensure high-quality services (McLaren & McIntyre, 2014) – can help improve children's cognitive outcomes at the population level. With respect to the potential of early childhood care and education to attenuate the detrimental impact of maternal depression on children's cognitive development, the evidence is less clear. Although a number of studies have reported that attending high-quality childcare reduces the risk of emotional and behavioural problems in children exposed to maternal depression (Charrois et al., 2017, 2020; Herba et al., 2013), it is not clear whether this moderation effect applies to cognitive outcomes (Paquin et al., 2020). Further research exploring the moderating role of childcare services in the association between maternal depression and children's cognitive outcomes is therefore needed to inform public health and health promotion approaches.

Growing up in poor/low socioeconomic status households can also negatively impact cognitive outcomes across the lifespan (Aber, Bennett, Conley, & Li, 1997; Baker, Kainz, & Reynolds, 2018; Brooks-Gunn & Duncan, 1997; Heckman, 2011; Lacour & Tissington, 2011; Phillips & Shonkoff, 2000; Saitadze & Lalayants, 2020) – and is also a risk factor for maternal depression (Field, 2017; Fisher et al., 2012; Hammen, 2018; Howard et al., 2014; Lund et al., 2010; O'Connor et al., 2019). Interventions which aim to improve the socioeconomic conditions of families can therefore be used as a health promotion tool for healthy cognitive development. For example, the *Preparing for Life* community-based intervention in Ireland provided families from low socioeconomic backgrounds with developmental toys, facilitated access to preschool and an information officer who provided details about public services (e.g., childcare, housing), and assigned local health, social work, education, and mental health providers as mentors to support

and educate parents about child development throughout pregnancy and the first few years of life (Doyle & PFL Evaluation Team, 2016; Doyle, Harmon, Heckman, Logue, & Moon, 2013). The intervention led to significant improvements in cognitive functioning and language skills post-intervention, as well as improved school readiness at school entry (Doyle & PFL Evaluation Team, 2016). In another example, a systematic review of interventions that facilitated employment for single parents by providing financial incentives (e.g., free job/education training, healthcare subsidies, earning supplements) reported significant improvements in children's cognitive and mental health outcomes (Gibson et al., 2017). Both *Preparing for Life* and the interventions included in the review also found significant improvements in maternal mental health and psychosocial wellbeing outcomes (Doyle, Delaney, O'Farrelly, Fitzpatrick, & Daly, 2017; Gibson et al., 2017). Despite the consideration of paternal outcomes in the inclusion criteria of the systematic review and the inclusion of both parents in the *Preparing for Life* intervention, only intervention impacts on maternal outcomes were reported.

***Moving towards family-centered early childhood interventions***

Since mothers are most often the primary caregivers of young children, the overwhelming majority of early childhood interventions to promote cognitive development has focused on mothers (Jeong et al., 2018; Ramchandani & Psychogiou, 2009; Richter et al., 2011). However, this focus may inadvertantly place an undue burden on mothers to change their behaviours and thus lead to mother-blaming. For example, quantitative and qualitative evidence from the maternal depression literature highlight how mental health screening services during the perinatal period can be potentially stigmatizing. Specifically, mothers identified structural (e.g., experience of discrimination from healthcare providers) and individual (e.g., fear of being labelled with a

"disease", fear of having child referred to child protective services) factors which hindered the likelihood of seeking care for depressive symptoms (Canty, Sauter, Zuckerman, Cobian, & Grigsby, 2019; Leis, Mendelson, Perry, & Tandon, 2011; Lara-Cinimoso, Clark, & Wood, 2018). Mothers also identified potential improvements to address these barriers, including cultural sensitivity training for health professionals (Howard & Khalifeh, 2020; Lara-Cinimoso et al., 2018; Rojas-García, Ruíz-Pérez, Gonçalves, Rodríguez-Barranco, & Ricci-Cabello, 2014) and the implementation of psychoeducation programs by trusted health professionals (e.g., community nurses). This line of research highlights the need for public health and health promotion actors to reflect on the ethical implications of early childhood interventions which only target mothers.

