EXPLORATION IN THE BIOPSYCHOSOCIAL MODEL OF STRESS AND MENTAL HEALTH AND ILLNESS: RISK FACTORS, MODERATORS, MEDIATORS AND IMPACTS

A Thesis Submitted to the College of
Graduate and Postdoctoral Studies
In Partial Fulfillment of the Requirements
For the Degree of Doctor of Philosophy
In the School of Public Health
University of Saskatchewan
Saskatchewan

By

Yingying Su

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Canada

ABSTRACT

Stress has a profound impact on the brain and body in life. Stressors can lead to a wide range of adverse short- and long-term mental health problems, such as depression, post-traumatic stress disorder, anxiety, and reduced cognitive functioning. The biopsychosocial model proposed by Engel incorporates both biological and psychosocial factors and focuses on genetic predispositions, and environmental factors which play a crucial role in the process of individual's development across the life span. The primary goal of this thesis is to better understand the relationship between social stress and mental disorders with the application of a variety of epidemiological techniques using a variety of data sources.

This thesis is composed of eight chapters. The first introductory chapter describes the biopsychosocial perspective. The second chapter describes the data sources and methods used in the five substantive studies reported in each of the following chapter.

The first substantive study (Chapter 3) using a population-based survey examined the rural-urban differences in the experience of abuse during pregnancy in Canada. The study findings indicated that living in an urban environment was associated with a slightly increased risk of experiencing abuse around the time of pregnancy. In addition, being aboriginal, young, unmarried, economically disadvantaged, a non-immigrant, and having more than four pregnancies, as well as cigarette smoking, alcohol drinking and drug use before the pregnancy were correlated with the abuse around the pregnancy. Postnatal depression and stressful life events were also found to be associated with the abuse experience around the time of pregnancy both in urban and rural areas.

Using a cross-sectional study design, our second study (Chapter 4) investigated the mediating roles of social support and positive coping skills in the relationships between childhood maltreatment and both psychological distress and positive mental health in a national Canadian population sample. Social support and positive coping skills were both found partially mediated the negative consequences of childhood maltreatment on mental health outcomes with coping skills having a greater impact on positive mental health. No sex differences were observed among these associations.

In the third study (Chapter 5), the dynamic relationships between income and self-perceived mental health were explored in a longitudinal prospective community study at both population level and individual level. The effect of income on the self-perceived mental health was only found at population level. In addition, correlations between income and self-perceived mental health were significant among different sex and age groups only at population level, with stronger effects of income in men and older adults.

The fourth study (Chapter 6), a systematic review and meta-analysis of prospective longitudinal studies, found that the maternal experience of childhood maltreatment had a small but significant effect on the offspring's depression and internalizing behaviors. Maternal depression and ethnicity were found to be the moderators among this relationship. Maternal depression reduced the effect size of the impact of maternal maltreatment on offspring's depression and internalizing disorders. The offspring of non-Caucasian mothers who themselves had childhood maltreatment experience had a higher risk of mental disorders.

With the biopsychosocial model framework, the final study (Chapter 7), a systematic review with meta-analysis and qualitative analyses, found that low birth-weight, premature birth, small gestational age, maternal education, socioeconomic status, having young parents (<20 years), having older parents (≥35 years), maternal smoking, paternal smoking, maternal stress, maternal anxiety, and maternal prenatal depression significantly increased the risk of depression in offspring.

The final Chapter 8 summarizes our findings and conclusions. The key takeaway message of this research is that various stress across the life span has an adverse impact on the mental health well-beings. And stress-related factors, including biological factors, social factors and psychological factors (external and internal personal resources) both separately or combined contribute to mental disorders. Also evident is the impact of early life experiences on adult mental health. From a public health prevention perspective attention needs to be paid to the healthy pregnancies and an emotionally healthy childhood and adolescence.

ACKNOWLEDGMENTS

First, I would like to express my special appreciation and thanks to my supervisor Dr. Carl D'Arcy for his invaluable advice, permanent support and encouragement, and patience during my PhD study. He has set an example of excellence as a researcher, mentor, instructor, and role model. Without his guidance and constant feedback this PhD would not have been achievable.

I would also like to thank my advisory committee members, Dr. Xiangfei Meng, Dr. Cindy Feng, Dr. Lodhi Rohit and Dr. Rein Lepnurm, for their insightful comments and guidance, and timely feedbacks throughout my studies. I also want to thank Mrs. Marylin Rana, thesis-based program assistant, for her support and help in managing and organizing committee meetings. I truly appreciate all the effort and work they have done to me.

I truly acknowledge my family and friends for their enduring support of me during my doctoral program and my dissertation. Thank them for sharing both of my excitement moments and frustration moments during my research studies. More importantly they always encourage me to follow by dreams no matter where they may lead and no matter how long it may take me to realize them. It is their unconditional love that make me go this far and complete my program in time.

I acknowledge the financial support received from the China Scholarship Council for my doctoral program. I would like to acknowledge the Saskatchewan Research Data Centre (SKY-RDC) for granting me accesses to national health survey data. I also acknowledge the travel awards received jointly from the College of Graduate and Postdoctoral Studies, the International Student and Study Abroad Centre, the Graduate Students Association and the University of Saskatchewan Students' Union.

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LIST OF ABBREVIATIONS

5-HTTLPR	Serotonin-transporter polymorphism
CCHS-MH	Canadian Community Health Survey-Mental Health
CFA	Confirmatory factor analysis
CLPM	Cross-lagged panel model
CNS	Central nervous system
CRH	Corticotrophin-releasing hormone
DALYs	Disability adjusted life years
DOHaD	Developmental origins of health and disease
EPDS	Edinburgh postnatal depression scale
FKBP5	FKBP Prolyl Isomerase 5
GA	Gestational age
HPA	Hypothalamic-pituitary-adrenal
LBW	Low birth weight
MES	Maternity Experience Survey
MLR	Robust maximum likelihood
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NOS	Newcastle-Ottawa Scale
PB	Preterm birth
PTSD	Post-traumatic stress disorder
RI-CLPM	Random intercept cross-lagged panel model
SEM	Structural equation modeling
SEP	Socio-economic position
SES	Socioeconomic status
SGA	Small gestational age
SNS	Sympathetic nervous systems
SPMH	Self-perceived mental health
YLDs	Years lived with disability
ZEPSOM	Social and Psychiatric Epidemiology Catchment Area of the South West

CHAPTER 1. INTRODUCTION

1.1 The Burden of mental illness

Mental health is stated by World health organization (WHO) as: "*… a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*." Rather than just the absence of mental disorders or disabilities, mental health implies "*a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community*" (World Health Organization, 2014). A systematic review and meta-analysis across 155 general population surveys undertaken in 59 countries, showed that on average one in five adults (20%) experienced a common mental disorder during the previous 12 months and 29.2% during their lifetime (Steel et al., 2014).

In 2010 WHO estimated that 12.3% of global burden of diseases was attributable to mental disorders (World Health Organization, 2011), and this was expected to rise to 15% by the year 2020 (Murray, Lopez, & World Health Organization, 1996). Mental disorders are seen leading causes of the growth of overall morbidity and disability worldwide. The Global Burden of Disease calculation of disability adjusted life years (DALYs) ranked mental disorders as high as cardiovascular diseases and respiratory diseases and surpassed all types of cancer, with major depression ranking second and anxiety disorders ranking ninth among non-communicable diseases in terms of disability (Ustün, 1999; Vos et al., 2015; Whiteford et al., 2013). The disease burden for mental illness is estimated to account for 32.42% of years lived with disability (YLDs) and 13.03% of disability adjusted life years (DALYs) (Vigo, Thornicroft, & Atun, 2016). The economic costs of mental disorders are also substantial, including both direct disability costs and societal costs, such as loss of productivity. The World Economic Forum estimates that mental disorders account for one-third of the costs associated with non-communicable diseases (Bloom et al., 2012).

1.2 Stress and mental health

Stress is seen as a significant risk factor in the etiology of mental illnesses. Stress itself is not just caused by a specific experience happening to the individual but it is also due to lack of resources

for dealing with the initial stressor that results in stress (Lazarus & Folkman, 1984). A stressor is formally defined as "*conditions of threat, challenge, demands, or structural constraints that, by the very fact of their occurrence or existence, call into question the operating integrity of the organism*" (Aneshensel, Phelan, & Bierman, 2013). The catalogue of individual stressors is extensive as they range from the broadest of social forces and large-scale social organization to the personal social environments in which people function on a daily basis (Weiss & Lonnquist, 2017). At a basic level, stressors are classified into two broad categories: discrete and continuous stressors (Wheaton, 1996). Discrete stressors refer to individual major events, for example divorce, job loss and bereavement which happened rarely but may result in observable and dramatic life changes. However, continuous stressors are ongoing stressors that permeate our daily reality (Serido, Almeida, & Wethington, 2004). For Aneshensel and colleagues stress is a continuum from sudden traumas that naturally occur as events to chronic conditions which may build slowly. In-between there are various other types of stressors including life-course transitions, daily hassles, nonevents and chronic stressors (Aneshensel, Phelan, & Bierman, 1999).

Research suggests that exposure to various stressors, including major events, common hassles and chronic stressors, can threaten the well-being of individuals both directly and indirectly. Through the influence on physiological processes such as immune function, chronic stress can directly increase risk of diseases (Folkman, 2013). Many common stressors have been linked to mental disorders, including depression and anxiety, as well as post-traumatic stress disorder (PTSD) (Esch, Stefano, Fricchione, & Benson, 2002; Kendler, Gardner, & Prescott, 2003; McNally, 2003).

1.2.1 Stressors during childhood and adolescence and mental disorder

Most etiological studies of child and adolescent mental health have focused on exposure to maltreatment and violence (physical abuse, emotional abuse, sexual abuse, neglect and witnessing violence). There has been a substantial increase in the study of traumatic stress in recent years (Folkman, 2013). Childhood and adolescence stressful life-event studies focus on psychosocial stressors such as family turmoil and conflict among family members (Evans & English, 2002). Other common stressors that children and adolescent experience are chronic stressors and daily hassles, such as school-related stressors (e.g., bullying by peers, and academic

problems) and interpersonal relationships (e.g., conflicts or problems with family members) (Donaldson, Prinstein, Danovsky, & Spirito, 2000; Undheim & Sund, 2010).

The adverse childhood experiences studies have established a strong association between childhood maltreatment and poor mental well-being (Wu, Schairer, Dellor, & Grella, 2010). Childhood maltreatment is linked to a wide array of adverse short- and long-term adverse mental health outcomes, such as depression, PTSD, anxiety, and reduced cognitive functioning (Gibb, Chelminski, & Zimmerman, 2007; Irigaray et al., 2013; Roth, Newman, Pelcovitz, Van Der Kolk, & Mandel, 1997). Children exposed to the marital conflict have higher risk of adverse mental health outcomes in the adulthood (Ayoub, Deutsch, & Maraganore, 1999; Cherlin, Chase-Lansdale, & McRae, 1998) as does the quality of family life. Children and adolescents living in families with high scores of family functioning have better mental health than those in "low" functioning families (Pless, Roghmann, & Haggerty, 1972). Bullying has also become a growing concern, being bullied and interpersonal aggressive behavior negatively affect children and adolescents' mental health (Nansel, Craig, Overpeck, Saluja, & Ruan, 2004). Hawker & Boulton (2000) demonstrated that bullying victims show signs of distress such as depression and anxiety (Hawker & Boulton, 2000). Being bullied is also related to higher risk of self-harm behaviours and suicidal ideations among victims (Klomek et al., 2009).

1.2.2 Stressors during adulthood and mental disorder

Individuals may be exposed to a wide array of potentially traumatic events throughout life. Females experience more and different types of traumatic events than men, having higher levels of sexual and domestic violence. Among battered women, sexual and domestic violence has been found to have adverse mental health outcomes, such as depression and PTSD (Campbell & Soeken, 1999; Hossain et al., 2014). The stressful nature of events, including anticipated negative life events (such as separation or divorce, and interpersonal conflicts) and unanticipated life events (such as the death of a close family member, loss of a job, or poverty) act as precipitating factors in the onset of mental health symptomatology (Dalgard, Bj, & Tambs, 1995). Stressful life events can provoke neuroendocrine and brain neurotransmitter changes that may increase the risk of mental health issues such as depression and anxiety (Anisman, Merali, & Stead, 2008; Bifulco, Bernazzani, Moran, & Ball, 2000; Franko et al., 2004). However, not all events need to be sudden dramatic and to be stressful, research showed that even minor negative

experiences can have strong effects on wellbeing. Their continual presence may be as important as or more important than major discrete but rare life events (Repetti & Wood, 1997). Chronic strains, such as threats, conflicts, and under-rewarded activities that many people may face in their daily lives affect the number and severity of depressive symptoms (Avison & Turner, 1988). It is also believed that chronic stains may have greater impact on health than life events (Lepore, Palsane, & Evans, 1991). Daily hassles are defined as "*irritating, frustrating demands that occur during everyday transactions with the environment*", the difference from chronic stressors lies in the micro-transactions and interactions of daily life (Kanner, Coyne, Schaefer, & Lazarus, 1981). Previous studies have established association between daily hassles and depression, and psychological distress (Grzywacz, Almeida, Neupert, & Ettner, 2004; Mackrell, Johnson, Dozois, & Hayden, 2013).

Figure 1-1 provides a graphic illustration of the dimensions in the stress universe. Figure 1-2, following, provides a schematic outline of various stressors and the social context in which they occur.

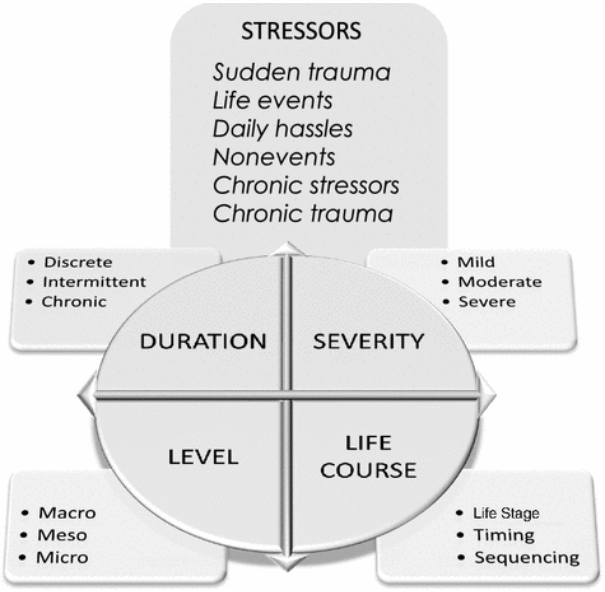

Figure 1-1 Dimensions in the stress universe. Based on Wheaton (1994) (Wheaton, 1996) and Wheaton et al. (2013) (Wheaton, Young, Montazer, & Stuart-Lahman, 2013).

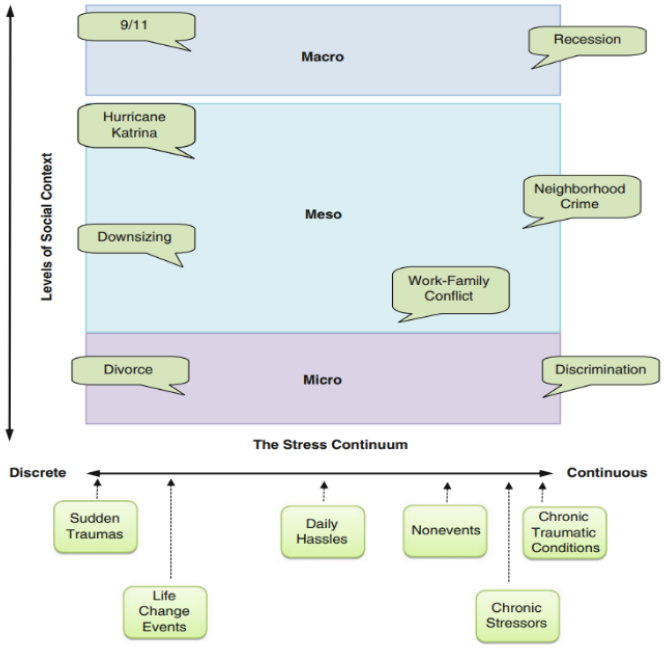

Figure 1-2 A catalogue of a two-dimension classification of stressors. Based on Aneshensel et al. (2013) (Aneshensel et al., 2013).

1.3 Biopsychosocial model of stress and mental disorders

The biopsychosocial model incorporates both biological factors and psychosocial factors and focuses on predisposing, environmental and maturation factors that play a crucial role in the process of individual development throughout the lifespan (Delfos, 2004). Intergenerational stress transmission (Thornberry, Knight, & Lovegrove, 2012), antenatal/postnatal parental emotional wellbeing (Kingsbury et al., 2016), and early childhood adversities (Raposa, Hammen, Brennan, O'Callaghan, & Najman, 2014) have been found closely linked to offspring's mental health. Studies have suggested that the developmental origins of health and disease (DOHaD) model helps to articulate roles of in-utero and perinatal adversities in the development of mental disorders during the life course, which are associated with long-term changes in the regulation of the stress hormone system (Lupien, McEwen, Gunnar, & Heim, 2009), and may be causally related to the development of disease. In addition to the strong effects of the environment, there is a significant genetic contribution to the development of these disorders (Kendler, Gatz,

Gardner, & Pedersen, 2006). Epigenetic modifications such as DNA methylation, histone modifications and non-coding RNAs are involved in mediating how early life environment impacts later health well-being (Bianco-Miotto, Craig, Gasser, van Dijk, & Ozanne, 2017). It is well established that trauma events in the childhood elevated the risk of mental illnesses, different people and groups may vary in their vulnerability and sensitivity to situations, genetic vulnerability might determine an individual's vulnerability to different psychiatric disorders given similar environmental exposures (Barker, Gumley, Schwannauer, & Lawrie, 2015).

Environmental factors can generate epigenetic modifications in response to genetic predisposition for stress-related diseases. It is suggested that emotional reactions may affect physiological function contributing to diseases (Brannon & Feist, 1992). The central nervous system (CNS) effector of stress responds to the stress system to regulate the peripheral activities of the hypothalamic-pituitary-adrenal (HPA) axis and the systemic/adreno-medullary sympathetic nervous systems (SNS). Systemic elevations of glucocorticoids and catecholamines then will be activated to maintain homeostasis. Activation of the stress system leads to physical adaptation that includes changes in cardiovascular function, intermediary metabolism, and modulation of the immune and inflammatory reaction (Chrousos, 2000).

The effects of exposure to stressors and the development of stress-related outcomes including depression, anxiety, or PTSD can be mediated by social and psychological resources (Folkman, 2013). A growing body of research suggested that various mediating factors are implicated in connection with mental health outcomes (Calvete, Corral, & Estévez, 2008; Gloria & Steinhardt, 2016; Mitchell et al., 2006; Schönfeld, Brailovskaia, Bieda, Zhang, & Margraf, 2016; Soler, Kirchner, Paretilla, & Forns, 2013). Mental resilience aids quick and effective recovery after stress (Tugade & Fredrickson, 2004). Studies found that higher levels of resilience can lower the negative influence of stressors toward the mental health. For example, social support and different domains of coping strategies have been found to mediate the effect of stressful events on individuals' mental health (Coker et al., 2002; Runtz & Schallow, 1997). Some researchers conclude that self-esteem mediates adversities and that different psychological resilience accounts for meaningful variation in mental health outcomes (Hall, Kotch, Browne, & Rayens, 1996; Meng & D'Arcy, 2016). Self-efficacy is another positive resistance resource that

is part of the cognitive appraisal process and essential for the regulation of stress (Wilburn & Smith, 2005).

Problem solving approach strategies have been found to moderate the negative effects of adversities and trauma on psychological adjustment (Scarpa, Haden, & Hurley, 2006). Emotion-oriented coping strategies moderated the relationship between pessimism stress and autism symptomatology (Lyons, Leon, Phelps, & Dunleavy, 2010). In addition, both problem-solving confidence and social support moderated the relationship between childhood abuse and suicidal ideation (Esposito & Clum, 2002). Figure 1-3, Figure 1-4 and Figure 1-5 provide schematic diagrams of biopsychosocial, psychological and social models of the stress-mental health/illness process, respectively.

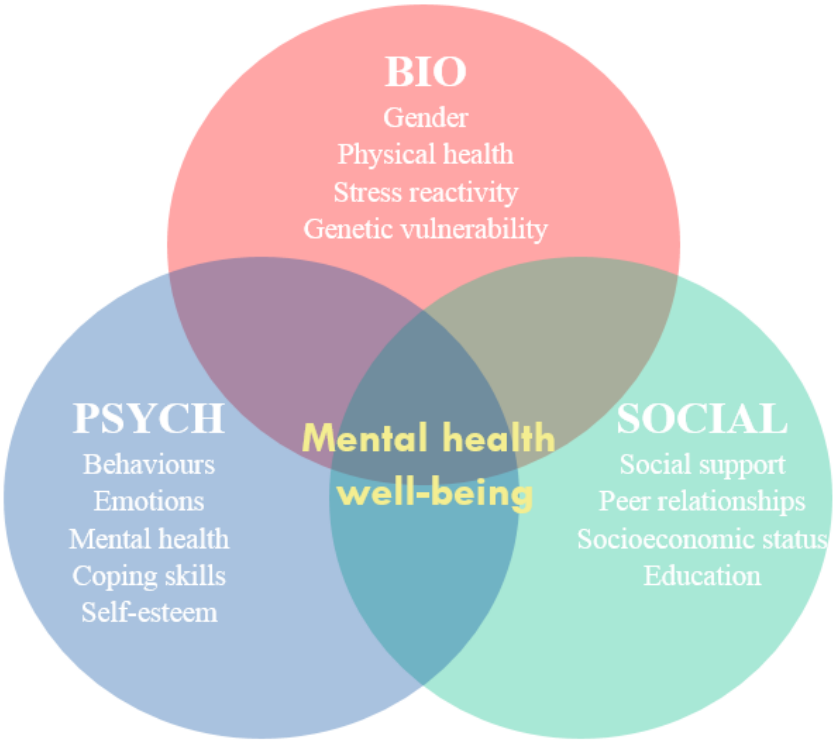

Figure 1-3 Biopsychosocial model of stress and mental health.