Another limitation of the focus on mothers in early childhood interventions is that doing so minimizes the important contributions of fathers to their child's development. In the past two decades, there has been a burgeoning interest in understanding how paternal charactersitics (including paternal depression) independently – and in interaction with maternal characteristics – influence child development (Barker et al., 2017; Connell & Goodman, 2002; Cui et al., 2020; Ramchandani & Psychogiou, 2009; Panter-Brick et al., 2014; Sweeney & MacBeth, 2016; Wanless et al., 2008; Wickersham, Leightley, Archer, & Fear, 2020). Ramchandani & Psychogiou (2009) even adapted Goodman & Gotlib's (1999) model, using it as a framework to understand the mechanisms of the association between paternal depression and child development. Although there is little evidence to suggest that treating paternal depression alone leads to improved cognitive outcomes in children (Galbally & Lewis, 2017; Goldstein, Rosen, Howlett, Anderson, & Herman, 2020; Rominov, Pilkington, Giallo, & Whelan, 2016), parenting interventions which have included fathers have found significant impacts on children's cognitive outcomes (Doyle & PFL Evaluation Team, 2016; Jeong et al., 2018; Panter-Brick et al., 2014). Moving forward,

interventions which aim to improve children's developmental outcomes need to actively engage both mothers and fathers as co-beneficiaries and evaluate intervention impacts on child, maternal, paternal, and overall family wellbeing outcomes (Howard & Khalifeh, 2020; Panter-Brick et al., 2014).

### *Promoting healthy cognitive development in different population subgroups*

In light of these considerations, public health and health promotion actors need to work on multiple levels (family, community, school/learning environments) to leverage the strengths and limitations of each approach to promote children's healthy cognitive development. Furthermore, priorities concerning which level to act on should be established based on the target population of interest: the general population, subgroups at increased risk of experiencing maternal – and/or paternal – depression, and subgroups experiencing maternal – and/or paternal – depression.

Given that most mental health problems begin in childhood or adolescence, an effective way to promote mental health across the lifespan – including during child-bearing years – for the general population is the implementation of school- and community-based universal mental health promotion interventions that focus on improving social and emotional skills, positive behaviours, social inclusion, and effective problem-solving skills (Barry, 2019; Fazel, Hoagwood, Stephan, & Ford, 2014; Mendez, Ogg, Loker, & Fefer, 2013; National Scientific Council on the Developing Child, 2020; O'Donnell & Meaney 2017). Promoting the mental health of future parents can help ensure the healthy development of children. These health promotion interventions can be coupled with universal primary preventive interventions that prevent the onset of parental depression by targeting the social determinants of mental health (Lund et al., 2018). Targeted preventive interventions can also be used to prevent the onset of depression in subgroups of the population

who are at increased risk of experiencing parental depression. However, because few studies have specifically assessed the effectiveness of mental health promotion and universal primary preventive interventions to improve mental health during the perinatal period, further empirical evidence is needed to clarify the promise of such interventions to prevent the onset of parental depression (Howard & Khalifeh, 2020; Lund et al., 2018). This will require the implementation of a range of study designs, including randomized controlled trials to determine the effectiveness and efficacy of targeting specific determinants, qualitative research to ensure that interventions are culturally and contextually relevant, and mixed-method implementation research to assess the scaling up of evidence-based interventions (Arango et al., 2018; Howard & Khalifeh, 2020; Lund et al., 2018).

For subpopulations experiencing maternal – and/or paternal – depression, a two-pronged approach should be prioritized. For families with young children, integrated interventions that target parental depression and the modifiable risk processes through which it influences child outcomes may help attenuate the impact on child outcomes (Galbally & Lewis; Goodman & Garber, 2017; Howard & Khalifeh, 2020). Given that parenting behaviours mediate the association between maternal depression and children's cognitive development, and evidence that teaching parents how to better care for and interact with their children does lead to improved cognitive outcomes in children (Aboud & Yousafzai 2015; Barker et al., 2017; Britto et al., 2017; Goodman et al., 2020; Jeong et al., 2018; Teti et al., 2017), integrated interventions that promote positive parenting behaviours and parental mental health could help improve both child and parental outcomes (Galbally & Lewis; Goodman & Garber, 2017; Howard & Khalifeh, 2020).

For families with older children, findings from *Article 2* suggest that the school microsystem may be an important focus for mitigating the negative impact of maternal depression

on children's cognitive outcomes. Such school-based interventions could help improve the outcomes of children who have been exposed to maternal – and/or – depression. However, there is currently little evidence to indicate their potential impact on parental depression itself. Nevertheless, given the efficiency of school-based interventions for both parents and children and that some studies have found significant positive effects of school-based mental health interventions on parental outcomes (e.g., improved parent-child communication, decreased parenting stress), it is worth exploring their potential for attenuating the impact of parental depression on child outcomes (Fazel et al., 2014; Mendez et al., 2013).