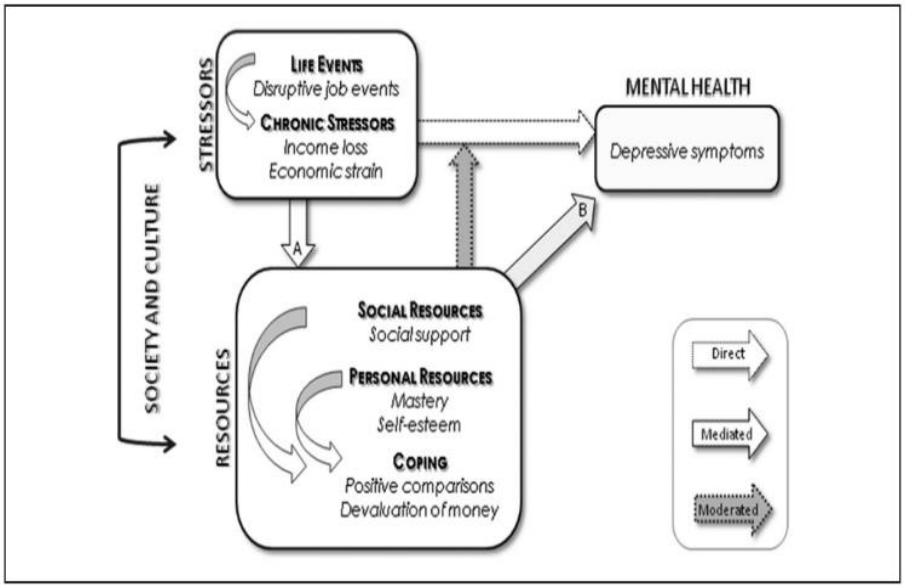

Figure 1-4 The original stress process model. Based on Pearlin et al. (1981) (Pearlin, Menaghan, Lieberman, & Mullan, 1981).

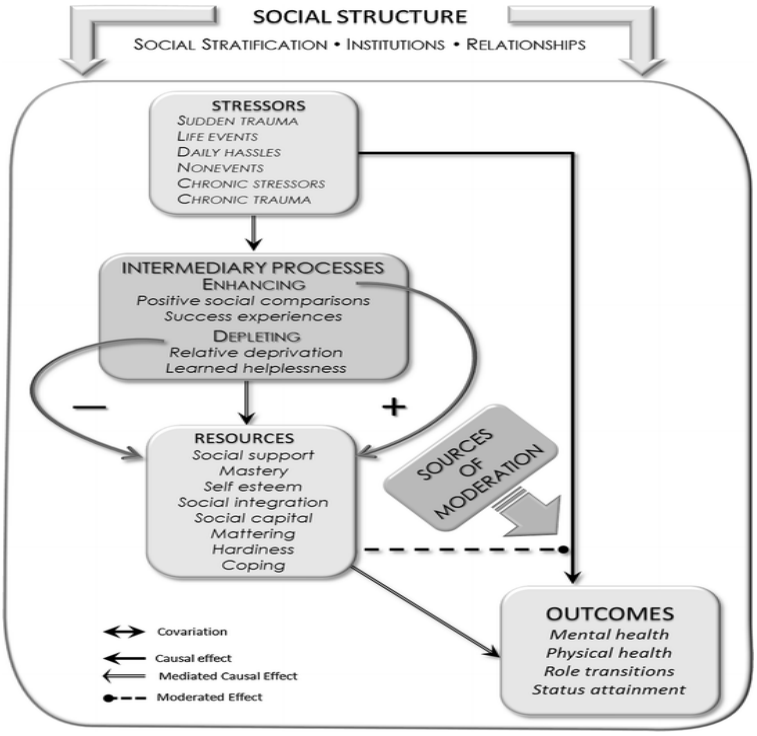

Figure 1-5 The stress process model with consideration of mediating factors. Based on Aneshensel et al. (2014) (Aneshensel & Mitchell, 2014).

1.4 Context of this research

The primary goal of this thesis is to contribute to a better understanding of the relationship between social stress and mental health disorders with the application of a variety of epidemiological techniques using a variety of data sources. These individual studies provide different levels of evidence on different dimensions of the biopsychosocial model of mental health/illness. They have implications for enhancing public awareness of social stress-mental health association as well providing information for policy making with regard to potential interventions.

This thesis is composed of five substantive chapters which aim to:

- Explore serious outcomes and identity of the potential modifiable risk factors for abuse around pregnancy in rural and urban areas at a national level in Canada.
- Examine the mediating roles of both social support and positive coping skills in the relationship between childhood maltreatment and psychological distress and positive mental health in the general Canadian population using national health survey data.
- Test the temporal order of the relationship between income and self-perceived mental health and to explore the roles of age and gender in this relationship at both within-person and between-person levels using a longitudinal community mental health survey.
- Examine, in a systematic review and meta-analysis of the literature, the intergenerational effect of maternal childhood maltreatment on their offspring's psychopathology and potential moderator in the relationship between maternal childhood maltreatment and offspring's psychopathology.
- Summarize the evidence on the effect of in-utero and perinatal conditions on the offspring's depression in a comprehensive meta-analysis and systematic review.

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CHAPTER 2. METHODS AND PROCEDURES

2.1 Study designs

Cross sectional study designs are relatively quick and cheap to conduct and are useful at identifying associations that can then be more rigorously studied using a cohort study or randomized controlled study (Mann, 2003). Whereas systematic reviews and meta-analyses are generally the best form of evidence as a way of summarizing research evidence, positioning at the top of the hierarchy of evidence (Gopalakrishnan & Ganeshkumar, 2013). Three basic epidemiology designs and several advanced epidemiological and statistical techniques were applied in this thesis: population-based cross-sectional studies (Chapter 3 and 4), prospective cohort (Chapter 5), systematic reviews and meta-analyses (Chapter 6 and Chapter 7). Structural equation modeling was used to model the relationships between exposure and health related outcomes and both direct and mediated effects of exposures on the outcomes, portraying and exploring the sequentially influencing pathways from exposure to outcomes and the mediating role of mediators. In addition, a cross-lagged panel model (CLPM) and random intercept cross-lagged panel model (RI-CLPM) which are well suited to analyze systematic stability and changes in the longitudinal data over a certain period of time were also used. RI-CLPM modeling permits the examination and differentiation of both within-person as well as between-person differences in true change compared to conventional multiple-regression analyses.

Griffin, Jordan & El Gawad (2016) used the following diagram to illustrate the hierarchy of levels of evidence in epidemiology (Figure 2-1).

Three basic epidemiology designs and several advanced epidemiological and statistical techniques were applied in this thesis. In terms of research design, the following designs are used:

- population-based cross-sectional studies (Chapter 3 and 4);
- prospective cohort (Chapter 5);
- systematic reviews and meta-analyses (Chapter 6 and Chapter 7).

Figure 2-1 Hierarchy of evidence in Epidemiology.

2.2 Data sources

Data used in this thesis research include national Canadian population based cross-sectional data: 1) the Maternity Experiences Survey (MES)-Chapter 3; and 2) the 2012 Canadian Community Health Survey-Mental Health (CCHS-MH)-Chapter 4. A prospective community cohort study – The Social and Psychiatric Epidemiology Catchment Area Study of South West Montreal (ZEPSOM) is used as the data source in the Chapter 5.

Chapter 6 and Chapter 7 are systematic reviews and meta-analyses, all eligible studies were retrieved and collected through both computerized search and manual search. An extensive and systematical literature search was performed to identify primary studies from databases such as PubMed, Embase, PsycINFO, Medline, and Cochrane Library with search strategies. The most appropriate studies were selected based on the inclusion and exclusion criteria. Gray literature

resources including dissertations, conference abstracts, and unpublished manuscripts were also searched to avoid publication bias. In addition, other resources were manually searched to maximize the relevant studies. The reference lists of selected articles, review articles on relevant topic, and the gray literature were all screened. Only articles published in English were included.

2.3 Statistical analysis

Descriptive analyses (Chapter 3, 4 and 5) were conducted to obtain the prevalence of each condition and understand sociodemographic characteristics of study populations, such as age, gender, education level, household income, area of the residence, and marital status, etc.

Multivariate statistics were also employed for binary outcomes with adjustment for the potential confounders (Chapter 3 and 4). In Chapters 4 and 5 more advanced statistical techniques were used. Structural equation modeling (SEM) and confirmatory factor analysis (CFA) were both applied to investigate the multivariate relationships and explore the mediating effect among these latent constructs (Chapter 4). SEM was used to model both direct and mediated effects on the outcomes, portraying and exploring the sequentially influencing pathways from exposure to outcomes and the mediating role of mediators. In addition, in Chapter 5, a cross-lagged panel model (CLPM) and random intercept cross-lagged panel model (RI-CLPM) were used to analyze systematic stability and changes in the longitudinal data over period of time. RI-CLPM modeling permits the examination and differentiation of both within-person as well as between-person differences in true change compared to conventional multiple-regression analyses. CLPM and RI-CLPM with maximum likelihood with Huber-White robust standard errors estimator (MLR) were applied to multiple waves of data in the prospective study. They are well suited to analyze changes in longitudinal data over time.

A meta-analysis of all prospective studies was introduced in Chapter 6, effect sizes were calculated based on the method of Lipsey and Wilson. Pearson's coefficients were converted into Fisher's Z values to calculate the pooled effect sizes. The pooled effect sizes then were converted back to coefficients for interpretation. A sample wise approach was used to handle dependent correlations. Also, meta-regression was used to explore potential confounders.

Chapter 7 is a meta-analysis study which included only prospective longitudinal studies. Based on the results of heterogeneity tests, random-effects model was used to calculate pooled

estimates, which is more conservative compared to fixed-effects model. Meta-regression analysis was conducted to identify possible explanations for the heterogeneity. Sensitivity analysis was also performed to explore the effects of the potential confounders. We conducted subgroup analysis for different prenatal and perinatal/postnatal factors. We used both funnel plots and Egger/Begg tests to examine publication bias. We then applied the trim and fill method to explore potential publication bias.

Table 2-1 below summarizes study design and methods of analysis used in subsequent chapters of the thesis.

Table 2-1 A Summary of thesis studies.

Study design/ Level of evidence	Title of study	Method & analysis
Meta-analysis/ High	Chapter 7. Developmental origins of depression: a systematic review and meta-analysis	Systematic review. Meta-analysis. Meta-regression analysis. Sensitivity analysis
Meta-analysis/ High	Chapter 6. Intergenerational effect of maternal childhood maltreatment on next generation's vulnerability to psychopathology: a systematic review with meta-analysis	Systematic review. Meta-analysis. Effect size transformation. Moderator analysis
Prospective cohort/ Moderate	Chapter 5. Increased income over time predicts better self-perceived mental health only at a population level but not for individual changes: An analysis of a longitudinal cohort using cross-lagged models	Descriptive analysis. Cross-lagged panel model. Random intercept cross-lagged panel model. Wald Chi-square (χ^2) tests
Cross-sectional/ Low to medium depending on the specifics of the survey design	Chapter 4. Social support and positive coping skills act as mediators buffering the impact of childhood maltreatment on psychological distress and positive mental health in adulthood: Analysis of a national population-based sample	Descriptive analysis. Confirmatory factor analysis. Structural equation modeling. Cross-validation test

Cross-sectional/ Low to medium depending on the specifics of the survey design	Chapter 3. Violence and abuse experiences by Canadian mothers around the time of pregnancy: risk factors, rural-urban differences and selected birth outcomes – analysis of a national sample	Descriptive analysis. Logistics regression

2.4 References

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CHAPTER 3. VIOLENCE AND ABUSE EXPERIENCES BY CANADIAN MOTHERS AROUND THE TIME OF PREGNANCY: RISK FACTORS, RURAL-URBAN DIFFERENCES AND SELECTED BIRTH OUTCOMES – ANALYSIS OF A NATIONAL SAMPLE

A version of this chapter titled "Violence and abuse experiences by Canadian mothers around the time of pregnancy: risk factors, rural-urban differences and selected birth outcomes – analysis of a national sample." authored by Su, Y., and D'Arcy, C has been submitted to Journal of Interpersonal Violence for publication review. My contributions to this study included study design, data analysis, results interpretation, and manuscript writing as well as editing.

3.1 Abstract

Background: Abuse during pregnancy is of increasing global public health concern affecting both women themselves and their children. Previous research found a variety of risk factors as well as rural-urban variations in the experience of abuse during pregnancy with higher rates generally been reported in urban areas. The primary aim of this study is to explore and identify potentially modifiable risk factors predictive of abuse including rural-urban differences and to examine maternal and birth outcomes subsequent to that abuse in a nationally representative sample of Canadian women.

Methods: The data are from the Maternity Experiences Survey (MES), a Canadian population-based post-census survey administered to 6,421 Canadian mothers in 2006. Survey participants were 15 years and older and had given birth to a singleton and continued live with their infant at the time of the survey. The survey response rate was 78%. Multivariable logistic regression analyses were used in the analysis with adjustments made for confounding variables.

Results: The study findings indicated that living in an urban environment was associated with an increased risk of abuse experience around the time of pregnancy (OR=1.31, 95% CI: 1.03-1.66) after full adjustment for other risk factors. In addition, being aboriginal, young, unmarried, economically disadvantaged, a non-immigrant, and having more than four pregnancies, as well as cigarette smoking, alcohol drinking and drug use before the pregnancy were correlated with the abuse around the time of pregnancy. Maternal abuse was also associated with postnatal depression and stressful life events among both urban and rural mothers. However, maternal abuse was only predictive of increased risk for preterm birth among rural mothers but not among urban mothers.

Conclusions: The present study highlights the need for the implementation of effective interventions for women experiencing abuse during pregnancy due to its potential impact on maternal and newborn's physical and mental health. Screening and intervention should be targeted high risk women particularly those who are indigenous, young, unmarried, non-immigrants, of lower socioeconomic status, and manifesting high risk health behaviors.

3.2 Introduction

Since 1970s abuse of women and girls has been recognized as a global public health concern associated with morbidity and mortality as well as a violation of women's rights (Granja, Zacarias, & Bergstrom, 2002). It is reported that approximate one in every five women worldwide suffers different types of abuse during lifetime that would give rise to injury or even death (Gender, 2005). Abuse (including physical or sexual abuse) during pregnancy and the postpartum period has many serious clinical adverse consequences for both mother, fetus and child and far-reaching societal implications (Kingston et al., 2016). Pregnancy can be a stressful and anxious time. It is a vulnerable period when physical, emotional, and social change occurs (Van Parys, Deschepper, Michielsen, Temmerman, & Verstraelen, 2014). If pregnant women experience abuse around pregnancy, either physical or emotional, it can have a detrimental effect for both themselves and their offspring (Campbell & Lewandowski, 1997). A growing body of literature reports that pregnant women who suffered abuse often present with multiple risk factors that may increase the risk of physical damage and perinatal mental health adversity for mothers and child. These adversities include increased risk of preterm birth, low birth weight or mortality for their newborns (Bailey, 2010; Beydoun, Beydoun, Kaufman, Lo, & Zonderman, 2012; Howard, Oram, Galley, Trevillion, & Feder, 2013; Janssen, Heaman, Urquia, O'Campo, & Thiessen, 2012; Urquia, O'Campo, Heaman, Janssen, & Thiessen, 2011). For the mothers themselves there is an increased risk of chronic diseases, sexually transmitted diseases, and post-traumatic stress disorder, etc. (Coker, M. Sanderson, & B. Dong, 2004; Curry, Perrin, & Wall, 1998).

Abuse and violence against pregnant women still persists in developed and developing countries (Nasir & Hyder, 2003). From the research in North America and Europe, the prevalence of abuse and violence suffered by pregnant women varies between 0.9% and 22.0%. The variation in prevalence reported in these studies may be due to sampled populations and different materials, methodologies, and cultural context differences across different study sites and countries (Finnbogadottir, Dykes, & Wann-Hansson, 2014; Hedin, Grimstad, Moller, Schei, & Janson, 1999; James, Brody, & Hamilton, 2013; Stenson et al., 2001). Physical abuse is reported as the most frequent type of abuse and it may lead to adverse pregnancy outcomes, at

the same time, it is a modifiable risk factor for those adverse pregnancy outcomes (Gazmararian et al., 1996; Rodrigues, Rocha, & Barros, 2008).

There has been much theorizing about rural/urban differences in mental health. Social theorists have long discussed the effects of the urbanization and industrialization in terms of the transformation of social relationships, social norms and culture. Durkhiem in his *Division of Labour in Society* (1993) characterized this development as a shift from "mechanic" to "organic" solidarity. Tönnies characterized the changes in terms of *Gemienschaft und Gessellschaft* (1957) (Community and Society). The changes are seen as altering the density, intensity and nature of social relationships. Modern social capital theory stresses structural features such as organizational membership and cognitive elements such as trust, reciprocity and mutual help to characterize differences among communities. These diverse social structural features of communities are seen to impact on both the physical and mental health of their inhabitants. Such theorizing underlies discussions of rural and urban differences in mental and emotional health. Rural-urban differences in the experience of abuse during pregnancy have been identified in some studies. The literature has reported that rural areas having lower levels of education, more socioeconomic deprivation, geographical remoteness, leading to a higher prevalence of abuse and violence being experienced by pregnant women in rural areas (Bhandari et al., 2015; Goins, Williams, Carter, Spencer, & Solovieva, 2005; Pong et al., 2011; Tiwari et al., 2008). Furthermore, the unavailability in specialist care in rural areas, which may have an additional negative effect on abuse experiences of pregnant women in rural areas. However, a prospective longitudinal study that recruited participants from three US urban clinics found that prevalence of physical abuse during pregnancy is high in urban mothers with low-income, with approximately 1 in 5 women reported abuse experience during pregnancies (Alhusen, Lucea, Bullock, & Sharps, 2013). In contrast a narrative review of 63 studies indicates that rates of intimate partner violence are generally similar across rural, urban, and suburban locales (Edwards, 2015). Whereas a survey from the South America generally found higher levels of domestic violence among urban women compared with rural women (Van Dis, Mahmoodian, Goddik, & Dimitrievich, 2002). Likewise, Van Horne (2010) found intimate partner violence was related to population density with higher levels occurring in more densely populated counties.

Canada has a very large geographical area but with a relatively small population that is largely spread-out. There are social structural inequalities between rural and urban areas in Canada and differences have also been identified between rural areas bordering on urban hubs and more remote rural areas (Pampalon, Hamel, & Gamache, 2010).

We are not aware of any Canadian research that has explored rural-urban differences in abuse and violence towards women during pregnancy. Our proposed study aims to fill this knowledge gap. This study explores:

1) rural-urban difference in the prevalence of violence and abuse against pregnant women;
2) risk factors related to the experience of violence and abuse among rural and urban pregnant women and;
3) related outcomes for mother and child.

3.3 Methods

3.3.1 Study subjects

The Maternity Experiences Survey (MES) was the first and only national survey devoted to pregnancy, labor, birth and postpartum experiences in Canada, a project conducted by Statistics Canada and sponsored by the Public Health Agency of Canadian Perinatal Surveillance System. It is a population-based post-census survey conducted between October 23, 2006, and January 31, 2007. The Canadian Census of 2006 was used to define the target population of women, who had given birth between 15th February and 15th May 2006 (for the provinces) and 1st November 2005 and 1st February 2006 (for the territories), were 15+ years of age at the baby's birth, whose baby was born in Canada and lived with the mother at least one night per month since then. Mothers living on First National reserves and in collective dwellings were excluded. An estimated 76,500 women met these criteria. The sample frame was stratified by residence, mother's age, other children in the household, with mothers less than 20 years of age being over sampled. A simple random sample was selected without replacement within each stratum. The sample targeted 8,542 women. 6,421 of them responded to the survey yielding the response rate of 78%. Computer-assisted telephone interviewing (CATI) technology was used combined with a personal interview with a paper version of the questionnaire where a telephone interview was

not possible. Response to the survey was voluntary and all participants provided informed consent.

The MES data is made available to bona fide researchers by Statistics Canada through the MES Master File, which does not contain any personal identifiers. Statistics Canada provided survey weights for researchers to use in estimating population parameters. The MES Master File was accessed at the Saskatchewan Research Data Centre (SKY-RDC), a joint Statistics Canada-university data on the University of Saskatchewan campus.

3.3.2 Measures

Demographic characteristics and correlates of abuse Standard Statistics Canada questions were asked concerning maternal age at birth, maternal education, marital status, total household income, aboriginal ancestry, location of residence, province or territory of residence, immigration status, sex of the baby, maternal age at their first pregnancy, total number of pregnancies, smoking status before pregnancy, alcohol consumption before pregnancy and drug use before pregnancy.

The variables were categorized as follows: participants' age at birth of survey reference baby – <20, 20 to 29, 30 to 39, and 40+ years; maternal age at first pregnancy – <20 years, 20 to 34 years, and 35+ years; maternal education – university graduation and above, post-secondary diploma, some post-secondary education, high school graduation, and less than high school; marital status – married/common-law, divorced/separated/widow and single; total household income – $100,000 or more, $60,000 to $100,000, $30,000 to $60,000, $10,000 to $30,000 and less than $10,000; residence location – rural (<1,000 inhabitants or population density <400/km^2) vs. urban; total number of pregnancies – 1, 2 to 3, ≥4.

Abuse experience Ten questions adapted from the Violence Against Women Survey were used to assess the acts of physical or sexual violence experience for Canadian women around the time of pregnancy (Statistics Canada, 1993). Participants were asked whether a spouse or partner or anyone else has done any of the following things to them in the last two years: (1) threatened to hit you with his or her fist or anything else that could have hurt you; (2) thrown anything at you that could have hurt you; (3) pushed, grabbed or shoved you in a way that could have hurt you; (4) slapped you; (5) kicked you, bit you or hit you with his or her fist; (6) hit you with

something that could have hurt you; (7) beaten you; (8) choked you; (9) used or threatened to use a gun or knife on you; and (10) forced you into any unwanted sexual activity by threatening you, holding you down, or hurting you in some way.

The above ten items were categorized as "Any abuse experience" – an affirmative answer to one or more of the 10 items; "Abuse, threats or potential hurting acts" – at least one affirmative answer to questions 1 to 3; "Physical abuse" – at least one affirmative answer to questions 4 to 9; "Sexual abuse" – an affirmative answer to question 10. Abuse victims were also asked about the *frequency* of these incidents happened in the past two years with responses ranging from 1 to more than 11 times. The response of women to the question about their relationship to the person who was violent towards to them was categorized as: husband or boyfriend, a family member, a friend or acquaintance, and a stranger and other person.