### 5.5 Emerging issues and future research

The evidence produced in the current dissertation is relevant to the new public health's aim of providing a healthy growing environment for children (Baum 2008; Black et al., 2017; Britto et al., 2017; Shonkoff et al., 2009; Richter et al., 2017; Walker et al., 2011). However, further research is needed to shed light on gaps in the literature that were not addressed in this dissertation.

One important avenue for future research on the association between maternal depression and children's cognitive development is the exploration of resiliency in children exposed to maternal depression. Given that not all children exposed to maternal depression experience negative outcomes, research into how children maintain positive physical health, socioemotional, behavioural, and cognitive outcomes despite exposure to risk can help inform the development of health promotion interventions to strengthen these factors (Chmitorz et al., 2018; Masten, 2001). Although I did not examine whether maternal depression was associated with positive child outcomes in the present dissertation, the findings align with the emerging literature on the role of resilience in the association between maternal depression and children's cognitive outcomes.

Studies have identified high maternal warmth and high child self-esteem as internal and external resources that protect children from the negative effects of maternal depression (Pargas, Brennan, Hammen, & Le Brocque, 2010; Reuben & Shaw, 2015). Further research on personal and family resources that promote resilience in children exposed to maternal depression – and parental mental health problems more broadly – is needed to inform the development of interventions to promote these skills. Finally, the resilience literature also highlights the importance of addressing the multiple risk and protective factors (including those discussed in Chapter 2 and section 5.4) that influence children's cognitive development in future studies (Reuben & Shaw 2015).

Another important aspect of the association between maternal depression and children's cognitive outcomes – which I was unable to address in this dissertation due to low paternal response rates in both the QLSCD and the QNTS (Boivin et al., 2013; Orri et al., 2020) – is the role of paternal characteristics. As described in Chapter 2 (section 2.3.1.2), although the majority of the paternal depression literature focuses on its impact on children's mental health outcomes, a handful of studies have examined its impact on their cognitive outcomes (Fredriksen et al., 2019; Paulson et al., 2009; Wanless et al., 2008). Importantly, these studies are reflecting the key role both mothers and fathers play in children's development by examining the independent and interacting effects of maternal and paternal depression on child outcomes. For this new wave of research to properly leverage what we already know about the associations between maternal depression and children's cognitive outcomes, researchers will need to shed light on existing gaps between the research and practice of how we promote early childhood development. As discussed in section 5.4, there is some evidence that addressing both maternal depression and parenting behaviours can lead to positive impacts on mothers and children, but further research is needed to understand impacts on fathers (Akbarzadeh, Dokuhaki, Joker, Pishva, & Zare, 2016; Singla,

Kumbakumba, & Aboud, 2015). I hope to contribute to this line of research during my postdoctoral fellowship by collaborating with early childhood development, parental mental health, parenting, and implementation researchers to develop an evidence-based intervention to promote both positive parenting behaviours and mental health in mothers and fathers and examine its impact on child development and overall family wellbeing.

I will also address another important emerging issue in my postdoctoral research, namely how multiple mechanisms interact with each other to explain the association of maternal and paternal depression with children's developmental outcomes (Goodman 2020). The methodology used in *Article 2* addressed this issue in part by not only examining school experiences as a mediator of the association between maternal depression and academic performance, but also testing whether sex moderated any of the associations between the exposure, mediator, and outcome variables. Using the extension of Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission* (***Figure 10***) as a guide, future research will need to reflect the complexity of how different characteristics interact to influence health outcomes by using models that allow for the testing of multiple mediators and the extent to which moderators influence mediated associations. In my postdoctoral research, I will do this by not only examining how parenting mediates the impact of the mental health component of the intervention on child outcomes, but also testing whether mental health mediates the impact of the parenting component on child outcomes, and accounting for the moderating roles of parent and child's sex on the direct and indirect effects of the different intervention components on children's developmental outcomes. I will also examine the independent and interactive effects of maternal and paternal characteristics and explore the impact of both components of the intervention on overall family wellbeing (e.g., marital quality/interparental conflict, family functioning). Finally, by addressing

mental health broadly – rather than focusing on a specific mental health problem – and targeting the intervention to a rural region in a lower-middle-income country, where children are more likely to be exposed to risk factors that co-occur with mental health problems, this research will enable us to examine the social determinants of mental health and how they influence children's developmental outcomes and family wellbeing.