Abuse related outcomes Abuse related outcomes included postnatal depression, stressful events, preterm birth, small for gestational age and type of delivery. Depression was measured using the Edinburgh postnatal depression scale (EPDS) (Cox, Holden, & Sagovsky, 1987). The scale consisted of 10 questions with four response categories scored from 0 to 3, a cut-off score of 11 or more is used to indicate a high probability of having postpartum depression (with reasonable sensitivity and specificity) (Smith-Nielsen, Matthey, Lange, & Væver, 2018).

Stressful life events – using a modified Newton and Hunt Stressful Life Events Scale (Newton & Hunt, 1984), respondents were asked about the occurrence of 13 stressful life events during the 12 months prior to giving birth.

Low birth weight (LBW) was defined as less than 2,500 grams at birth.

Preterm birth (PB) was defined as a delivery before 37 completed gestational weeks.

Type of delivery was categorized as caesarean or vaginal.

3.3.3 Statistical analysis

In estimating the prevalence of abuse, violence and related variables and to account for the complex sampling design, Statistics Canada survey sample weights and bootstrapping procedures were used.

Descriptive statistics were used to summarize perpetrators of abuse, abuse times, abuse types and abuse related to pregnancy period in rural and urban locales. The Chi-square test was used to determine the difference in socio-demographic characteristics between the urban and rural groups. The relationships between location of residence and abuse were analyzed with univariable and multivariable logistic regression. Three models were constructed while controlling for different types of potential confounders and effect modifiers. In addition, multivariable logistic regression analyses were used to further investigate the urban-rural differences in the maternal and newborn outcomes of abuse with adjustments for a variety of intervening variables. Odds ratios and their 95% confidence intervals (95%CI) were calculated to indicate the strength of the association. Stata, version 9.0, was used in these analyses.

3.4 Results

Our study finding indicated that 9.8% (95% CI = 9.3%–10.3%) mothers in rural areas compared with 11.1% (95% CI = 10.9%–11.4%) mothers in urban areas had ever experienced abuse and violence around the time of pregnancy. All rural/urban differences were noted in Table 3-1 which provides the basic characteristics of rural and urban mothers in the MES survey sample. All differences are statistically significant except for drug use before the pregnancy. In *rural areas*, more than half of (51.5%) the mothers were 20-29 years of age at the birth of the survey reference child, most were married (92.7%) and had completed high school (91.2%), 9.6% were immigrants, and more than half (52.8%) had a household income of less than $60,000 annually. Approximately half the mothers (51.5%) had two to three pregnancies. In *urban areas*, approximately half of (49.0%) participants were 30-39 years of age at the birth of survey reference child and 91.5% were married or living common-law. 24.4% mothers were immigrants and one third (39.8%) were highly educated (university graduation and above). Similarly, a large proportion of mothers' (50.5%) household income was less than $60,000 per year and less than half (49.7%) had 2 to 3 pregnancies. The proportion of mothers living in rural areas reporting abuse around the time of pregnancy was 9.8% (95% CI = 9.3%–10.3%) whereas 11.1% (95% CI = 10.9%–11.4%) mothers living in urban regions reported abuse. While the proportion of mothers reporting abuse in rural and urban areas is statistically significantly different, they are broadly similar, 10% vs 11%.

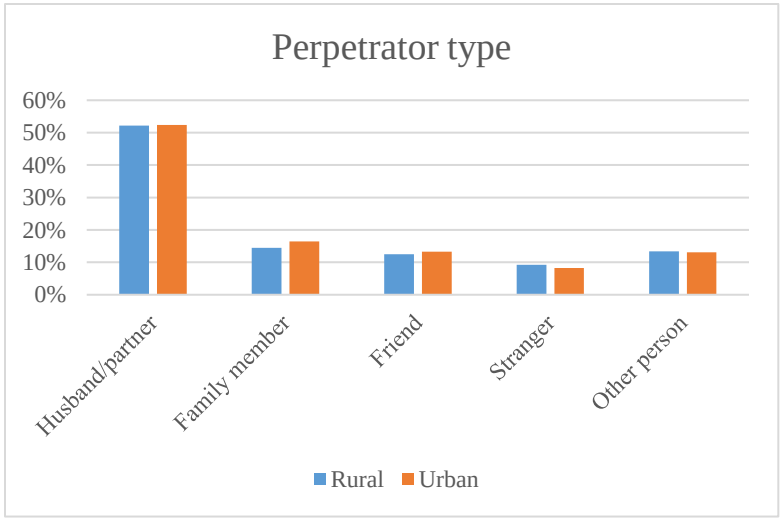
Table 3-1 Basic characteristics of the rural and urban mothers in the Maternal Experience Survey (MES).

Variables		Rural (weighted n=13,108)		Urban (weighted n=63,400)		χ^2	P value
		Frequency	%	Frequency	%		
Sex of the baby	Male	7,042	53.7%	32,526	51.3%	25.5	0.000
	Female	6,066	46.3%	30,874	48.7%		
Maternal age at birth of survey reference baby (years)	15-19	392	3.0%	1,870	2.9%	198.3	0.000
	20-29	6,754	51.5%	28,521	45.0%		
	30-39	5,647	43.1%	31,068	49.0%		
	Above 40	315	2.4%	1,941	3.0%		
Immigrant status	Yes	1,258	9.6%	15,500	24.4%	1393.0	0.000
	No	11,850	90.4%	47,900	75.6%		
Marital status	Married/common-law	12,151	92.7%	57,983	91.5%	552.0	0.000
	Divorced/Separated/Widow	234	1.8%	1,204	1.9%		
	Single	723	5.5%	4,213	6.6%		
Mother's education	Less than high school	1,153	8.8%	4,633	7.3%		
	High school graduation	2,023	15.4%	8,026	12.7%		
	Some post-secondary education	984	7.5%	3,626	5.7%		
	Post-secondary diploma	5,143	39.2%	21,890	34.5%		
	University graduation and above	3,805	29.0%	25,224	39.8%		
Household income	Less than $10,000	176	1.3%	1,435	2.3%	219.1	0.000
	$10,000 to less than $30,000	1,879	14.3%	8,797	13.9%		
	$30,000 to less than $60,000	4,878	37.2%	21,784	34.3%		
	$60,000 to less than $100,000	4,071	31.1%	19,043	30.0%		
	$100,000 or more	2,104	16.1%	12,341	19.5%		
Province or territory of residence	Newfoundland and Labrador	350	2.7%	671	1.1%	3053.7	0.000
	Prince Edward Island	141	1.1%	147	0.2%		

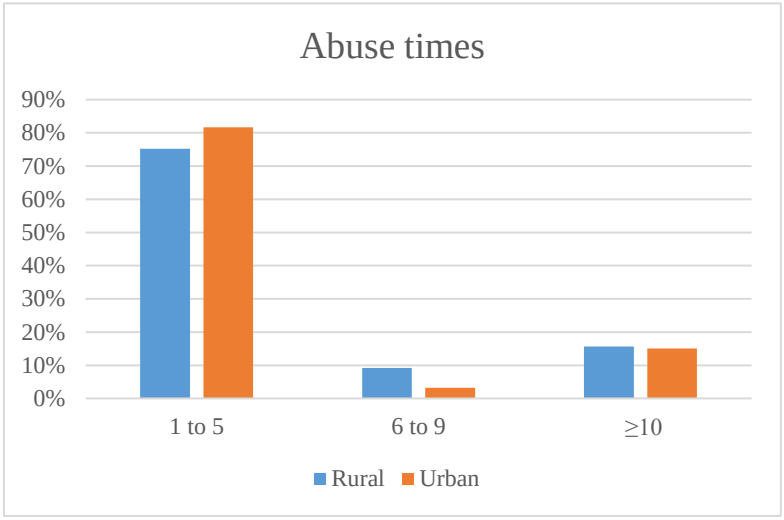
	Nova Scotia	708	5.4%	1,017	1.6%		
	New Brunswick	641	4.9%	847	1.3%		
	Quebec	3,674	28.0%	14,659	23.1%		
	Ontario	4,564	34.0%	25,124	39.6%		
	Manitoba	503	3.8%	2,189	3.5%		
	Saskatchewan	513	3.9%	1,930	3.0%		
	Alberta	736	5.6%	8,699	13.7%		
	British Columbia	1,087	8.3%	7,910	12.5%		
	Yukon	27	0.2%	55	0.1%		
	Northwest Territories	66	0.5%	80	0.1%		
	Nunavut	98	0.7%	72	0.1%		
Maternal age at first pregnancy (years)	15-19	2,564	19.6%	10,402	16.4%	126.6	0.000
	20-34	10,164	77.5%	50,176	79.1%		
	Above 35	380	2.9%	2,821	4.5%		
Total number of pregnancies	1	3,909	29.8%	21,801	34.4%	115.4	0.000
	2 to 3	6,802	51.9%	31,514	49.7%		
	≥4	2,397	18.3%	10,085	15.9%		
Aboriginal ancestry	Yes	695	5.3%	2,529	4.0%	46.4	0.000
	No	12,413	94.7%	60,871	96.0%		
Experienced Abuse around the time of this pregnancy	Yes	1,286	9.8%	7,060	11.1%	19.6	0.000
	No	11,823	90.2%	56,339	88.9%		
Smoked before this pregnancy	Yes	3,445	26.3%	13,377	21.1%	182.2	0.000
	No	9,663	73.7%	50,022	78.9%		
Alcohol consumption before this pregnancy	Yes	8,516	65.0%	39,079	61.6%	203.4	0.000
	No	4,592	35.0%	24,321	38.4%		
Drug use before this pregnancy	Yes	929	7.1%	4,216	6.7%	3.3	0.069

No	12,179	92.9%	59,183	93.3%	

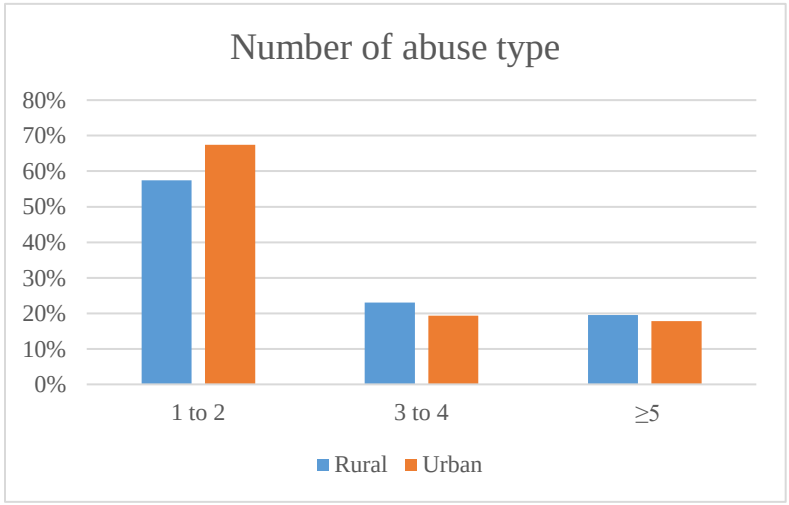
Among mothers who reported abuse around the time of pregnancy, 75.2% of the abused mothers in rural areas and 81.7% of the abused mothers in urban areas reported 1 to 5 instances of abuse. A husband or partner was the most common perpetrator of abuse in both areas, accounting for 52.2% and 52.4% of abusers in rural and urban areas, respectively. The prevalence of abuse by a family member, friend, stranger, or other perpetrator was significantly lower in both areas. More than half of abused mothers in rural and urban areas had experienced one to two different types of abuse (57.5% and 64.5%, respectively). Threats or potential hurting acts were the most common types of abuse, with sexual abuse being the least frequent type of abuse among both rural and rural mothers. Mothers who suffered physical or sexual abuse also usually experienced threats or hurting acts as well. The patterns of abuse experienced before pregnancy, during pregnancy and after childbirth were similar for both rural and urban mothers. Abuse incidents were less frequent during the pregnancy than before the pregnancy, and dropped dramatically after the child birth. Among rural mothers who had experienced abuse around the time of pregnancy, 81.1% reported abuse incidents before the pregnancy, 30.4% reported abuse incidents during the pregnancy and 26.9% reported abuse incidents since childbirth; and the same percentages for urban mothers were 87.0%, 30.4% and 18.7%. Figure 3-1 provides details.


Perpetrator type
60%
50%
40%
30%
20%
10%
0%
Husband/partner
Family member
Friend
Stranger
Other person
Rural
Urban

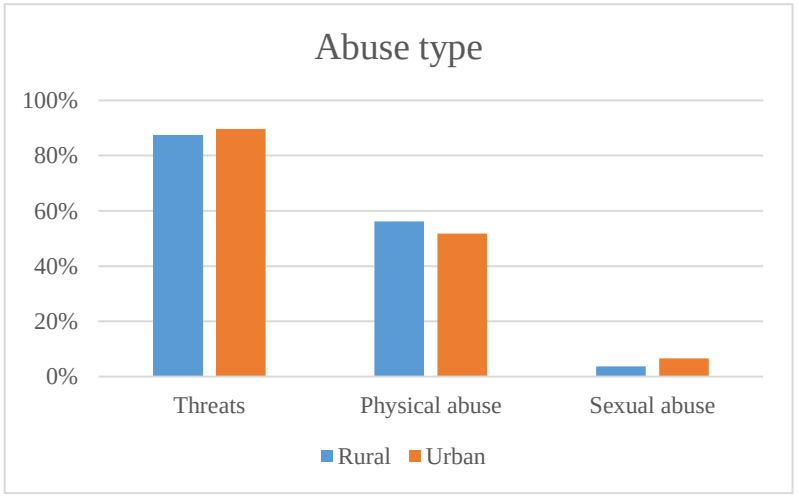
(a)


Abuse times
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1 to 5
6 to 9
≥10
Rural
Urban

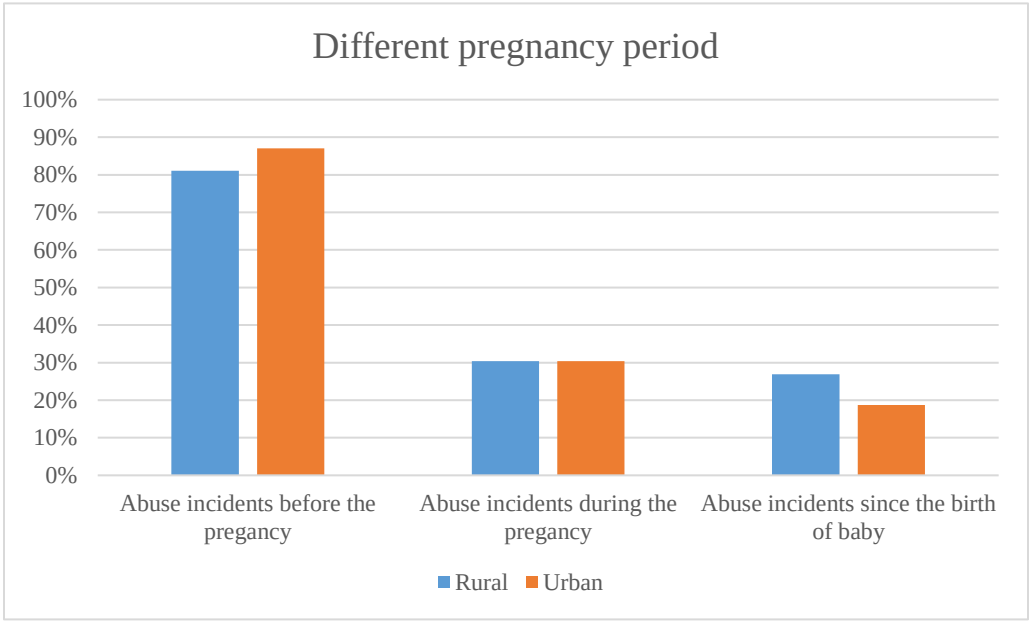
(b)


Number of abuse type
80%
70%
60%
50%
40%
30%
20%
10%
0%
1 to 2
3 to 4
≥5
Rural
Urban

(c)


Abuse type
100%
80%
60%
40%
20%
0%
Threats
Physical abuse
Sexual abuse
Rural
Urban

(d)



(e)

Figure 3-1 Abuse characteristics in rural and urban areas.

In the unadjusted analyses, there was no difference in the risk factors for abuse and violence experience around the time of pregnancy between mothers living in rural and urban areas. However, after adjusting for maternal education, household income, marital status, aboriginal ancestry, province/territory of residence, sex of baby, immigration status, mother's age at birth of survey reference child, mother's age at first pregnancy, and total number of pregnancies, urban mothers were at 1.32 times increased odds of experiencing abuse and violence around the time of pregnancy compared to rural mothers (OR 1.32, 95% CI 1.05-1.67). In the final multivariable logistic regression model with full adjustment (See Table 3-2), this association was slightly attenuated but still significant indicating that living in an urban environment was associated with an increased risk of experiencing abuse around the time of pregnancy (OR=1.31, 95% CI: 1.03-1.66). In addition, mothers who were young (OR=2.19, 95% CI: 1.51-3.18), single or divorced (OR_{single}=2.70, 95% CI: 2.04-3.56; $OR_{divorced}$=2.87, 95% CI: 1.74-4.73), with low income (OR=1.99, 95% CI: 1.13-3.51), a non-immigrant (OR=1.62, 95% CI: 1.17-2.27), of aboriginal ancestry (OR=1.48, 95% CI: 1.04-2.09), and had more than four pregnancies (OR=1.60, 95% CI: 1.17-2.19) were more likely to experience abuse. In addition, cigarette smoking (OR=1.65, 95% CI: 1.34-2.03), alcohol consumption (OR=1.30, 95% CI: 1.05-1.62) and drug use (OR=2.01, 95% CI: 1.53-2.64) before the pregnancy was significantly associated with an increased risk of abuse around the time of pregnancy. Details are presented in the Table 3-2.

Table 3-3 shows the outcomes associated with pregnancy related abuse in this sample of mothers and their neonates. Among *all* Canadian mothers, abuse experience around the time of pregnancy was significantly associated with postnatal depression (OR=2.51, 95% CI: 2.05-3.09). After adjusting for confounding factors, the significant association remained (OR=2.35, 95% CI: 1.86-2.97). Likewise, a history of abuse was significantly associated with the experience of stressful life events (OR=3.82, 95% CI: 3.06-4.77). This association was attenuated but still remained significant after adjusting

for confounders (OR=2.64, 95% CI: 2.09-3.33). No association was found between abuse around pregnancy and adverse birth outcomes, including preterm birth, caesarean delivery and low birth weight baby.

In a rural-urban stratified analysis, mothers who experienced abuse were at greater risk of postnatal depression in the non-adjusted model for both rural and urban areas (OR_{rural}=2.36, 95% CI: 1.45-3.81; OR_{urban}=2.53, 95% CI: 2.02-3.18). After adjustment for potential intervening variables the rural and urban differences were attenuated to 1.92 times increased odds (OR=1.92, 95% CI 1.17-3.18) and 2.50 times increased odds (OR=2.50, 95% CI 11.92-3.25) respectively. Similar patterns were observed for stressful events. In the unadjusted models, abuse in the past two years was associated with increased frequency of stressful events in rural areas (OR=3.62, 95% CI: 2.20-5.95), and also in urban areas (OR=3.86, 95% CI: 3.01-4.94). After further adjustments for potential confounders, the experience of abuse and violence was still associated with stressful events among rural mothers (OR=2.45, 95% CI: 1.44-4.17) and urban mothers (OR=2.66, 95% CI: 2.05-3.45). Whereas there were no instances of LBW among the offspring of abused mothers in comparison with non-abused mothers in either rural or urban environments, the experience of abuse was associated with an increased risk for a preterm birth among rural mothers only in both unadjusted and fully adjusted models ($OR_{unadjusted}$=2.15, 95% CI 1.10-4.19; $OR_{adjusted}$=2.30, 95% CI 1.09-4.88) but not so for urban mothers.

Table 3- 2 Association between residency and abuse around the time of pregnancy.

Variables		Model 1		Model 2		Model 3	
Demographic							
Area size	Rural	1		1.00		1.00	
	Urban	1.15	0.93,1.43	1.32	1.05,1.67	1.31	1.03,1.66
Mother age at birth of survey reference child (years)	15-19			2.03	1.40, 2.94	2.19	1.51, 3.18
	20-29			1.00		1.00	
	30-39			0.68	0.53, 0.87	0.70	0.54, 0.90
	Above 40			0.65	0.34, 1.26	0.69	0.35, 1.35
Mother's education	University graduation and above			1.00		1.00	
	Post-secondary diploma			1.06	0.83,1.34	0.98	0.76,1.25
	Some post-secondary education			1.71	1.20,2.44	1.42	0.99,2.03
	High school graduation			1.25	0.94,1.68	1.06	0.78,1.44
	Less than high school			1.34	0.95,1.89	1.12	0.78,1.61
Household income	$100,000 or more			1.00		1.00	
	$60,000 to less than $100,000			0.99	0.72, 1.36	0.98	0.71, 1.34
	$30,000 to less than $60,000			1.11	0.81, 1.53	1.04	0.75, 1.45
	$10,000 to less than $30,000			1.85	1.30, 2.64	1.61	1.12, 2.30
	Less than $10,000			2.15	1.22, 3.78	1.99	1.13, 3.51
Marital status	Married/common-law			1.00		1.00	
	Divorced/Separated/Widow			2.98	1.82,4.89	2.87	1.74,4.73
	Single			3.12	2.39,4.08	2.70	2.04,3.56
Aboriginal ancestry	No			1.00		1.00	
	Yes			1.71	1.22,2.38	1.48	1.04,2.09
Province or territory of residence	Newfoundland and Labrador			1.00		1.00	
	Prince Edward Island			0.83	0.42,1.61	0.80	0.41,1.57
	Nova Scotia			1.36	0.81,2.29	1.35	0.79,2.28

	New Brunswick	1.38	0.81,2.35	1.39	0.81,2.37
	Quebec	1.38	0.88,2.15	1.43	0.91,2.24
	Ontario	1.30	0.84,2.03	1.32	0.85,2.06
	Manitoba	1.78	1.07,2.98	1.82	1.08,3.07
	Saskatchewan	1.35	0.81,2.26	1.45	0.87,2.44
	Alberta	1.41	0.87,2.28	1.45	0.90,2.35
	British Columbia	1.60	0.99,2.60	1.58	0.97,2.57
	Yukon	2.05	0.88,4.74	2.27	0.97,5.32
	Northwest Territories	3.50	1.73,7.06	3.68	1.81,7.51
	Nunavut	2.00	0.94,4.25	1.84	0.84,4.06
Immigrant status	Yes	1.00			
	No	2.18	1.60, 2.98	1.62	1.17, 2.27
Obstetric factors					
Sex of the survey reference baby	Male	1.00		1.00	
	Female	1.01	0.85,1.21	1.04	0.87,1.25
Mother's age at first pregnancy (years)	15 to 19	1.00		1.00	
	20-34	0.49	0.38,0.63	0.54	0.42,0.70
	≥35	0.50	0.26,0.98	0.56	0.29,1.11
	1	1.00		1.00	
Total number of pregnancies	2 to 3	1.14	0.92, 1.42	1.20	0.96, 1.50
	≥4	1.51	1.12, 2.05	1.60	1.17, 2.19
Health behaviors	No			1.00	
Smoked before this pregnancy	Yes			1.65	1.34,2.03
	No			1.00	
Alcohol consumption before this pregnancy	Yes			1.30	1.05,1.62
	No			1.00	
Drug use before this pregnancy	Yes			2.01	1.53,2.64

Table 3- 3 Impact of abuse around the time of pregnancy among rural and urban mothers.