### 5.6 Conclusion

The present dissertation strengthens empirical support for the association between maternal depression and children's cognitive development by advancing our understanding of the role of mediators and moderators in this association. In line with Goodman & Gotlib's (1999) *Developmental Model for Understanding Mechanisms of Transmission*, we found that maternal cognitions, behaviours, and affect mediated the association between maternal depression and children's cognitive outcomes (*Article 1*) and that boys experienced poorer cognitive outcomes than girls (*Article 4*). We also extended the model by exploring the extent to which maternal depression moderates genetic and environmental contributions to children's cognitive school readiness (*Article 3*) and identifying school engagement as a mediator in the association between maternal depression and academic performance in girls (*Article 2*). These findings underscore the importance of the early childhood environment for ensuring healthy child development and reinforces both preventive public health measures and health promotion strategies to promote healthy cognitive development. Furthermore, this research highlights important issues in the maternal depression-child development literature that need to be addressed to further our understanding of the early childhood environment and ensure that children are given the best start in life.

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Appendix I – Ethics Approval for Québec Longitudinal Study of Child Development and Québec Newborn Twin Study

Québec Longitudinal Study of Child Development

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Université de Montréal

Le 25 septembre 2020

Docteur Richard E. Tremblay
CHU Sainte-Justine

| Objet | Renouvellement de l'approbation éthique - CÉR |
|---|---|
| | 2009-200, 2762 BANQUE DE DONNÉES ÉLDEQ : ÉLDEQ (EN 2002) Étude longitudinale du développement des enfants au Québec<br>Co-chercheurs: Michel BOIVIN; Sylvana Côté, PhD; Dr Frank Vitaro; Jean Séguin; Nathalie Fontaine<br>F9-26426 |

Docteur,

Ayant reçu les résumés des demandes d'accès aux données GRIP pour analyses exploratoires (DADex) et pour publication (DADpub) pour les périodes de l'année 2018 à 2019, nous avons le plaisir de vous annoncer que votre projet cité en rubrique a été renouvelé par le comité d'éthique de la recherche en date du 23 septembre 2020. La durée de votre approbation sera effective jusqu'au 23 **septembre 2021.** Le document suivant est approuvé :

- Politique de gestion des banques de données modifié daté du 14 août 2018

Il est de votre responsabilité d'aviser le comité dans les plus brefs délais de toute modification au protocole.

Un résumé des demandes d'accès aux banques doit être acheminé au comité du CHU Sainte-Justine 1 fois par année lors du renouvellement.

En vous souhaitant une bonne poursuite de votre projet,

Samira Akrah
Responsable administrative des projets de recherche en cours
Bureau de l'éthique de la recherche
Pour Carolina Martin, conseillère en éthique

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Université de Montréal

Le 23 septembre 2020

Monsieur Frank Vitaro
CHU Sainte-Justine

| Objet | Renouvellement de l'approbation éthique - CÉR |
|---|---|
| | 2009-202, 2764 BANQUE DE DONNÉES ÉJNQ : Projet ÉJNQ Étude des jumeaux nouveau-nés du Québec<br>Co-chercheurs: Mara Rosemarie Brendgen; Ginette DIONNE; Michel BOIVIN<br>F9-26427 |

Monsieur,

Ayant reçu les résumés des demandes d'accès aux données GRIP pour analyses exploratoires (DADex) et pour publication (DADpub) pour les périodes de l'année 2019-2020, nous avons le plaisir de vous annoncer que votre projet cité en rubrique a été renouvelé par le comité d'éthique de la recherche en date du 23 septembre 2020. La durée de votre approbation sera effective jusqu'au **23 septembre 2020.** Le document suivant est approuvé :

- Politique de banque modifiée datée du 03 juillet 2019

Il est de votre responsabilité d'aviser le comité dans les plus brefs délais de toute modification au protocole.

Un résumé des demandes d'accès aux banques doit être acheminé au comité du CHU Sainte-Justine 1 fois par année lors du renouvellement.

En vous souhaitant une bonne poursuite de votre projet,

Samira Akrah
Responsable administrative des projets de recherche en cours
Bureau de l'éthique de la recherche
Pour Carolina Martin, conseillère en éthique

Appendix II – Items used to assess maternal depression, school engagement, peer victimization, and mother-child interactions

**Maternal depression: Center for Epidemiologic Studies Depression Scale short version**

Mother-reported experience of depression symptoms over the last 7 days (5 months, 1½ , 3½ , and 5 years in the QLSCD and 5 months and 1½ years in the QNTS ). The frequency of each symptom was rated on a scale of: “Rarely or none of the time (< 1 day)”; “Some or a little of the time (1-2 days)”; “Occasionally or a moderate amount of time (3-4 days)”; “Most or all of the time (5-7 days)”.