Variables	Rural area		Urban area		Overall sample	
	Non-adjusted model	Fully adjusted model	Non-adjusted model	Fully adjusted model	Non-adjusted model	Fully adjusted model
Postnatal Depression						
No	1	1	1	1	1	1
Yes	2.36(1.45,3.81)	1.92 (1.17,3.18)	2.53(2.02,3.18)	2.50(1.92,3.25)	2.51(2.05,3.09)	2.35(1.86,2.97)
Stressful events						
No	1	1	1	1	1	1
Yes	3.62(2.20,5.95)	2.45(1.44,4.17)	3.86(3.01,4.94)	2.66(2.05,3.45)	3.82(3.06,4.77)	2.64(2.09,3.33)
Type of delivery						
Vaginal	1	1	1	1	1	1
Caesarean	0.49 (0.30,0.82)	0.56(0.33,1.00)	0.94(0.76,1.16)	1.05(0.83,1.33)	0.86(0.71,1.04)	0.96(0.77,1.18)
Birth Weight of the baby, g						
<2500	1	1	1	1	1	1
≥2500	0.72(0.29,1.76)	0.65(0.26,1.64)	1.22(0.78,1.91)	1.27(0.79,2.04)	1.13(0.75,1.69)	1.14(0.75,1.74)
Gestational age, weeks						
≥37	1	1	1	1	1	1
<37	2.15(1.10,4.19)	2.30(1.09,4.88)	0.93(0.62,1.39)	0.82(0.53,1.27)	1.10(0.78,1.55)	0.99(0.68,1.43)

3.5 Discussion

This study explored violence and abuse experience around the time of pregnancy among rural and urban mothers in Canada identifying potential modifiable risk factors and examining related outcomes.

Our study findings indicated that in comparison with rural mothers, urban mothers may experience somewhat higher levels of violence and abuse around the time of pregnancy. Abuse across all three time periods around pregnancy was more common among mothers of aboriginal ancestry, non-immigrant and unmarried mothers who resided in an urban area, had a low income, who had more than four pregnancies and who had a history of smoking/drinking/drug use before the pregnancy. This experience of abuse was significantly correlated with postnatal depression, stressful events in both residential areas, but was only related to preterm delivery of the baby among rural mothers.

Our findings differ from previous reports that found the rural women reporting higher risk of abuse experience (Bueno & Lopes, 2018; Shannon, Logan, Cole, & Medley, 2006) who theorized that rural mothers usually have inadequate awareness of their rights and limited access to health services (Dimah & Dimah, 2004). However, the present findings of slightly higher levels of abuse in the urban areas may be due to competing resources for urban mothers which may make it less feasible for them to leave the abusive environment and rebuild their life, thus prolonging their dependency on abusive partners and making them more vulnerable to abuse (Shreya Bhandari et al., 2015). Our finding showed that urban mothers experienced more abuse incidents before the pregnancy and less abuse incidents after the birth of the baby which is consistent with previous studies (Beydoun, Al-Sahab, Beydoun, & Tamim, 2010). We also found similar patterns of perpetrator characteristics, abuse times, and abuse types in urban and rural areas in the present study. Several mechanisms were proposed to explain urban mothers' slightly higher abuse levels around the time of pregnancy. For example, subculture theory of urbanism proposes a mutually reinforcing relationship between population size/density and violence due to social differentiation and the intense subcultures. It suggests that residents of more populated areas behave in more unconventional and more violent manner than residents of less populated areas (Fischer, 1995). Similarly, density-pathology hypothesis suggests that areas with greater population densities suffer from increased pathologies (Choldin, 1978). In addition, social

disorganization theory links concentrations of disadvantaged individuals, residential instability, and ethnic heterogeneity with variations in social organization resulting in a lower collective capacity to control violence between intimates (Browning, 2002). Besides residency, other socioeconomic characteristics including being young, of aboriginal ancestry, and unmarried were found to be significantly associated with abuse around the time pregnancy. Our findings are in line with a USA National Crime Victimization Survey demonstrating that abuse around the time of pregnancy is more likely to occur in women who are young, separated or divorced, or who have low incomes (Rennison, 2001). Brown, McDonald, & Krastev (2008) found that young maternal age was an important factor linked to the abuse experienced by pregnant women. It is reported that young maternal age at childbirth may represent a more general socio-economically disadvantaged characteristic leading to a higher risk of intimate partner violence (Devries et al., 2010). Consistent with our findings, a meta-analysis and systematic review with 55 independent studies reported that being unmarried and of lower socioeconomic status was associated with abuse around the time of pregnancy (James et al., 2013). These relationships have also been confirmed in several studies (Heaman, 2005). Being of aboriginal ancestry has been associated with an increased risk of spousal abuse in several other Canadian studies (Nihaya Daoud, Smylie, Urquia, Allan, & O'Campo, 2013; Nelson, Lawford, Otterman, & Darling). Aboriginal women in abusive relationships may face unique challenges when seeking to change their abusive environment due to contextual factors such as differences in community social resources and/or services (Blagg et al., 2018; Nihaya Daoud et al., 2013). Furthermore, colonization theory suggests that contextual factors related to colonialism could account for increased violence around the time of pregnancy experienced by Aboriginal mothers (Daoud, Smylie, Urquia, Allan, & O'Campo, 2013).

Likewise, compared to Canadian-born mothers, immigrant mothers consistently report experiencing less abuse during pregnancy which is consistent with our study (Khanlou et al., 2017). Immigration from other countries to Canada are mostly economic migrants, hence they are more likely to be equipped with skills and have higher level of education. However, some suggest that the abuse may be under-reported by immigrant women. Lack of knowledge and access to social services, financial dependence on the partner, and fears of deportation discouraged immigrant women from reporting violence (Du Mont and Forte, 2012).

It is not surprising that women with more pregnancies were more likely to report the abuse since abuse often starts or gets worse during the beginning of pregnancy. In addition, more pregnancies increase the chance of unintended pregnancies. Women with unintended pregnancies had a greater risk of abuse during pregnancy (Lukasse et al., 2015).

In line with our study, a variety of research has documented behavioral risk factors were significantly related to experiencing violence – alcohol consumption before pregnancy (Nihaya Daoud et al., 2013; Stöckl, Watts, & Kilonzo Mbwambo, 2010), smoking before pregnancy (Chu, Goodwin, & D'Angelo, 2010) and drug use before pregnancy (Jacquelyn C Campbell, 2002).

Many research studies have noted the associations between the experience of abuse during pregnancy and negative maternal and neonatal outcomes (Alhusen, Ray, Sharps, & Bullock, 2015). The findings of the current study are generally consistent with those that described significant links between abuse experience and stressful events as well as postnatal depression with stronger associations being found among urban mothers. The results of our study are comparable with prior literature showing an association between abuse and negative health behaviors among mothers residing in both rural and urban areas (Bailey & Daugherty, 2007; Melville, Gavin, Guo, Fan, & Katon, 2010; Small et al., 2008). It is suggested that these relationships are stronger for urban populations because urban women have a greater tendency towards economic and emotional dependency (Sigalla et al., 2017). However, the increased risk of preterm birth was only found among abused mothers residing in rural areas. Direct and indirect mechanisms for how violence during pregnancy may influence adverse maternal and neonatal outcomes have been proposed (Coker, Sanderson & Dong, 2004). A direct causal path between physical abuse and preterm birth may occur through blows to the abdomen or sexual assault. Indirect mechanisms are through elevated stress-related hormones, such as levels of corticotrophin-releasing hormone (CRH). Higher levels of HPA hormones could initiate labor as well as restrict utero-placental perfusion (Kalantaridou et al., 2010).

Strengths and limitations There were several limitations in the present study. First, due to the nature of cross-sectional study design, our ability to draw causal inferences is limited and our findings should be interpreted only as correlations. Second, women with a history of abuse may be less likely to take part in the survey or reluctant to disclose abuse which would result in the

underestimation of the abuse prevalence. Third, mothers who lived on First Nations Reserves representing socially and economically disadvantaged populations were not surveyed in the MES, thereby reducing generalizability of the results. However, Aboriginal mothers living off reserve as well as mothers with aboriginal ancestry have been included in the MES. Fourth, data on emotional abuse, which appears to be the most prevalent form of abuse, was not collected in the MES though which appears to be the most prevalent form of abuse thus the present study has not captured the full scope of the abuse problem.

Even with these limitations in mind, the present study has several strengths. First of all, although the MES data was collected in 2006, it is the first and only population-based Canadian survey of the experiences of abuse around the time of pregnancy at the national level across all provinces, resulting in a representative picture of the Canadian population. Many other studies of abuse around pregnancy have been conducted in health care or social services settings thereby limiting the generalizability of study findings to a broader population context. Furthermore, the present study considered a variety of risk factors across various domains, mitigating the effects of confounders. Reducing abuse around the time of pregnancy could be achieved effectively by identifying women at potentially higher risk and providing support to reduce their social and economic disadvantages, and offering health care providers opportunities to intervene. Bystander intervention and structured community responses to abuse in both rural and urban areas should be enhanced.

3.6 Conclusions

Our findings indicate that abuse around pregnancy is somewhat more frequent among urban mothers compared with rural mothers with around 11% to 10% of both groups of mothers experiencing such abuse. Being of aboriginal ancestry, young, unmarried, a non-immigrant and economically disadvantaged, and having more than four pregnancies, a history of cigarette smoking, alcohol drinking and drug use before the pregnancy were all correlated with the increased abuse around the time of pregnancy. Pregnancy related abuse was positively and significantly associated with mothers experiencing a greater number of stressful life events and postpartum depression, irrespective of whether they lived in urban or rural areas of the country. However, the significant association between pregnancy abuse and preterm delivery was only observed among rural mothers. Given that mothers abuse exposures lead to adverse

consequences for the women themselves and their child's birth outcomes as well as their child's future physical and emotional development, identification of mothers at potentially greater risk, with counseling support and referral to appropriate agencies with effective programs should be encouraged to more effectively address reducing women's risk of abuse and the potential negative sequelae of that abuse for mother and child. The developmental origins of health and disease hypothesis stresses the fundamental role of early life experiences on future physical and particularly emotional development (Su, D'Arcy & Meng, 2020).

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CHAPTER 4. SOCIAL SUPPORT AND POSITIVE COPING SKILLS ACT AS MEDIATORS BUFFERING THE IMPACT OF CHILDHOOD MALTREATMENT ON PSYCHOLOGICAL DISTRESS AND POSITIVE MENTAL HEALTH IN ADULTHOOD: ANALYSIS OF A NATIONAL POPULATION-BASED SAMPLE

A version of this chapter has been published as: “Su, Y., D’Arcy, C., & Meng, X. (2020). Social support and positive coping skills act as mediators buffering the impact of childhood maltreatment on psychological distress and positive mental health in adulthood: analysis of a national population-based sample. American Journal of Epidemiology, 189:394-402”. My contributions to this study included study design, data analysis, results interpretation, and manuscript writing as well as editing.

4.1 Abstract

There is little research on how childhood maltreatment influences the use of resilience mechanisms that are key to mental health outcomes in the face of adversity. We assessed the mediating roles of social support and positive coping skills in the relationships between childhood maltreatment and both psychological distress and positive mental health. We analyzed data from a national population survey, the 2012 Canadian Community Health Survey-Mental Health (CCHS-MH 2012, n = 25,113). Confirmatory factor analysis and structural equation modeling were used to model the relationships between childhood maltreatment, social support, and positive coping skills and their direct and mediated effect on psychological distress and positive mental health. Childhood maltreatment was found to be negatively associated with social support, positive coping skills, and positive mental health but positively associated with psychological distress. Social support and positive coping skills were associated with higher levels of positive mental health but lower levels of psychological distress. Social support and positive coping skills partially mediated the negative consequences of childhood maltreatment on mental health outcomes. Surprisingly, no sex differences were observed among these associations. This research clearly demonstrates that social support and positive coping skills can mediate the negative impact of childhood maltreatment on mental health.

4.2 Introduction

The World Health Organization defines mental health as “a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community” (World Health Organization, 2014). It is both a flourishing state of mental health and being free of mental disorders. The concept of positive mental health was developed to reflect overall mental health including emotional, psychological and social well-being (Keyes, 2002). Gilmour (2014) underlines this point, showing in a large national study that the continuous positive mental health score was only moderately related to any mental disorder (-0.31) emphasizing that positive mental health is more than just the absence of mental illnesses. Childhood maltreatment encompasses both abuse and neglect and is defined as abusive behaviors towards to children prior to their 18 years of old (World Health Organization, 2016). It is a global problem with long-lasting negative consequences. World Health Organization reported that 25% of adults had been physically abused as children, and 1 in 5 women and 1 in 13 men report having been sexually abused as a child. Many children are subject to emotional abuse and neglect (4). It is also widely documented as a risk factor for adverse psychological and psychiatric outcomes in adolescence and adulthood (Chapman, Dube, & Anda, 2007; Mersky, Topitzes, & Reynolds, 2013).A substantial literature shows its multifaceted long-term adverse impact on mental health (Wark, Kruczek, & Boley, 2003; Kaplow & Widom, 2007; Li, D'Arcy, & Meng, 2016). Although the association between childhood experiences of maltreatment and mental health is well-established, details of their connections need further explication.

Social support has been found to have a mediation role between maltreatment and mental health (Salazar, Keller, & Courtney, 2011; Sperry & Widom, 2013). Exposure to maltreatment is associated with perceptions of less social support. Maltreated children experience a lower trustful “network orientation” which prevents them from accessing available social support (Pepin & Banyard, 2006; Sperry & Widom, 2013). Those with lower levels of social support were more likely to report distress (Holahan & Moos, 1981). Social support has been negatively associated with anxiety, mood disorders, suicidality, and eating disorders among adults and adolescents (Hefner & Eisenberg, 2009; Seeds, Harkness, & Quilty, 2010). Although previous studies have found social support buffers negative outcomes in maltreated children, it may also mediate the

impact of such experiences on adulthood mental health (Oshio, Umeda, & Kawakami, 2013). Runtz and Schallow (1997) found that the social support entirely mediated the association between child maltreatment and adult adjustment, confirming Baron and Kenny's (1986) mediation hypothesis. Positive coping skills have also been found to alleviate the negative psychiatric effects of abuse (Hager & Runtz, 2012). Afifi et al. (2016) reported that among those who were maltreated in childhood, coping strategies were associated with supportive relationships leading to better psychological wellbeing in adulthood. Similarly, coping strategies have been identified to play an important mediating role between stressors and the development of mental health problems, e.g., Post-Traumatic Stress Disorders, depression, etc. (Calvete, Corral, & Estévez, 2008). Research has explored the mediation effects of coping strategies on the psychological wellbeing of maltreated individuals (Fortier *et al.* 2009).

Despite this knowledge, little research has sought to understand how multiple mechanisms combine to mediate the translation of abuse experiences into manifestations of mental illnesses. Little is known about the roles of social support and coping skills in mediating the maltreatment experience. In addition, several studies have suggested that females may be more resilient to the effects of childhood maltreatment than their male counterparts (Hager & Runtz, 2012; Magdol *et al.* 1997).

In order to provide a target for effective treatment and prevention, it is important to have an understanding of how child maltreatment leads to the psychological distress and negatively affects positive mental health. Does sex impact this relationship? Although research has demonstrated complex interrelationships among childhood maltreatment, social support, coping strategies, and mental well-being, to the best of our knowledge, there is no study that has investigated the mediating effects of social support and coping strategies on the pathway between childhood maltreatment and mental health/illness. Given that the mechanisms and contexts of these relationships are not yet well understood, the current study is designed to assess in an integrated model the mediating roles of both social support and positive coping skills in the relationship between childhood maltreatment and psychological distress and positive mental health in the general population. We hypothesized that: 1) childhood maltreatment is directly related to social support, positive coping skills, and also directly related to psychological distress and positive mental health; 2) social support and positive coping skills are both directly and

indirectly related to psychological distress and positive mental health; 3) relationship between childhood maltreatment and mental health outcome is mediated by social support and positive coping skills. Structural equation modeling is used to examine these relationships.

4.3 Methods

4.3.1 Data and sample

The data analyzed were from CCHS-MH 2012, a cross-sectional national health survey designed to explore on the mental health and behaviors of Canadians. The sampling frame encompassed 97% of the Canadian population. Excluded were residents in the 3 northern territories and indigenous communities, full-time members of the Canadian Forces, and institutionalized individuals. The survey employed a multistage, stratified cluster design. Data were collected in 2012. The majority of interviews (87%) were conducted face to face at the respondents' home with the remaining done by telephone using computer assisted interviewing technology. All respondents signed an informed consent and completed the survey on a voluntary basis (Statistics Canada, 2011). The original survey received ethical approval through Statistics Canada procedures. The completed sample is representative of the population aged 15 years and above in the 10 provinces of Canada (N = 25,113).

4.3.2 Measures

Childhood maltreatment. Childhood maltreatment was indicated by participants' experiences of maltreatment before 16 years of age. It was assessed by 6 items covering 3 domains: intimate partner violence (1 item), physical abuse (3 items) and sexual abuse (2 items). Exposure to intimate partner violence and physical abuse were assessed using items from the Childhood Experiences of Violence Questionnaire (Walsh, MacMillan, Trocmé, Jamieson, & Boyle, 2008). Two items (used previously in a Statistics Canada survey (2013)) asked about sexual abuse prior to 16 years of age, including questions about unwanted and coercive sexual activity. In this analysis these domains were scored on a 5-point scale: none, 1 or 2 times, 3-5 times, 6-10 times and more than 10 times (5). The Cronbach alpha for the maltreatment items was 0.78.

Psychological distress. The 10-item Kessler Psychological Distress Scale measured psychological distress (Kessler *et al.* 2002). It has 4 factors: nervousness, agitation, fatigue and negative affect (Brooks, Beard, & Steel, 2006). Its Cronbach alpha was 0.78.

Positive mental health. The Mental Health Continuum-Short Form composed of 14 items with 3 items for emotional well-being and 11 items for positive functioning assessed positive mental health (Keyes, 2009). Emotional, social and psychological well-being have been identified as scale factors (Heather, Julie, Jennifer, & Gayatri, 2017). Its Cronbach alpha was 0.76.

Social support. The Social Provisions Scale-10 item measured availability of social support. It is a shortened version of the Social Provisions Scale (Cutrona & Troutman, 1986) with 5 subscales: attachment, guidance, reliable alliance, social integration, and reassurance of worth (Iapichino *et al.* 2016). The Cronbach alpha was 0.92.

Positive coping skills. Positive coping skills were assessed by 2 items used in previous research (Afifi *et al.* 2016). On a 5-item Likert response scale (1= poor, 5 = excellent), respondents were asked about their: 1) ability to handle unexpected and difficult problems (e.g., a family or personal crisis); and 2) ability to handle the day-to-day demands of their life.

4.3.3 Statistical analysis

Our analyses were completed in 2 phases. The sample was randomly split into 2 datasets, with 1 for training and the other for testing. First CFA was used to evaluate relationships between observed variables directly assessed by the questionnaires and the latent constructs used in the model (except positive coping skills). Then we applied SEM to investigate the multivariate relationships among these latent constructs. Missing data were imputed using a multiple imputation procedure (m=5) (Sterne *et al.* 2009). AMOS version 23.0 (SPSS Inc., Chicago, IL, USA) (Arbuckle, 2014) was used. According to Baron and Kenny (1986), in the 4-step analytical procedure for mediation effect, the independent variable should be significantly associated with dependent variable (direct path), and the pathways for independent variable to mediator as well as mediator to dependent variable should be significant. In addition, the association between independent variable and dependent variable should be significantly attenuated when the mediator is taken into consideration. To correct for bias in the model fit statistic due to non-

normalized variables, the Bollen-Stine bootstrap method was used (Enders, 2005). Several fit indices were used to evaluate a good fitness of model: less than 3 for χ^2/df; above 0.90 for the goodness-of-fit statistics (GFI), the adjusted goodness-of-fit statistics (AGFI), the non-normed fit index (NNFI (TLI)), the comparative fit index (CFI); and less than 0.08 for the root-mean-square error of approximation (RMSEA). We then applied cross-validation method to test the generalizability of the results (Anderson & Gerbing, 1988). Finally, to test indirect effects including 95% bootstrap confidence intervals (CI), we used the Mackinnon test by testing 2,000 bootstrap samples (MacKinnon, Lockwood, & Williams, 2004). Although the Type I error could be potentially inflated for other resampling methods to test indirect effects, the PRODCLIN program for computing asymmetric confidence limits is regarded as superior and can produce the specific indirect effect of each mediator. The Mackinnon PRODCLIN2 was used to obtain more accurate confidence limits for the indirect effect with more accurate Type I error and more power compared to bias corrected and percentile method (MacKinnon, Fritz, Williams, & Lockwood, 2007).

4.4 Results

4.4.1 Preliminary analyses and descriptive statistics

A total of 25,113 individuals were included in this study. Table 4-1 provides summary statistics for the study sample. More than half of the study sample (52.9%) had at least 1 type of childhood maltreatment; 23.1% were exposed to intimate partner violence; 47.6% had experienced physical abuse; and 20.5% had experienced sexual abuse.

CFA analyses were used to investigate latent constructs of childhood maltreatment (3 factors), social support (5 factors), psychological distress (4 factors), and positive mental health (3 factors). The CFA results indicate that all measurement models had good fit (χ^2/df = 77.660, $P < 0.001$, CFI = 0.960, RMSEA = 0.055 (95% CI: 0.054, 0.056)). All the scale items loaded significantly onto their corresponding latent constructs (standardized factor loadings ranged from 0.45 to 0.89, with most being above 0.65). The loadings were: 0.45 to 0.79 for childhood maltreatment; 0.76 to 0.89 for social support; 0.58 to 0.82 for psychological distress; and 0.69 to 0.87 for positive mental health. All factor loadings were significant ($P < 0.001$) (See Appendix A.1).

The correlation matrix among variables in the CFA model is reported in the Appendix A.2. All variables were significantly correlated among themselves. Positive correlations between all categories of childhood maltreatment and psychological distress-related variables were found, with r ranging from 0.12 to 0.21. Negative correlations among child maltreatment and positive mental health were also found, with r ranging from -0.10 to -0.17. The correlations among mediators and X (independent variable) and Y (dependent variable) were all significant ($P < 0.05$).

Table 4-1 Descriptive statistics for respondents in Canadian Community Health Survey-Mental Health, Canada, 2012 (N = 25,113).

Variables	Frequency	%
Age(years)		
15-24	4013	16.0
25-44	6906	27.5
45-64	8077	32.2
65+	6117	24.3
Gender		
Male	11340	45.2
Female	13773	54.8
Education Level		
Less than secondary school graduation	5338	21.3
Secondary school graduation	4022	16.0
Some post-secondary graduation	1655	6.6
Post-secondary graduation	14098	56.1
Household income		
Less than $20,000	1736	6.9
$20,000-$39,999	4410	17.6
$40,000-$59,999	5289	21.1
$60,000-$79,999	4190	16.7
$80,000+	9488	37.8
Province of residence		
Newfoundland and Labrador	1413	5.6
Prince Edward Island	1098	4.4
Nova Scotia	1714	6.8
New Brunswick	1672	6.7
Quebec	4348	17.3
Ontario	5492	21.9
Manitoba	1826	7.3
Saskatchewan	1709	6.8
Alberta	2785	11.1
British Columbia	3056	12.2
Visible minority		
White	20972	83.5
Non-white	4141	16.5
Immigrants		
Yes	4245	16.9
No	20868	83.1

4.4.2 Structural equation model

Figure 4-1 shows the structural model with standardized regression weights. Our structural model estimated 2 direct paths from child maltreatment (independent variable) to distress (dependent variable), and to positive mental health (dependent variable), and the potential indirect pathways via social support (mediator) and positive coping skills (mediator), respectively. Overall, the model had a good fit for the data after Bollen-Stine Chi-square correction, (Bollen-Stine χ^2 (93) = 129.320, $P < 0.001$; $\chi 2/df = 1.390$, GFI = 0.990, RMSEA = 0.004) with significant path coefficients and covariance. Our model meets the Baron and Kenny criteria (1986). Bootstrap resampling testing for indirect effects in the structural model shows all the path coefficients were significant (see Table 4-2).

Our findings indicate that childhood maltreatment was negatively associated with social support ($\beta = -0.13$) and positive coping skills ($\beta = -0.10$). Social support and positive coping skills were associated with better positive mental health ($\beta_{\text{social support}} = 0.33$; $\beta_{\text{positive coping skills}} = 0.38$), and lower risk of psychological distress ($\beta_{\text{social support}} = -0.17$; $\beta_{\text{positive coping skills}} = -0.40$). The total effects of childhood maltreatment indicate that it was associated with greater psychological distress ($\beta = 0.31$) and lower levels of positive mental health ($\beta = -0.24$). A stratified analysis developing SEMs for males and females was run separately. No sex differences were observed in the associations between childhood maltreatment and mental health outcomes mediated by resilient mediators (see Appendices A.3-A.4).

The cross-validation test shows that there was no significant difference between testing and training dataset ($P > 0.05$). We then applied the structural model in the full sample (N = 25,113). Table 4-3 presents the cross-validation test results.

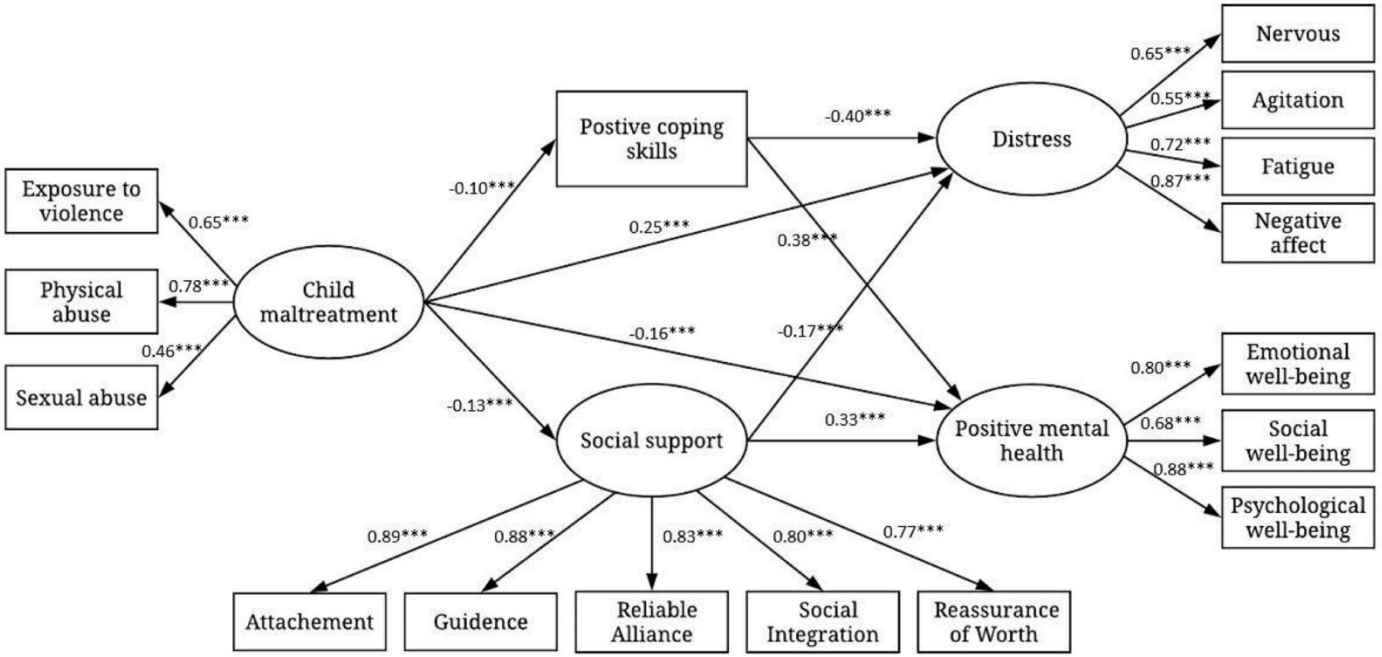

Figure 4-1 Measurement and structural model: standardized factor loadings for final model of relationships between childhood maltreatment, positive coping skills, social support, psychological distress and positive mental health, Canadian Community Health Survey-Mental Health, Canada, 2012 (N= 25,113).

***P<0.05

Table 4-2 Results of standardized and unstandardized coefficients, Canadian Community Health Survey-Mental Health, Canada, 2012 (N = 25,113).

Structural model	Unstandardized Estimate	S.E.	C.R.	*P* Value	Standardized Estimate
Positive coping skills←Child maltreatment	-0.279	0.022	-12.951	<0.001	-0.097
Social support←Child maltreatment	-0.188	0.011	-16.557	<0.001	-0.131
Distress←Social support	-0.190	0.007	-26.280	<0.001	-0.175
Positive mental health←Social support	0.827	0.017	48.264	<0.001	0.328
Positive mental health←Positive coping skills	0.478	0.008	59.680	<0.001	0.378
Distress←Positive coping skills	-0.217	0.004	-56.890	<0.001	-0.398
Distress←Child maltreatment	0.389	0.012	31.233	<0.001	0.249
Positive mental health←Child maltreatment	-0.589	0.026	-22.677	<0.001	-0.163

Abbreviations: C.R., critical ratio; S.E., standard error.

Table 4-3 Cross-validation test for calibration and validation sample, Canadian Community Health Survey-Mental Health, Canada, 2012 (N = 25,113).

Model	DF	CMIN	*P* Value	NFI	IFI	RFI	TLI
				Delta-1	Delta-2	rho-1	rho-2
Measurement weights	12	8.449	0.750	0.001	0.001	-0.002	-0.002
Structural weights	7	6.346	0.500	0.001	0.001	-0.001	-0.001
Structural covariance	1	0.170	0.680	0.001	0.001	-0.001	-0.001
Structural residuals	4	3.684	0.450	0.001	0.001	-0.001	-0.001
Measurement residuals	19	51.160	0.001	0.001	0.001	-0.003	-0.003

Abbreviations: CMIN, chi-square equivalent in confirmatory factor analysis; DF, degrees of freedom; IFI, Incremental Fit Index; NFI, Normed Fit Index; RFI, Relative Fit Index; TLI, Tucker-Lewis Index.

4.4.3 Tests of indirect effects

Estimates of the indirect effects were calculated by multiplication of the pathway coefficients between the independent and mediator variable and between the mediator and dependent variable. A 95% confidence interval produced by PRODCLIN2 program indicates the significance of indirect effect. The unstandardized total indirect effects from childhood maltreatment through positive coping skills and social support to mental health related outcomes were significant ($в_{\text{psychological distress}} = 0.10$, $в_{\text{positive mental health}} = -0.29$). The bootstrapping index for indirect effects was significant when 2 mediators were included as mediating variables. Thus, the mediating effects of social support and positive coping skills on the relationships between childhood maltreatment and both psychological distress and positive mental health were significant. The specific indirect effects through 2 mediators were separately significant (Table 4-4). Clearly, positive coping skills and social support mediated the relationship between childhood maltreatment and psychological distress (mediation proportion: 40.0% and 22.1%, respectively). Positive coping skills and social support also mediated the relationship between childhood maltreatment and positive mental health (mediation proportion: 13.2% and 14.9%, respectively).

To test if the mediation effect of each mediator was full or partial, we first conducted an analysis to explore the mediating role of social support in the relationship between child maltreatment and psychological distress or positive mental health separately when controlling for positive coping skills. Since all of the confidence intervals were exclusive of 0, the MacKinnon test method shows the direct paths from childhood maltreatment to distress and to positive mental health were both significant. These results demonstrate that social support served as a partial mediator for the association between the childhood maltreatment and psychological distress ($\beta = 0.27$, 95%CI: 0.26, 0.29) as well as positive mental health ($\beta = -0.19$, 95%CI: -.020, -0.17). Similarly, partial mediation results show the standardized direct effect of childhood maltreatment on psychological distress is 0.26 (95%CI: 0.25, 0.28) and -0.20 for positive mental health (95%CI: - 0.18, -0.21). The final model accounted for 32.4% of the variance in psychological distress via pathways, and 38.0% of the variance in positive mental health. The analysis did not find that the effects of resilient mediators on the relationships between childhood maltreatment and mental health outcomes varied by respondent's sex (Appendices A.5-A.6).

Table 4-4 The test of indirect effect in model of childhood maltreatment and distress/positive mental health, mediated by social support and positive coping skills, Canadian Community Health Survey-Mental Health, Canada, 2012 (N = 25,113).

Path	Estimate	MacKinnon PRODCLIN2 95% CI		
		Lower	Upper	*P* Value
Child maltreatment→Positive coping skills→Distress	0.0617	0.0522	0.0713	<0.001
Child maltreatment→Positive coping skills→Positive mental health	-0.1281	-0.1496	-0.1070	<0.001
Child maltreatment→Social support→Distress	0.0352	0.0299	0.0473	<0.001
Child maltreatment→Social support→Positive mental health	-0.1460	-0.1655	-0.1273	<0.001

4.5 Discussion

Building on previous findings of the negative effects of childhood maltreatment on psychiatric disorders, this study examined structural relationships among childhood maltreatment, psychological distress and positive mental health, and tested whether social support and positive coping skills in adulthood mediated these relationships in a national survey of the Canadian population. We found that childhood maltreatment was negatively associated with social support, positive coping skills and positive mental health but positively associated with psychological distress. Social support and positive coping skills were associated with higher levels of positive mental health but lower levels of psychological distress. As expected, social support and positive coping skills partially explained the negative consequences of childhood maltreatment on mental health. The protective roles of social support and positive coping skills can be targeted for intervention and prevention efforts to help maltreated victims in adjustments and facilitate recovery. Furthermore, a stratified analysis found there was no evidence to support that the associations between childhood maltreatment and mental health related outcomes via resilient mediators varied by sex.

Childhood maltreatment is an increasing public health issue, maltreated victims consistently reported higher levels of psychiatric symptoms and negative mental health outcomes (Norman, Byambaa, Butchart, & Vos, 2012). We found more than 50% of the study sample reported some type of childhood maltreatment. Notably, current study expands our knowledge by exploring mediating effects of social support and positive coping skills in the relationship between childhood maltreatment and mental health outcome. The results showing childhood maltreatment is negatively related to social support and positive coping skills are consistent with current literature (Barnett, Martinez, & Keyson, 1996; Cook *et al.* 2017). It has also been reported that individuals with maltreatment experiences may be less willing or able to utilize resilience mechanisms, which can buffer the traumatic experience. Iwaniec et al. (2006) found that maltreatment increased children's vulnerability and decreased their resilience ability. Mitchell and Hodson (1983) showed that individuals with the experience of intimate partner violence were at greater risk for experiencing lower levels of social support resources. Social support plays an important role in determining victims' reaction to violence exposure as well as mental health outcomes. Social support can alleviate the negative impacts of the maltreatment

experience, for instance, by reducing posttraumatic stress and depressive symptoms (Sperry & Widom, 2013). We also noted that the experience of childhood maltreatment may lead individuals to less frequently use positive coping strategies. Studies found that individuals reporting maltreatment experiences in childhood but not presenting with negative psychological effect actively used positive coping strategies (Dumont & Provost, 1999). Consistent with our finding, Popescu et al. (2010) found childhood victimization was associated with negative coping. In contrast, positive coping skills have been shown to buffer the effects of maltreatment experience on mental health (Flett, Druckman, Hewitt, & Wekerle 2012). Positive coping strategies are considered as an important component of resilience to trauma exposure.

In addition to direct effects, researchers have reported that social support may mediate the relations among abuse experience and mental health outcomes. Mitchel and Hodson (1983) reported supporting evidence for a partially mediating role of social support among battered women who reported physical abuse in childhood. The mediating role of coping skills has also been documented. Blechman (1996) demonstrated that coping strategies could mediate the effects of risk-protection variables on negative outcomes such as depressive symptoms by introducing coping-competence-based practices. Guerra et al. (2016) also found that coping strategies had a partial mediating effect on the association between poly-victimization and mental health issues. Together with previous literature, we suggest that although childhood maltreatment is associated with adverse outcomes in children's mental health and wellbeing, social support and positive coping strategies can serve as protectors to reduce negative effects of maltreatment on mental health. In addition, social support and coping skills can contribute to mediating the relationship between childhood maltreatment and vulnerability to adult mental disorders.

To our best knowledge, this study is the first to explore how childhood maltreatment affected the access to resilience mechanisms (social support and positive coping skills), which subsequently affected psychological wellbeing. The current study model accounts for 32.4% of the variance in psychological distress, and 38.0% of the variance in positive mental health. The remaining variances may be a result of direct effects of childhood maltreatment or the impact of other factors not examined in our model. In addition, findings of this study were based on a large-scale nationally representative population survey. The survey was conducted by a

professional organization with an established tracked record for quality. The SEM analyses used in our study portrays the sequentially influencing pathways from maltreatment exposure to mental health and the mediating role of resilience factors of social support and coping strategies.

Several limitations of this study should also be noted. The cross-sectional nature of the data limits inferences regarding causation, although this limitation is partially addressed by SEMs and path modeling which suggest a specific ordering of relationships among constructs. Future longitudinal studies following children exposed to maltreatment are required to definitively establish causal relationships as well as test how mental health issues and resilience interact over time. Secondly, it is noteworthy that data on emotional maltreatment and neglect are absent in this analysis as they were not collected in the CCHS-MH 2012 survey. Childhood maltreatment needs to be more comprehensively assessed to capture more dimensions of such experiences. Thirdly, different types of childhood maltreatment were based on retrospective self-report. Some studies have demonstrated that retrospective reports of childhood maltreatment led to under-reporting. Such misclassifications tend to lead results toward the null hypothesis (Fergusson, Horwood, & Woodward 2000) and concurrent mental health factors such as mood may influence the reporting of traumatic childhood experiences (Colman *et al*. 2016).

4.6 Conclusions

We found a mediation model in which childhood maltreatment was linked with mental health outcomes via social support and coping skills, respectively. Social support and positive coping skills, served as resilient indicators, which partially mediated the relationships between childhood maltreatment and psychological distress as well as positive mental health. Our findings clearly demonstrate that social support and positive coping skills buffered the negative effects of maltreatment on mental health outcomes and suggest avenues for treatment and prevention of mental health problems for those exposed to maltreatment. This study contributes to the literature by evaluating an integrative model that incorporates the interrelationships between social support and coping strategies in the relationship between child maltreatment and mental health. Our findings also have important social and mental health implications indicating the important roles of social support and positive coping skills in the trajectory of mental health recovery for trauma exposure, thereby providing individuals resilience strategies when confronting maltreatment experiences.

4.7 References

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Appendix A.1. Construct reliability by confirmatory factor analysis for the measurement model, Canadian Community Health Survey-Mental Health, Canada, 2012 (N= 25,113).

Construct	Indicators	Unstandardized Factor Loadings	S.E.	C.R.	*P* Value	Standardized Factor Loadings	R^2
Child maltreatment	Intimate partner violence	1.00				0.65	0.42
	Physical abuse	3.52	0.70	50.52	<0.001	0.79	0.62
	Sexual abuse	0.91	0.02	54.11	<0.001	0.45	0.20
Social support	Attachment	1.00				0.89	0.79
	Social integration	0.99	0.01	160.09	<0.001	0.79	0.63
	Reassurance of worth	0.89	0.01	150.37	<0.001	0.76	0.58
	Reliable alliance	0.86	0.01	175.32	<0.001	0.84	0.70
	Guidance	1.01	0.01	195.83	<0.001	0.88	0.77
Distress	Nervous	1.00				0.68	0.47
	Agitation	0.97	0.01	79.24	<0.001	0.58	0.34
	Fatigue	1.39	0.01	93.03	<0.001	0.73	0.53
	Negative affect	2.13	0.02	100.08	<0.001	0.82	0.68
Positive mental health	Emotional well-being	1.00				0.74	0.55
	Psychological well-being	2.16	0.02	101.46	<0.001	0.87	0.75
	Social well-being	2.09	0.02	98.82	<0.001	0.69	0.48

Abbreviations: C.R., critical ratio; S.E., standard error.

Appendix A.2. Correlations among maltreatment, positive coping skills, social support, distress and positive mental health, Canadian Community Health Survey-Mental Health, Canada, 2012 (N= 25,113).

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1-Exposure to intimate partner violence	-															
2-Physical abuse	0.51*	-														
3-Sexual abuse	0.29*	0.35*	-													
4-Positive coping skills	-0.06*	-0.07*	-0.08*	-												
5-Attachment	-0.07*	-0.08*	-0.05*	0.25*	-											
6-Guidance	-0.07*	-0.08*	-0.06*	0.24*	0.79*	-										
7-Reliable alliance	-0.08*	-0.09*	-0.06*	0.24*	0.73*	0.75*	-									
8-Social integration	-0.09*	-0.11*	-0.08*	0.29*	0.70*	0.67*	0.66*	-								
9-Reassurance of worth	-0.06*	-0.06*	-0.05*	0.32*	0.67*	0.66*	0.62*	0.68*	-							
10-Nervous	0.12*	0.14*	0.13*	-0.34*	-0.13*	-0.12*	-0.14*	-0.17*	-0.14*	-						

11-Agitation	0.13*	0.18*	0.13*	-0.24*	-0.11*	-0.10*	-0.10*	-0.14*	-0.11*	0.42*	-					
12-Fatigue	0.14*	0.18*	0.15*	-0.37*	-0.21*	-0.20*	-0.20*	-0.25*	-0.23*	0.47*	0.44*	-				
13-Negative affect	0.17*	0.21*	0.18*	-0.39*	-0.26*	-0.26*	-0.25*	-0.30*	-0.27*	0.57*	0.46*	0.61*	-			
14-Emotional well-being	-0.13*	-0.17*	-0.13*	0.38*	0.32*	0.31*	0.29*	0.36*	0.33*	-0.39*	-0.32*	-0.49*	-0.63*	-		
15-Psychological well-being	-0.11*	-0.16*	-0.09*	0.30*	0.25*	0.24*	0.22*	0.34*	0.30*	-0.26*	-0.24*	-0.33*	-0.38*	-0.51*	-	
16-Social well-being	-0.11*	-0.15*	-0.10*	0.45*	0.35*	0.32*	0.30*	0.39*	0.40*	-0.34*	-0.28*	-0.41*	-0.51*	-0.64*	-0.60*	-

*P<0.001(2-tailed). Coefficients are Pearson correlations.

Appendix A.3. Results of standardized and unstandardized coefficients among males, Canadian Community Health Survey-Mental Health, Canada, 2012 (N = 11,340).