1. I did not feel like eating: my appetite was poor
2. I felt that I could not shake off the blues even with help from my family or friends
3. I had trouble keeping my mind on what I was doing
4. I felt depressed
5. I felt that everything I did was an effort
6. I felt hopeful about the future
7. My sleep was restless
8. I was happy
9. I felt lonely
10. I enjoyed life
11. I had crying spells
12. I felt that people disliked me

**School engagement: Early Development Instrument**

Teacher-reported cognitive school engagement in QLSCD children over the past 12 months. The frequency of each behaviour was rated on a scale of: “Never”; “Rarely”; “Sometimes”; “Often”; “Always”.

At 6 years:

1. Is curious about the world
2. Is willing to play with a new toy
3. Is willing to play a new game
4. Shows a keen interest in playing with or reading a new book

At 7, 8, and 10 years:

1. Challenges the teacher in a positive way
2. Shows creativity
3. Is capable of resolving problems
4. Puts a lot of effort into work
5. Participates in class
6. Asks questions when he/she does not understand

Teacher-reported behavioural school engagement in QLSCD children over the past 12 months. The frequency of each behaviour was rated on a scale of: “Never”; “Rarely”; “Sometimes”; “Often”; “Always”.

At 6 years:

1. Listens attentively
2. Follows instructions
3. Finishes assignments on time
4. Works autonomously
5. Works cleanly and carefully
6. Is capable of resolving daily problems on his/her own
7. Is capable of following instructions with only one step
8. Is capable of following class routines without being reminded
9. Is capable of adapting to changes in the schedule

At 7, 8, and 10 years:

1. Listens attentively
2. Follows instructions
3. Finishes assignments on time
4. Works autonomously
5. Works cleanly and carefully

Child-reported emotional school engagement in QLSCD children over the past 12 months (6, 7, 8, and 10 years). Reponses to each item were rated on a scale of: “Strongly disagree”; “Disagree”; “Uncertain”; “Agree”; “Strongly agree”

1. I am proud to be studying at this school
2. I am happy to be studying at this school
3. I feel safe at my school
4. Most mornings, I feel like going to school
5. I like my school

**Peer victimization: Adapted version of Self-report Victimization Scale**

Mother- and father-reported (6 years) and teacher- and child-reported (6, 7, 8, and 10 years) peer victimization in QLSCD children over the past 12 months. The frequency of each perceived victimization behaviour was rated on a scale of: “Never or not true”; “Once or twice or somewhat true”; “More often or very true”

Has the [INSERT TARGET CHILD NAME] been…

1. Called names or had mean things said to them by other children?
2. Hit, pushed, or kicked by other children?
3. Laughed at or teased by other children?

**Mother-child interactions: Home Observation for Measurement of the Environment**

Trained research assistants observed and rated the behaviours of mothers and each of their twin children in the QNTS (2½ years). Behaviours were rated on a scale of: "Never"; "Rarely"; "Sometimes"; "Often"; "Always"

Coercive behaviours

1. The mother shouts at the child
2. The mother seems visibly annoyed by the child and is hostile towards child
3. The mother hits or spanks the child
4. The mother scolds and criticizes the child

Stimulation behaviours

1. The mother consciously encourages the progress of her child in the child's development
2. The mother values educational games by the amount of attention she gives them
3. The mother structures her child's play time
4. The mother provides toys which stimulate her child and helps the child develop new skills
5. The mother provides toys or interesting activities for the child during the visit

Verbalization behaviours

1. The mother spontaneously vocalizes (makes sounds) with her child (excluding shouting)
2. The mother responds to her child's vocalizations by talking to her child
3. The speech of the mother when talking to her child is audible, clear, and distinct

4. During the visit, the mother (i) talks a little; (ii) talks in an almost intelligible way; (iii) talks in a moderate and coherent manner; (iv) talks almost constantly
5. The mother initiates verbal exchanges with the interviewer, asks questions, makes spontaneous comments
6. The mother expresses her ideas freely and easily and gives answers of an appropriate length in the conversation (e.g., gives more than short answers)
7. The mother spontaneously praises the qualities or the behaviour of her child
8. When she speaks to or about her child, the mother's voice expresses positive sentiments
9. The mother caresses or hugs her child during the visit
10. The mother manifests positive sentiments when the interviewer makes flattering comments with respect to her child