Structural model	Unstandardized Estimate	S.E.	C.R.	*P* Value	Standardized Estimate
Positive coping skills←Child maltreatment	-0.462	0.056	-8.207	<0.001	-0.100
Social support←Child maltreatment	-0.285	0.030	-13.649	<0.001	-0.140
Distress←Social support	-0.175	0.010	-20.649	<0.001	-0.185
Positive mental health←Social support	0.840	0.025	34.447	<0.001	0.319
Positive mental health←Positive coping skills	0.466	0.012	45.102	<0.001	0.384
Distress←Positive coping skills	-0.199	0.005	-41.290	<0.001	-0.382
Distress←Child maltreatment	0.563	0.030	24.954	<0.001	0.253
Positive mental health←Child maltreatment	-0.890	0.068	-18.417	<0.001	-0.172

Abbreviations: C.R., critical ratio; S.E., standard error.

Appendix A.4. Results of standardized and unstandardized coefficients among females, Canadian Community Health Survey-Mental Health, Canada, 2012 (N = 13,773).

Structural model	Unstandardized Estimate	S.E.	C.R.	*P* Value	Standardized Estimate
Positive coping skills←Child maltreatment	-0.213	0.021	-10.214	<0.001	-0.094
Social support←Child maltreatment	-0.150	0.011	-9.543	<0.001	-0.116
Distress←Social support	-0.217	0.011	-17.894	<0.001	-0.180
Positive mental health←Social support	0.810	0.024	33.429	<0.001	0.336
Positive mental health←Positive coping skills	0.488	0.011	38.851	<0.001	0.369
Distress←Positive coping skills	-0.224	0.005	-37.935	<0.001	-0.407
Distress←Child maltreatment	0.316	0.013	18.691	<0.001	0.236
Positive mental health←Child maltreatment	-0.466	0.025	-13.132	<0.001	-0.144

Abbreviations: C.R., critical ratio; S.E., standard error.

Appendix A.5. The test of indirect effect in model of childhood maltreatment and distress/positive mental health, mediated by social support and positive coping skills among males, Canadian Community Health Survey-Mental Health, Canada, 2012 (N = 11,340).

Path		MacKinnon PRODCLIN2 95% CI		
	Estimate	Lower	Upper	*P* Value
Child maltreatment→Positive coping skills→Distress	0.1046	0.0783	0.1319	<0.001
Child maltreatment→Positive coping skills→Positive mental health	-0.2764	-0.3470	-0.2078	<0.001
Child maltreatment→Social support→Distress	0.0846	0.0636	0.1074	<0.001
Child maltreatment→Social support→Positive mental health	-0.3239	-0.0525	-0.0152	<0.001

Abbreviation: CI, confidence interval.

Appendix A.6. The test of indirect effect in model of childhood maltreatment and distress/positive mental health, mediated by social support and positive coping skills among females, Canadian Community Health Survey-Mental Health, Canada, 2012 (N = 13,773).

Path		MacKinnon PRODCLIN2 95% CI		
	Estimate	Lower	Upper	*P* Value
Child maltreatment→Positive coping skills→Distress	0.0544	0.0433	0.6660	<0.001
Child maltreatment→Positive coping skills→Positive mental health	-0.1275	-0.1540	-0.1017	<0.001
Child maltreatment→Social support→Distress	0.0539	0.0448	0.0634	<0.001
Child maltreatment→Social support→Positive mental health	-0.1751	-0.2036	-0.1475	<0.001

Abbreviation: CI, confidence interval.

CHAPTER 5. INCREASED INCOME OVER TIME PREDICTS BETTER SELF-PERCEIVED MENTAL HEALTH ONLY AT A POPULATION LEVEL BUT NOT FOR INDIVIDUAL CHANGES: AN ANALYSIS OF A LONGITUDINAL COHORT USING CROSS-LAGGED MODELS

A version of this chapter titled “Increased income over time predicts better self-perceived mental health only at a population level but not for individual changes: An analysis of a longitudinal cohort using cross-lagged models” authored by Su, Y., D’Arcy, C., and Meng, X has been submitted online to Journal of Affective Disorders for publication review. My contributions to this study included study design, data analysis, results interpretation, and manuscript writing as well as editing.

5.1 Abstract

Background: The literature identifies a strong relationship between mental health and income, but there is little research that clarifies the directional association between household income and self-perceived mental health (SPMH) overtime either at a population or an individual level. This study investigates whether higher income predicts better SPMH overtime and poor SPMH predicts lower income overtime both at a population and an individual level.

Methods: Data analyzed was from the Montreal Southwest Social and Psychiatric Epidemiology Catchment Area study (ZEPSOM), a large, longitudinal, community-based cohort. The baseline survey was conducted in 2007/8 with follow-up every two years. We traced a total of 3464 participants over a period of 8 years. To examine the associations between income and SPMH at both population and individual levels, cross-lagged panel models (CLPMs) and random intercept cross-lagged panel models (RI-CLPMs) were used. Gender and age effects were examined using multiple group analyses. Complete case analyses evaluated the findings' robustness.

Results: At a population level, higher household income predicted higher SPMH, but not vice versa. Correlations between income and SPMH varied among age- and gender- groups and they were stronger among men and older adults. At the individual level, higher income did not predict higher SPMH. No significant gender- or age- group differences were observed. Complete case analyses supported the findings.

Conclusions: This study suggests that higher household income predicts higher SPMH at a population level. Policy and programs aiming at promoting mental health should focus on low-income individuals, especially men and older adults.

5.2 Introduction

Self-perceived health, or self-rated health, is a valid measure of health that can be used to predict quality of life, morbidity, and mortality (Idler & Benyamini, 1997; Kaplan et al., 1996; Ocampo, 2010). However, less is known about self-perceived mental health (SPMH). SPMH assesses an individual's perception of his or her mental health status and provides an estimate of the population suffering from mental disorders, distress, and emotional problems (Statistics Canada, 2014). SPMH has been used as a stand-alone item since the 1970s and has been increasingly used in research and population health surveys. SPMH is associated with multi-item health indicators of mental health, physical health, and health utilization (Ahmad et al., 2014; Statistics Canada, 2014).

Income is a core indicator of socioeconomic position (SEP) and a key determinant of both mental and physical health (Duncan, Daly, McDonough, & Williams, 2002). Disparities in income contribute to the health inequalities as people with higher income are more likely to have access to better living conditions, have their basic needs met, and have less chronic stress (Blakely, Kennedy, Glass, & Kawachi, 2000; Government Canada, 2006). Two major hypotheses (health selection and social causation) have been proposed to infer causal directions of the SEP – health relationship (Goldman, 1994). Social causation posits that health, including mental health, is affected by adversity and stress related to low income. In contrast, health selection theory asserts that individuals who may have a genetic predisposition to mental illness end up in poverty as a result of their limited skills, ability, and effort (Hudson, 2005). Having a mental illness increases the likelihood of experiencing socioeconomic difficulties and disadvantages. With respect to mental illnesses, the health selection hypothesis has been supported mostly for severe mental illness while social causation has been supported for less severe mental illnesses. But these two theories are not mutually exclusive as both mechanisms may lead to social and health stratification. A combination of social causation and health selection processes has been proposed for explaining the relationship between income conditions and well-being (Evans, 2016). A recent systematic review on the relative importance of these two hypotheses does not find evidence to support a preference between these two hypotheses (Kroger, Pakpahan, & Hoffmann, 2015).

5.2.1 Bi-directional relationship between income and self-perceived mental health

A large body of research has shown that high income promotes population's mental health (Shervin Assari, Lisa M. Lapeyrouse, & Harold W. Neighbors, 2018; Kondo, Kawachi, Subramanian, Takeda, & Yamagata, 2008; Lindahl, 2005; Senn, Walsh, & Carey, 2014). From a sociological perspective income and social capital inequalities features of social hierarchies are linked with a wide range of adverse psychosocial and health consequences (Khawaja & Mowafi, 2006). It is reported by the Pan-Canadian Health Inequalities Reporting Initiative that adults in the lowest income group have approximately four times higher risk of low SPMH than those in the highest income group in Canada (Initiative, 2019). Studies also found that people with poor mental health were more likely to experience economic disadvantages–a health selection perspective (Kessler et al., 2008). The White Hall II study of civil servants (n=10 830) supported the health selection hypothesis by finding a significant effect of mental health on changes in social position among male servants (Chandola, Bartley, Sacker, Jenkinson, & Marmot, 2003). Consistently, a nationally representative longitudinal Australia survey concurs with health selection explanations. The study found that poor mental health independently predicted the utilization of income support programs (Kiely & Butterworth, 2014). Although empirical evidence supports the link between income and health, there is a paucity in the research to explore this relationship from a self-perception on mental health status. Most research does not differentiate self-perceived physical health from SPMH (Gunasekara, Carter, & Blakely, 2011; Piumatti, 2017; Wada, Higuchi, & Smith, 2015).

5.2.2 Bi-directional relationships at both individual (within-person) and population (between-person) levels

The bi-directional relationship between income and SPMH can express both at within-person and between-person levels. These two hypotheses (health selection and social causation) could be further explicated by asking the following questions: 1) When individuals have a higher income (relative to others) will they experience a subsequent increase in SPMH compared to individuals with lower income (between-person difference)? 2) When an individual makes a higher income than he/she did in the past, will he/she experience a subsequent increase in SPMH (within-person difference)?

Most empirical evidence documenting the link between income and self-rated health and self-rated mental health is from cross-sectional studies and between-person analyses therefore cannot answer these above-stated questions (Assari & Lankarani, 2017; Shervin Assari, Lisa M Lapeyrouse, & Harold W Neighbors, 2018; Hutton, Nyholm, Nygren, & Svedberg, 2014; Poulton et al., 2002). In addition, some studies have only looked at the longitudinal associations between income and SPMH at a population level and some of them have examined only uni-directional effect from income to SPMH or from SPMH to income, with fewer estimating bi-directional effects in which income and SPMH are hypothesized to affect each other simultaneously (Jones & Wildman, 2008; Lorgelly & Lindley, 2008; Pega et al., 2013). Longitudinal studies at both within-person and between-person levels are able to better inform health policy by understanding whether income or SPMH has a dominant role in the relationship between income and SPMH.

5.2.3 Age and gender as potential moderators

Studies have suggested the impact of social class inequalities on self-rated health is differentially distributed in men and women (Hanibuchi, Nakaya, & Honjo, 2016). Men and women may experience different social inequalities since men may benefit from social capital in different ways than women (Martikainen et al., 2004; Nishi, Makino, Fukuda, & Tatara, 2004). However, this effect has not been consistently found in the literature, some researchers have failed to find this differential impact of social class inequalities among men and women (Matthews, Manor, & Power, 1999). In a large Japanese study, Honjo et al. (2006) only identified the effect of social inequalities on self-rated mental health only among women. Gender may act as a moderator in the relationship between social inequalities and self-rated mental health.

Likewise, there is some evidence that age has a moderating role in the income-health relationship. A life-course perspective points out how socioeconomic factors influence health across the life span and the dynamic relationship between socioeconomic status at different ages and its disproportional impact on health (Graham, 2002). A general population survey in the United State found that age acted as a moderator in the relationship between income and mental illnesses with the strongest association being observed among young- and middle-aged group (20-54 years) rather than the older-aged group (55 years or older) (Sareen, Afifi, McMillan, &

Asmundson, 2011). This could be explained by the fact that older adults have a stable economic background and sense of self and don't rely on the income as much as younger people do in order to define themselves (Sareen et al., 2011). A systematic review of 55 studies indicated that the association between low socioeconomic status and mental health problems was particularly pronounced in early life (4-18 years old) (Reiss, 2013). Taken together, the roles of age and gender in the relationship between social inequalities and SPMH are inconclusive and warrant further research. Finally, we were not aware of any study examining associations among different gender or age subgroups both at the population and individual levels.

5.2.4 The present study

To understand the longitudinal and bi-directional relationship between income and SPMH, we aimed to test the temporal order of the relationship between income and SPMH and to explore the roles of age and gender in this relationship at both within-person and between-person levels. An in-depth understanding of the directionality of associations between income and SPMH at both the population and the individual levels will be informative for public health and health policymaking to promote positive mental health.

5.3 Methods

5.3.1 Data source

The Longitudinal Montreal South-West Catchment Area Study-Zone d' Épidémiologie Psychiatrique du Sud-Ouest de Montréal (ZEPSOM), is a longitudinal community-based cohort study of a representative sample of five neighborhoods in the South-West sector of Montreal, Canada. It had a target population of 269 720 in 2007. Data were collected at a two-year interval starting from the baseline year of 2007. Trained interviewers conducted face-to-face interviews either at participants' homes or in a research facility. Each interview took around 1.5 to 3 hours. The interview, conducted in either French or English, included comprehensive information on a wide range of psychological and sociological factors related to psychological distress, mental health, and mental illnesses. All participants provided written informed consent to take part in the longitudinal study. The ZEPSOM was approved by the Douglas Mental Health University Ethics Committee. Figure 5-1 presents a summary of the sample size across the four data

collections. More detailed information on this study is available in related publications (Caron et al., 2012; Meng, Liu, D'Arcy, & Caron, 2020).

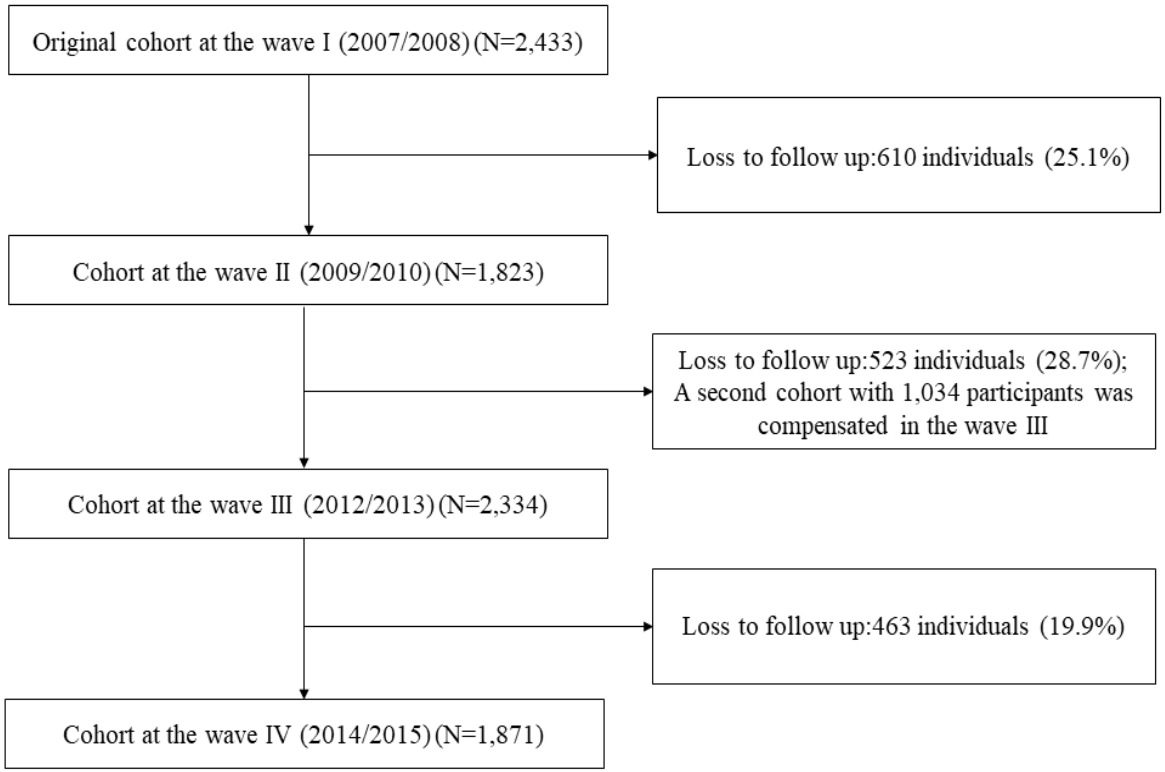

Figure 5-1 The summary of the Montreal South-West Longitudinal Catchment Area study sample.

5.3.2 Study sample

To explore the temporal order of the relationship between income and SPMH the final study sample included in the RL-CLPM and CLPM is 3464 participants who had complete the four data collections of the ZEPSOM.

5.3.3 Measures

Self-perceived mental health (SPMH) was assessed by asking the respondents “In general, would you say your mental health is…”. This is a five-point scale ranging from excellent to poor categories: (1) excellent (2) very good (3) good (4) fair and (5) poor (Ahmad et al., 2014).

Total household income was based on questions about income before taxes and deductions, of all household members from all sources in the past 12 months prior to each data collection. To increase the comparability of income among different waves and constraint the variance within the compatibility of the Mplus software, we divided income into five with four quintile cut-off points equally represented 20% of the sample from lowest income to highest income. SPMH and income were measured by established approaches, which were also used in the Canadian Community Health Survey (CCHS 1.2) (CCHS 1.2) (Tremblay, Ross, & Berthelot, 2002).

Socio-demographic characteristics

The study subjects were categorized into 4 age groups: youth (15 to 17 years), young adulthood (18 to 35 years), middle adulthood (36 to 55 years), and older adulthood (56 years and older). Gender was binary (men vs. women). Marital statuses were single, married/common-law, and separated/divorced/widowed. Level of education was categorized as less than junior education, high school graduation, and post-high school. Two binary variables (yes vs. no) covered whether the household dwelling was owned and whether the respondent had access to a vehicle.

5.3.4 Statistical analysis

Descriptive analyses were done to describe the characteristics of the study sample at each data collection. Then, we calculated zero-order correlations to assess the relationships between income and SPMH over time. Two types of autoregressive models (cross-lagged panel model (CLPM) and random intercept cross-lagged panel model (RI-CLPM)) (Hamaker, Kuiper, &

Grasman, 2015)) were used to assess the dynamic relationship between income and SPMH both at a population level and an individual level. CLPM is a structural equation model used to gather information at two or more time points and is primarily used to assess causal relationships both directionally and bi-directionally in non-experimental settings. It has been widely used to examine longitudinal and bidirectional associations between constructs in sociological and psychological research (Tak, Brunwasser, Lichtwarck-Aschoff, & Engels, 2017; Wang, Lynne, Witherspoon, & Black, 2020). The CLPM involves an autoregressive component that captures stability of the constructs over time, and a cross-lagged component that estimates the causal link between constructs at a time point and the other construct at a subsequent time point (Hamaker et al., 2015). CLPM has advantages over traditional approaches in simultaneously modeling and estimating bidirectional and temporal processes between the two constructs. Recently, RI-CLPM has been proposed as an alternative specification of the traditional CLPM to allow the pure within-person autoregressive and cross-lagged effects (Hamaker et al., 2015; Mund & Nestler, 2019). Even though RI-CLPM takes stable between-person differences into consideration to estimate the within-person effects, there is insufficient evidence to demonstrate which model outperforms the other, as RI-CLPMs may not have adequate statistical power to detect statistically significant effects when more parameters are being estimated (De Jong, 2019). As suggested, CLPM should be used for examining prospective between-person effects and RI-CLPM be used for examining prospective within-person effects, and in the situations that both between- and within-person effects are of interest, both CLPM and RI-CLPM should be used to examine and compare the direction of the between- and within-person effects, in order to gain a full understanding of the nature of the casual effects being studied (Orth, Clark, Donnellan, & Robins, 2020).

We started with a fully restricted model that imposed cross-time equality constraints on all of the autoregressive parameters, cross-lagged parameters, and time-specific covariance, and then fit the models with freely estimated paths. The basic theoretical models of CLPM and RI-CLPM are presented in Figure 5-2 and Figure 5-3, respectively. As suggested, the robust maximum likelihood estimator with (Huber-White) robust standard errors (MLR) was applied to estimate all models with available information for each individual under the assumption of missing-at-random by accounting for non-normality data (Satorra & Bentler, 1994; White, 1980). Since we used maximum likelihood estimation which does not impute values for those that were

missing but used all data that was available to estimate the model, thus, the final sample size is 3464 for conducting the analysis of CLPM and RI-CLPM models. The goodness of fit for both CLPM and RI-CLPM were comprehensively evaluated by using Chi-square test (χ^2), comparative fit index (CFI), Tucker-Lewis Index (TLI), and Root Mean Square Error of Approximation (RMSEA). CFI $\geq$ 0.95, TLI $\geq$ 0.95, and RMSEA $\leq$ 0.06 indicate the model having a good fit, and CFI and TLI $\geq$ 0.90, and RMSEA $\leq$ 0.08 as acceptable fit (Browne & Cudeck, 1992; Hu & Bentler, 1999).

To explore potential moderation effects of gender and age in the relationship between income and SPMH both at between-person and at within-person levels, multiple-group CLPMs and RI-CLPMs were conducted by comparing the cross-lagged paths and autoregressive paths by gender and age. First, we conducted the CLPM and RI-CLPM multiple-group analyses with autoregressive paths and cross-lagged paths freely estimated for each age and gender group, then cross-lagged paths were constrained to be equal for each gender group and age group. Wald Chi-square (χ^2) tests were then performed to test the difference between the unconstrained model and the constrained model. Significant chi-square differences suggest an interaction between income and gender/age, respectively. Additionally, complete case analysis (excluding those with incomplete data) was conducted as a sensitivity analysis to assess the robustness of the findings of our study. The significance level was defined as $p < 0.05$. All analyses were implemented in Mplus 8.0 (Muthen & Muthen, 1998).

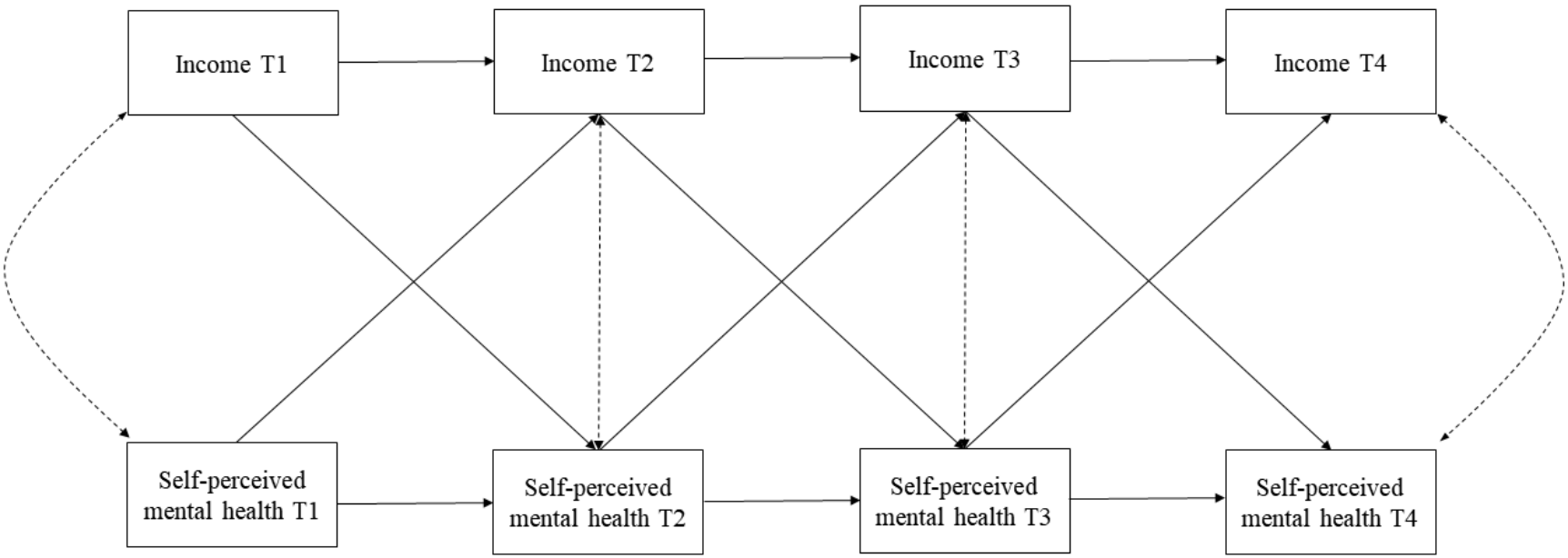

Figure 5-2 Conceptual cross-lagged panel models of the associations between income and self-perceived mental health.

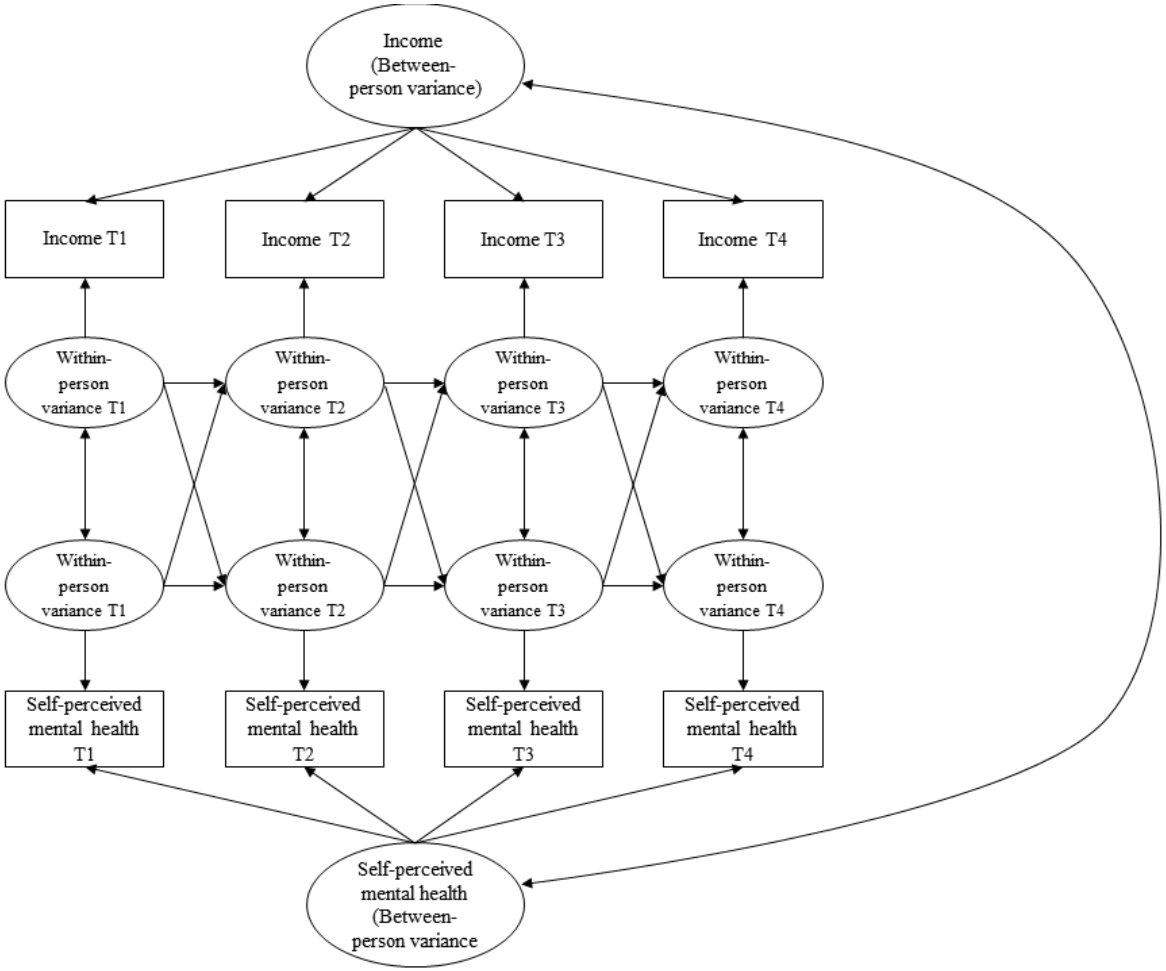

Figure 5-3 Conceptual random intercepts cross-lagged panel model of relationship between income and self-perceived mental health.

5.4 Results

5.4.1 A summary of the study sample

Table 5-1 presents the characteristics of the study sample across the four data collections. The longitudinal sample had a higher proportion of women and participants aged 35 to 55 years old. Most of participants were married/common-law and had post-high school education. Income for the cohort increased over time. Most participants reported good to very good SPMH at each data collection. Table 5-2 provides correlations among the studied variables across the four data collections. There were significantly statistical correlations between adjacent time points for income and for SPMH (Income: $r_{T1\text{-}T2} = 0.685$, $r_{T2\text{-}T3} = 0.094$, $r_{T3\text{-}T4} = 0.752$; SPMH: $r_{T1\text{-}T2} = 0.173$, $r_{T2\text{-}T3} = 0.090$, $r_{T3\text{-}T4} = 0.057$). In addition, income and SPMH were significantly correlated within T1 and T2 ($r_{T1} = -0.111$; $r_{T2} = -0.074$).

Table 5-1 Socio-demographic characteristics of the study sample.

Variables (n, %)	Wave 1 (N = 2,433)	Wave 2 (N= 1,823)	Wave 3 (N = 2,334)	Wave 4 (N = 1,871)
Gender				
Women	1,503(61.8%)	1,147(62.9%)	1,393(59.7%)	1,126(60.2%)
Men	930(38.2%)	676(37.1%)	941(40.3%)	745(39.8%)
Age (%)				
15-17 years	97(4.0%)	40(2.2%)	69(3.0%)	23(1.2%)
18-35 years	768(31.6%)	472(25.9%)	676(29.0%)	427(22.8%)
36-55 years	1,127(46.3%)	873(47.9%)	1,010(43.2%)	840(44.9%)
56 years and above	441(18.1%)	438(24.0%)	579(24.8%)	581(31.1%)
Marital status				
Single	886(36.4%)	620(34.0%)	850(36.4%)	613(32.8%)
Married/Common-law	1,110(45.6%)	860(47.2%)	1,082(46.4%)	909(48.6%)
Separated/Divorced/Widowed	437(18.0%)	343(18.8%)	402(17.2%)	349(18.7%)
Highest level of education				
Less than junior education	128(5.3%)	86(4.7%)	111(4.8%)	59(3.2%)
High school graduation	285(11.7%)	145(8.0%)	196(8.4%)	152(8.1%)
Post-high school	2,020(83.0%)	1,592(87.3%)	2,027(86.8%)	1,660(88.7%)
Income (mean, SD)	$58,601, $46,243	$64,991, $49,656	$67,912, $48,709	$75,186, $59,080
Income				
Lowest quintile	497(20.4%)	367(20.1%)	467(20.0%)	384(20.5%)
Second quintile	482(19.8%)	400(21.9%)	498(21.3%)	397(21.2%)
Middle quintile	541(22.2%)	335(18.4%)	461(19.7%)	381(20.4%)
Fourth quintile	450(18.5%)	373(20.5%)	529(22.7%)	353(18.9%)
Top quintile	463(19.0%)	348(19.1%)	379(16.3%)	356(19.0%)
Self-perceived mental health				
Excellent	555(22.8%)	291(16.0%)	379(16.2%)	319(17.1%)
Very good	864(35.5%)	661(36.3%)	602(34.4%)	649(34.6%)
Good	739(30.4%)	611(33.5%)	744(31.9%)	614(32.8%)
Fair	235(9.7%)	205(11.2%)	333(14.3%)	231(12.4%)
Poor	40(1.6%)	53(2.9%)	74(3.2%)	58(3.1%)
Household dwelling owned				
Yes	930(38.2%)	798(43.8%)	1,028(44.0%)	890(47.6%)
No	1,503(61.8%)	1,025(56.2%)	1,306(56.0%)	981(52.4%)
Access to a car				
Yes	1,662(68.3%)	1,352(74.2%)	1,696(72.6%)	1,407(75.2%)
No	771(31.7%)	471(25.8%)	638(27.4%)	464(24.8%)

Table 5-2 Correlations between incomes and self-perceived mental health.

Variables	1	2	3	4	5	6	7	8
1. Income T1	–	–	–	–	–	–	–	–
2. Income T2	0.685*	–	–	–	–	–	–	–
3. Income T3	-0.452*	0.094*	–	–	–	–	–	–
4. Income T4	-0.280*	0.127*	0.752*	–	–	–	–	–
5. Self-perceived mental health T1	-0.111*	0.016	0.042*	0.048*	–	–	–	–
6. Self-perceived mental health T2	-0.012	-0.074*	0.019	0.041	0.173*	–	–	–
7. Self-perceived mental health T3	0.033	0.034	-0.038	-0.003	0.176*	0.090*	–	–
8. Self-perceived mental health T4	0.017	0.017	0.001	-0.041	0.169*	0.153*	0.057*	–

* $p < 0.05$ (2-tailed).

5.4.2 Income and self-perceived mental health: Population-level (between-person) associations

The fully constrained CLPM for the overall sample was retained as the most parsimonious model with good model fit ($\chi^2(23) = 29.86$, $p = 0.15$, CFI = 0.94, TLI = 0.93, RMSEA = 0.01). The autoregressive paths reveal that a higher income at T1 was associated with a higher income at T2 ($\beta = 0.54$, $p < 0.001$). The similar results were repeatedly found from T2 to T3 and from T3 to T4 for income ($\beta_{T2\text{-}T3} = 0.52$, $p < 0.001$; $\beta_{T3\text{-}T4} = 0.54$; $p < 0.001$). These associations reflect a high level of income stability. Whereas the stability for SPMH was much weaker. Only one path from T3 to T4 was significant ($\beta = 0.09$; $p = 0.02$). As shown in Table 5-3 and Figure 5-4, the cross-lagged effects of income on SPMH were significant between all adjacent time points (T1 and T2, T2 and T3, T3 and T4), which suggest a higher income predicts better SPMH. In contrast, the cross-lagged paths of SPMH on income were not significant indicating higher SPMH was not associated with higher income. Additionally, a significant between-person association between higher income and better SPMH observed in the RI-CLPM analysis ($\beta = -0.24$; $p < 0.001$) also supports the findings of CLPM.

Table 5-3 Standardized coefficients of income and self-perceived mental health for the overall sample, men and women based on cross-lagged panel model.

Parameter	All			Men			Women		
	β	SE	p	β	SE	p	β	SE	p
Correlation									
T1	-0.105	0.017	**0.000**	-0.093	0.016	**0.000**	-0.092	0.016	**0.000**
Correlated change									
Residual correlation T2	-0.038	0.012	**0.002**	-0.030	0.014	**0.042**	-0.036	0.016	**0.025**
Residual correlation T3	-0.041	0.014	**0.004**	-0.032	0.015	**0.000**	-0.038	0.018	**0.038**
Residual correlation T4	-0.038	0.014	**0.005**	-0.111	0.019	**0.000**	-0.029	0.011	**0.007**
Stability paths									
Income 1→Income 2	0.539	0.016	**0.000**	0.498	0.020	**0.000**	0.491	0.018	**0.000**
Income 2→Income 3	0.522	0.016	**0.000**	0.459	0.019	**0.000**	0.467	0.017	**0.000**
Income 3→Income 4	0.538	0.015	**0.000**	0.460	0.016	**0.000**	0.462	0.016	**0.000**
SPMH 1→SPMH 2	0.030	0.024	0.216	0.012	0.014	0.389	0.015	0.018	0.400
SPMH 2→SPMH 3	0.109	0.082	0.185	0.053	0.082	0.515	0.050	0.059	0.397
SPMH 3→SPMH 4	0.089	0.039	**0.023**	0.142	0.086	0.097	0.030	0.035	0.385
Cross-lagged effects									
Income 1→SPMH 2	-0.030	0.024	**0.017**	-0.027	0.014	**0.050**	-0.036	0.017	**0.034**
Income 2→SPMH 3	-0.033	0.012	**0.005**	-0.030	0.014	**0.027**	-0.037	0.018	**0.038**
Income 3→SPMH 4	-0.030	0.014	**0.034**	-0.096	0.022	**0.000**	-0.025	0.010	**0.013**
SPMH 1→Income 2	-0.011	0.008	0.194	-0.010	0.008	0.190	-0.009	0.007	0.188
SPMH 2→Income 3	-0.035	0.022	0.113	-0.036	0.016	**0.020**	-0.028	0.025	0.262
SPMH 3→Income 4	-0.032	0.026	0.217	-0.096	0.022	**0.000**	-0.023	0.024	0.303

SPMH: self-perceived mental health.

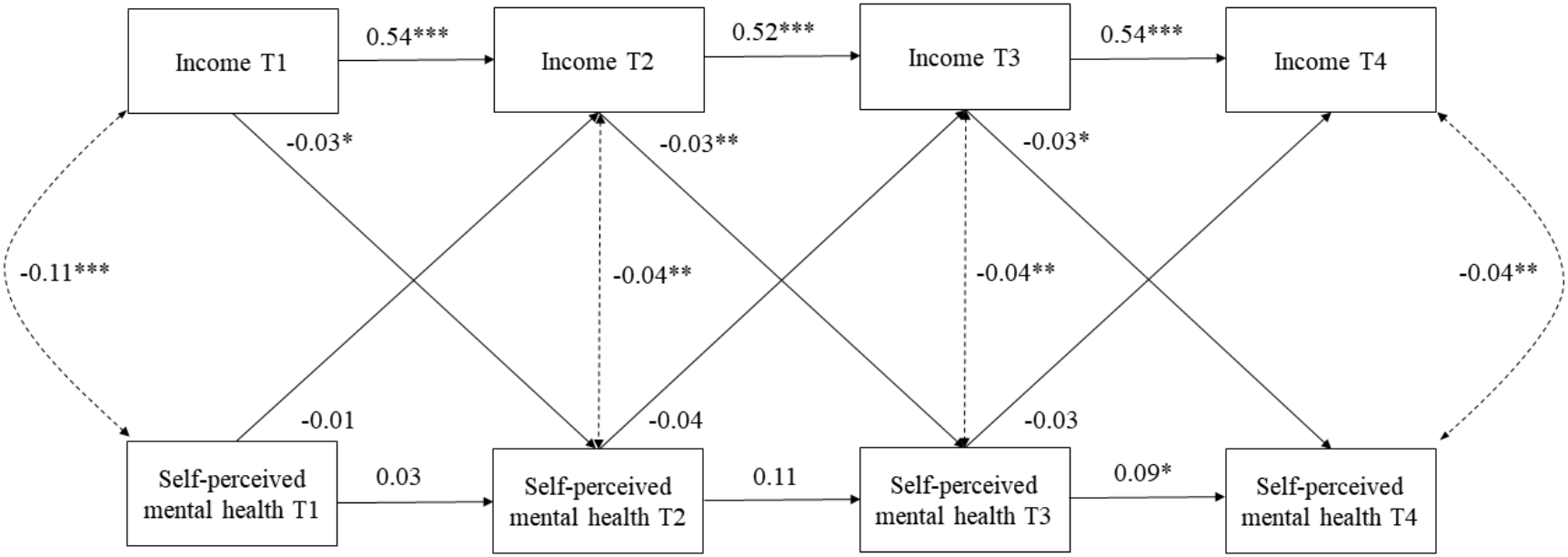

Figure 5-4 Cross-lagged panel analyses on income and self-perceived mental health for the total sample.

*p < 0.05, **p < 0.01, ***p < 0.001.

5.4.3 Income and self-perceived mental health: Individual-level (within-person) associations

Likewise, the constraint final model for the overall sample revealed excellent model fit, $\chi^2(20) = 3.97$, p = 1.00, CFI = 1.00, TLI = 1.00, RMSEA = 0.01. Freeing the across-time equality constraints did not significantly improve model fit (ΔS-B$\chi^2(16) = 2.50$, p = 1.00, CFI = 1.00, TLI = 1.00, RMSEA = 0.01). For the principle of parsimony, all longitudinal structural parameters were constrained in the final RI-CLPM. The only statistically significant autoregressive paths were observed for income but not for SPMH over time (Table 5-4 and Figure 5-5). The significant autoregressive association indicates that individuals with higher income were likely to have higher income at later adjacent time point. RI-CLPM tested the within-person dynamics between income and SPMH. However, no within-person cross-lagged effects were found, neither from income on SPMH (all p>0.05) nor from SPMH on income (p>0.05).

Table 5-4 Standardized coefficients of income and self-perceived mental health for the overall sample, men, and women based on random-intercept cross-lagged panel model.

Parameter	All			Men			Women		
	β	SE	p	β	SE	p	β	SE	p
Correlation									
Between-person	-0.243	0.048	**0.000**	-0.306	0.048	**0.000**	-0.240	0.059	**0.000**
T1	0.024	0.036	0.506	0.014	0.033	0.675	0.012	0.029	0.674
Stability paths									
Income 1→Income 2	0.084	0.029	**0.004**	0.082	0.029	**0.005**	0.082	0.030	**0.006**
Income 2→Income 3	0.089	0.030	**0.003**	0.084	0.030	**0.005**	0.087	0.030	**0.004**
Income 3→Income 4	0.090	0.031	**0.004**	0.087	0.030	**0.005**	0.088	0.032	**0.006**
SPMH 1→SPMH 2	0.003	0.005	0.592	-0.002	0.002	0.289	-0.003	0.003	0.257
SPMH 2→SPMH 3	0.015	0.030	0.618	-0.014	0.008	0.155	-0.013	0.012	0.270
SPMH 3→SPMH 4	0.012	0.018	0.506	-0.050	0.056	0.373	-0.008	0.007	0.271
Cross-lagged effects									
Income 1→SPMH 2	0.016	0.011	0.143	0.015	0.010	0.142	0.021	0.013	0.122
Income 2→SPMH 3	0.019	0.016	0.244	0.018	0.013	0.155	0.023	0.017	0.185
Income 3→SPMH 4	0.017	0.012	0.176	0.078	0.042	0.061	0.015	0.009	0.102
SPMH 1→Income 2	0.001	0.007	0.836	0.002	0.007	0.773	0.002	0.007	0.776
SPMH 2→Income 3	0.007	0.034	0.842	0.010	0.039	0.790	0.008	0.028	0.775
SPMH 3→Income 4	0.006	0.029	0.831	0.009	0.032	0.774	0.008	0.024	0.749
Correlated change									
Residual correlation T2	0.005	0.007	0.508	0.002	0.006	0.672	0.003	0.007	0.683
Residual correlation T3	0.005	0.009	0.529	0.003	0.007	0.679	0.003	0.008	0.691
Residual correlation T4	0.005	0.007	0.507	0.012	0.029	0.676	0.002	0.005	0.676

SPMH: self-perceived mental health.

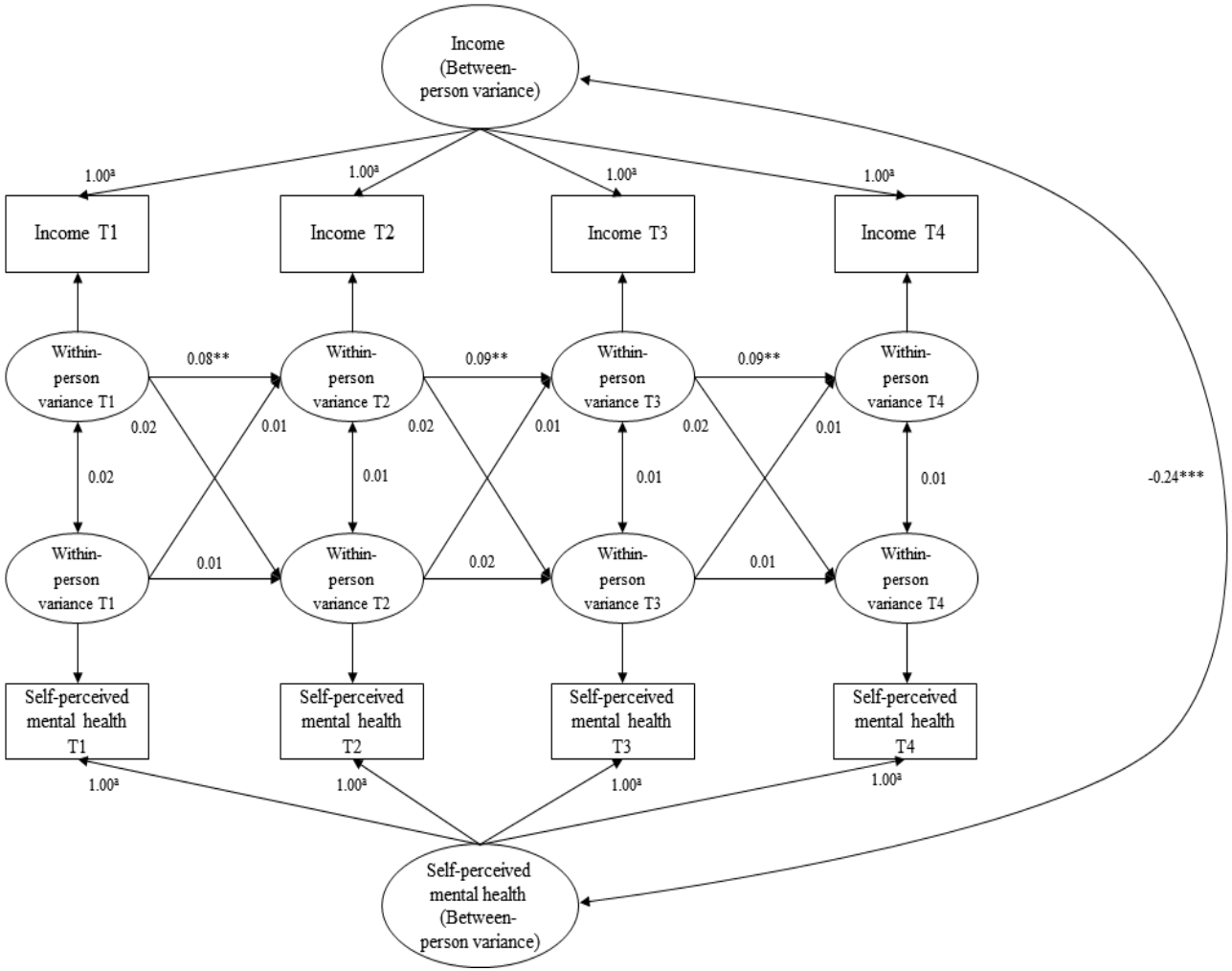

Figure 5-5 Random intercepts cross-lagged panel model of relationship between income and self-perceived mental health for the total sample.

*p < 0.05, **p < 0.01, ***p < 0.001. ª Pathways constrained to 1.00 to isolate between-person factor

5.4.4 Differences between men and women

We also examined the moderating role of gender using multiple group analyses in the CLPM and RI-CLPM, respectively. All models revealed satisfactory model fit (χ^2_{CLPM} (45) = 61.03, p = 0.06, CFI = 0.95, TLI = 0.94, RMSEA = 0.01; $\chi^2_{RI\text{-}CLPM}$ (45) = 27.30, p = 0.98, CFI = 1.00, TLI = 1.00, RMSEA = 0.01). At the individual level, autoregressive paths of income and cross-lagged effects of income on SPMH were all significant ($p < 0.01$). The autoregressive effects and the cross-lagged effects displayed similar patterns between men and women ($p < 0.01$). This similarity between men and women suggests that changes in income in the previous data collections predicted positive changes in subsequent income for both men and women. Furthermore, there was no significant within-person cross-lagged effect for both men and women. Wald Chi-square difference tests showed no differences between the models for men and women, $\Delta \chi^2(17) = 41.21$, p = 1.00. In addition, the moderating effect of gender on this relationship was assessed by multiple-group CLPM at the population level. As expected, significant gender differences were found for the cross-lagged paths ($\Delta \chi^2(10) = 58.71$, $p < 0.001$). The between-person correlation between income and SPMH was marginally stronger for men compared to women ($\beta_{men} = -0.31$, $p < 0.001$; $\beta_{women} = -0.24$, $p < 0.001$). This suggests that men had stronger correlations between income and SPMH than women at the population level.

5.4.5 Differences between age groups

Multigroup analyses were conducted to explore the differences in the relationships among different age groups at both within- and between- person levels. In the RI-CLPM, at the within-person level, the model fit had acceptable fit indices for each age group ($\chi^2(55) = 218.82$, p = 0.01, CFI = 0.94, TLI = 0.92, RMSEA = 0.05). Furthermore, the Wald Chi-square test did not yield a statistically significant difference among youth, young adults, middle-aged adults, and older adults ($\Delta \chi^2(10) = 26.77$, p = 1.00). However, CLPM analysis had different findings. The CLPM provided an acceptable model fit to the data, $\chi^2(55) = 164.68$, p=0.01, CFI = 0.96, TLI = 0.92, RMSEA = 0.05. The findings of CLPM suggest that, at the between-person level, the cross-lagged paths were significant in the unidirectional effect of income on SPMH for all age groups ($p < 0.01$). A statistically significant difference for the CLPM was observed ($\Delta \chi^2(22) = 42.25$, p = 0.01).

Specifically, the between-person association between income and SPMH was particularly pronounced among older and middle-aged adults in comparison with the younger generations (β_{youth} = -0.23, p = 0.06; $\beta_{young\ adults}$ = -0.27, p < 0.001; $\beta_{middle\text{-}aged\ adults}$= -0.28, p < 0.001; $\beta_{older\ adults}$ = -0.33, p <0.001). Parameters estimates for all models are presented in Tables 5-5 and 5-6.

Table 5-5 Standardized coefficients of income and self-perceived mental health by different age group based on cross-lagged panel model.

Parameter	Youth			Young adults			Middle-aged adults			Older adults		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Correlation												
T1	-0.122	0.021	**0.000**	-0.131	0.022	**0.000**	-0.112	0.019	**0.000**	-0.120	0.021	**0.000**
Correlated change												
Residual correlation T2	0.091	0.073	0.214	-0.062	0.050	0.219	-0.108	0.033	**0.001**	-0.073	0.052	0.166
Residual correlation T3	0.086	0.098	0.381	-0.016	0.065	0.806	0.033	0.039	0.388	0.006	0.060	0.920
Residual correlation T4	-0.076	0.119	0.523	-0.021	0.074	0.771	-0.109	0.041	**0.008**	-0.014	0.064	0.828
Stability paths												
Income 1→Income 2	0.434	0.026	**0.000**	0.468	0.022	**0.000**	0.480	0.018	**0.000**	0.498	0.023	**0.000**
Income 2→Income 3	0.458	0.034	**0.000**	0.424	0.024	**0.000**	0.438	0.019	**0.000**	0.411	0.022	**0.000**
Income 3→Income 4	0.464	0.093	**0.000**	0.395	0.057	**0.000**	0.387	0.037	**0.000**	0.218	0.059	**0.000**
SPMH 1→SPMH 2	0.448	0.031	**0.000**	0.459	0.027	**0.000**	0.103	0.007	**0.000**	0.497	0.030	**0.000**
SPMH 2→SPMH 3	0.281	0.105	**0.008**	0.308	0.064	**0.000**	0.049	0.047	0.300	0.398	0.051	**0.000**
SPMH 3→SPMH 4	0.321	0.091	**0.000**	0.395	0.057	**0.000**	0.048	0.017	**0.005**	0.384	0.057	**0.000**
Cross-lagged effects												
Income 1→SPMH 2	-0.036	0.017	**0.034**	-0.035	0.017	**0.034**	-0.008	0.004	**0.034**	-0.037	0.017	**0.034**
Income 2→SPMH 3	-0.042	0.020	**0.035**	-0.035	0.016	**0.035**	-0.009	0.004	**0.034**	-0.032	0.015	**0.035**
Income 3→SPMH 4	-0.042	0.020	**0.037**	-0.005	0.002	**0.035**	-0.018	0.009	**0.038**	-0.036	0.017	**0.035**
SPMH 1→Income 2	0.001	0.007	0.953	0.001	0.008	0.953	-0.001	0.008	0.953	-0.001	0.008	0.953
SPMH 2→Income 3	0.001	0.007	0.953	0.001	0.007	0.953	-0.002	0.034	0.953	0.001	0.007	0.953
SPMH 3→Income 4	-0.254	0.091	**0.005**	-0.029	0.057	0.608	-0.070	0.028	**0.013**	-0.053	0.051	0.294

SPMH: self-perceived mental health.

Table 5-6 Standardized coefficients of income and self-perceived mental health by different age group based on random-intercept cross-lagged panel constrained model.

Parameter	Youth			Young adults			Middle-aged adults			Older adults		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Correlation												
Between-person	-0.233	0.025	0.058	-0.272	0.069	**0.000**	-0.275	0.048	**0.000**	-0.333	0.066	**0.000**
T1	0.023	0.025	0.347	0.034	0.036	0.353	0.030	0.031	0.346	0.033	0.035	0.349
Stability paths												
Income 1→Income 2	0.079	0.03	**0.008**	0.074	0.028	**0.008**	0.079	0.029	**0.007**	0.079	0.028	**0.009**
Income 2→Income 3	0.088	0.032	**0.006**	0.076	0.028	**0.006**	0.087	0.031	**0.008**	0.076	0.028	**0.007**
Income 3→Income 4	0.076	0.030	**0.010**	0.091	0.035	**0.009**	0.086	0.033	**0.008**	0.105	0.038	**0.006**
SPMH 1→SPMH 2	0.021	0.011	**0.049**	0.021	0.010	**0.045**	0.003	0.002	0.107	0.022	0.011	**0.046**
SPMH 2→SPMH 3	0.022	0.011	**0.049**	0.021	0.010	**0.048**	0.025	0.026	0.322	0.021	0.011	**0.046**
SPMH 3→SPMH 4	0.023	0.012	0.051	0.002	0.002	0.155	0.102	0.017	**0.000**	0.021	0.011	**0.048**
Cross-lagged effects												
Income 1→SPMH 2	0.049	0.031	0.118	0.037	0.023	0.104	0.007	0.005	0.143	0.043	0.027	0.107
Income 2→SPMH 3	0.053	0.034	0.116	0.041	0.025	0.107	0.008	0.007	0.230	0.045	0.028	0.106
Income 3→SPMH 4	0.054	0.034	0.115	0.005	0.004	0.205	0.039	0.024	0.103	0.049	0.030	0.103
SPMH 1→Income 2	-0.001	0.006	0.872	-0.001	0.007	0.872	-0.001	0.007	0.872	-0.001	0.007	0.872
SPMH 2→Income 3	-0.001	0.006	0.872	-0.001	0.007	0.872	-0.007	0.045	0.869	-0.001	0.006	0.872
SPMH 3→Income 4	-0.001	0.006	0.872	-0.001	0.008	0.872	-0.006	0.042	0.879	-0.001	0.008	0.872
Correlated change												
Residual correlation T2	0.178	0.085	0.050	-0.029	0.072	0.687	-0.126	0.045	**0.005**	-0.020	0.058	0.733
Residual correlation T3	0.165	0.145	0.256	0.027	0.072	0.707	0.071	0.042	0.086	0.067	0.079	0.393
Residual correlation T4	-0.067	0.155	0.668	-0.043	0.016	**0.006**	-0.112	0.061	0.065	0.005	0.074	0.943

SPMH: self-perceived mental health.

5.4.6 Sensitivity analysis

Sensitivity analysis was done to evaluate the robustness of the study findings. We did a complete case analysis with all participants with complete data. Appendix A.1-A.2 in the Supplementary Material presents the results of the complete case analysis for both RI-CLPM and CLPM, respectively. Both of the models showed appropriate mode fit, $\chi^2_{\text{RI-CLPM}}$ (13) = 40.97, p = 0.01, CFI = 0.99, TLI = 0.97, RMSEA = 0.04; χ^2_{CLPM} (13) = 42.76, p = 0.01, CFI = 0.98, TLI = 0.90, RMSEA = 0.05. The findings of the complete case analyses were consistent with the analyses conducted with the total sample with missing data by using the MLR approach. Consistent with our primary analyses, the findings of complete case analysis of the RI-CLPM and CLPM showed that income predicted later SPMH at the population level but not at the individual level during the 8-year follow-up period.

5.5 Discussion

The present study identified the significant effect of income on SPMH overtime at a population level, but not at an individual level in a longitudinal population-based cohort. The effect of SPMH on income was not found neither at the population nor the individual levels. The dynamic effect of income on SPMH was stronger among men and older adults and only at the population level. The findings of the study provide robust evidence to support the social causation hypothesis, which highlights the social gradient of health. Public mental health policymaking and promotion strategies should pay close attention to those economically disadvantaged groups, especially men and older adults.

Both CLPMs and RI-CLPMs results support a causal link between income and SPMH at a population level. People with higher income were likely to have better SPMH. We did not find SPMH had an effect on income at the population level. This uni-directional finding from income to SPMH is consistent with Reche (2019), but not with a ten European countries study demonstrating bidirectional relationships between self-rated health and income (Hoffmann, Kröger, & Pakpahan, 2018). There are a number of reasons behind this inconsistent finding, including different measurements on income and SPMH, especially the European study assessed self-rated health in general not for mental health and the studies had different follow-up periods.

Although we did not find income predicting SPMH at the individual level (within-person) after adjusting for between-person stability in income and SPMH, RI-CLPMs results indicate the association between income and SPMH was largely explained by between-person difference. In other words, individuals with higher income, compared to those with lower income, tended to have higher levels of SPMH across the four measurements. And we didn't find evidence that when individuals had a change in income that they experienced a subsequent change in their SPMH or vice versa. Changes in an individual's income compared to his/her previous income was not as informative for SPMH as compared to change in income compared to their peers. It may be that in itself, a change in an individual's income does not have a strong effect, but that income is mostly predictable for SPMH in the population context. There is no study conducted to explore the effect of changes in income on SPMH at an individual level (Fleishman & Zuvekas, 2007). Previous literature on family income and mental diseases has suggested that changes in family income would influence the risk of mental diseases at an individual level (Dearing, Taylor, & McCartney, 2004; Kiely, Leach, Olesen, & Butterworth, 2015). The within-person effects of socioeconomic status on mental disorders were smaller than those with combined within- and between-person components (Lorant et al., 2007). Further research on income and SPMH is needed to validate our study findings at an individual level.

Previous research on gender differences in income inequalities on self-rated health where men were influenced more by income than women, we similarly found the effect of income on SPMH was stronger among men than women at the population level. In this vein, the magnitude of income inequalities in self-rated health differed between men and women, where self-rated health improved substantially with rising income for men (Lim, Ma, Heng, Bhalla, & Chew, 2007; Nishi et al., 2004; Orpana, Lemyre, & Kelly, 2007; Seubsman, Kelly, Yiengprugsawan, Sleigh, & Team, 2011). Theoretical hypotheses on such gender differences may be explained in part by different social roles that men and women played in life which makes men are more sensitive to socioeconomic changes than women (Jeon, Jang, Rhee, Kawachi, & Cho, 2007). Men have been traditionally socialized to act as a main or solo income maker in a family so a fluctuation in income may have a greater effect on the mental health of men compared to women.

Age was also a significant moderator in the relationship between income and SPMH. The effect of income on SPMH varied across different life stages with stronger correlations being found with the increasing age of the respondents. Consistently, previous studies have also demonstrated that the increasing effect of socioeconomic status on health with older age which could be explained by an increase in social inequality derived from the accumulation of assets across the life span (Hoffmann et al., 2018; Macran, Clarke, Sloggett, & Bethune, 1994). Arber et al. (Arber, Fenn, & Meadows, 2014) found a weaker relationship between income and self-reported health in later life (65 years and above) than in mid-life (45-64 years). In the process of determining whether the health advantage of individuals who experienced growth in income would be diminished at older ages, how age was grouped may account for a part of the differences as many countries are moving beyond the official retirement age of 65 years since more and more people strike balance between work life and retirement (Auer & Fortuny, 2000). Those people aged 65 and more, who still work and their main income resource is from a paid job, may be more susceptible to changes in their economic status when their health conditions deteriorate, which in turn, impact their ability to work and their income. Among youth, there was little or no impact of income inequalities on their SPMH in the present study. This is in line with previous studies which showed that no or weak socioeconomic status differences for self-rated health among adolescents/youth compared to adults (Glendinning, Love, Hendry, & Shucksmith, 1992; Siahpush & Singh, 2000). The limited association among youth could be explained by the socioeconomic equalization theory. It proposes that young people are characterized by relative health equality which is largely influenced by school and peer groups during the youth-adult transition (Hutton et al., 2014; West, 1997). Our results did not find any gender and age differences in the relationships between income and SPMH at the individual level. Future research examining gender and age differences in the relationship between income and SPMH will be beneficial for developing policy and programs aimed at improving general population health or narrowing health inequalities in society.

Strengths and limitations

The present study applied both CLPM and RI-CLPM models not only to explore the bi-directional relationship between household income and SPMH but also to detect differences at both between-person and within-person levels in a Canadian longitudinal cohort study. In line

with the social causation theory, the findings of the study support the influence of income on SPMH as being significant at a population level. This is particularly evident among men and older adults. The differentiation of within- and between-person processes provides the first look to a more detailed understanding of the causal relationships between income and SPMH.

There are several limitations to note. First, the loss to follow-up during the 8-year follow-up may affect the generalizability of the research findings. However, sensitivity analyses of non-imputed data (complete case analysis) confirmed the robustness and reliability of the current findings. Second, SPMH was evaluated by a one-item self-report measure, which cannot capture complex and comprehensive dimensions of mental health. However, the literature still recommends the use of this item to capture the subjective measure of mental health and notes the benefits of its simplicity and ease of administration (Ahmad et al., 2014).

Future research is needed to address the challenges of the dynamic and heterogeneous within-person associations

5.6 Conclusion

Overall, the present study supports a causal link between household income and SPMH only at a population level, not at an individual level. In other words, an individual's income can predict his/her SPMH when compared to other people in the community. This phenomenon is most evident among men and older adults. The findings of the present study provide robust evidence to support effective strategies targeted at people with low-income to promote positive mental health. Future research is warranted to corroborate or disprove the null results at the individual level.

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Appendix A.1. Standardized coefficients for cross-lagged panel model of complete case analyses on the relationship between income and self-perceived mental health (N = 1,093).

Parameter	β	SE	p
Correlation			
T1	-0.168	0.029	**0.000**
Correlated change			
Residual correlation T2	-0.018	0.030	0.546
Residual correlation T3	0.023	0.028	0.405
Residual correlation T4	-0.416	0.031	**0.000**
Stability paths			
Income 1→Income 2	0.547	0.022	**0.000**
Income 2→Income 3	0.331	0.021	**0.000**
Income 3→Income 4	0.320	0.021	**0.000**
SPMH 1→SPMH 2	0.528	0.021	**0.000**
SPMH 2→SPMH 3	0.171	0.011	**0.000**
SPMH 3→SPMH 4	0.525	0.029	0.000
Cross-lagged effects			
Income 1→SPMH 2	-0.068	0.024	**0.004**
Income 2→SPMH 3	-0.022	0.008	**0.004**
Income 3→SPMH 4	-0.021	0.007	**0.004**
SPMH 1→Income 2	-0.036	0.026	0.160
SPMH 2→Income 3	-0.066	0.026	**0.010**
SPMH 3→Income 4	-0.058	0.023	0.010

SPMH: self-perceived mental health.

Appendix A.2. Standardized coefficients for random-intercept cross-lagged panel model of complete case analyses on the relationship between income and self-perceived mental health (N = 1,093).

Parameter	B	SE	p
Correlation			
Between-person	-0.331	0.045	**0.000**
T1	0.026	0.052	0.621
Stability paths			
Income 1→Income 2	0.083	0.031	**0.007**
Income 2→Income 3	0.091	0.032	**0.005**
Income 3→Income 4	0.093	0.035	**0.007**
SPMH 1→SPMH 2	0.044	0.040	0.278
SPMH 2→SPMH 3	0.010	0.013	0.467
SPMH 3→SPMH 4	0.042	0.013	**0.006**
Cross-lagged effects			
Income 1→SPMH 2	0.028	0.049	0.570
Income 2→SPMH 3	0.019	0.016	0.241
Income 3→SPMH 4	-0.014	0.012	0.236
SPMH 1→Income 2	0.081	0.050	0.104
SPMH 2→Income 3	-0.021	0.043	0.624
SPMH 3→Income 4	-0.046	0.023	**0.046**
Correlated change			
Residual correlation T2	0.070	0.046	0.124
Residual correlation T3	0.048	0.031	0.124
Residual correlation T4	-0.028	0.013	**0.023**

SPMH: self-perceived mental health.

CHAPTER 6. INTERGENERATIONAL EFFECT OF MATERNAL CHILDHOOD MALTREATMENT ON NEXT GENERATION'S VULNERABILITY TO PSYCHOPATHOLOGY: A SYSTEMATIC REVIEW WITH META-ANALYSIS

A version of this chapter has been published as: “Su, Y., D’Arcy, C., & Meng, X. (2020). Intergenerational effect of maternal childhood maltreatment on next generation’s vulnerability to psychopathology: a systematic review with meta-analysis. Trauma, Violence, & Abuse”. My contributions to this study included study design, data collection, data synthesis, results interpretation, and manuscript writing as well as editing.

6.1 Abstract

Many studies have identified the multiple negative consequences of childhood maltreatment on subsequent mental health. However, research on the intergenerational effect of maternal childhood maltreatment has not been systematically synthesized. This meta-analysis aimed to provide a quantitative estimate of the intergenerational effect of maternal childhood maltreatment on their offspring's psychopathology. Electronic databases and gray literature were searched for English-language prospective cohort studies. Two reviewers independently extracted data and assessed study quality with the Newcastle-Ottawa Scale. This review only included those studies with (1) maternal childhood maltreatment occurring prior to 18 years of age, (2) using a clear and reliable assessment for maltreatment exposure and offspring's mental health problems prior to age 18. Random-effect models were used to calculate the pooled effect size of maternal childhood maltreatment on offspring's psychopathology, and meta-regression was used to explore potential confounders. Twelve studies met eligibility criteria. Significant heterogeneity was found across selected studies. Maternal childhood maltreatment was found to have a small but significant effect on the offspring's depression and internalizing behaviors (r = .14, 95% confidence interval [.09, .19]). Two moderators were found, maternal depression and ethnicity. Maternal depression reduced the effect size of maternal maltreatment on offspring's depression and internalizing disorders. The offspring of non-Caucasian mothers who had a history of childhood maltreatment faced a higher risk of mental health problems. There was no evidence of publication bias. This review provides robust evidence to reinforce the need for policies to reduce its occurrence, as it can influence not just one but two or possibly more generations.

6.2 Introduction

Childhood maltreatment significantly increases the risk of subsequent psychiatric disorders, including depression (Li, D'Arcy, & Meng, 2016; Widom, DuMont, & Czaja, 2007), anxiety (Nanda, Reichert, Jones, & Flannery-Schroeder, 2016), alcohol misuse (Elliott et al., 2014), and emotional and behavioral functioning difficulties (Choi et al., 2019). The World Mental Health Surveys compared data on childhood maltreatment and psychiatric problems in 21 countries and confirmed this association existed across all sociocultural samples (Kessler et al., 2010). The economic and societal implications of both maltreatment and severe psychiatric disorders are considerable (Gilbert et al., 2009; Vigo, Thornicroft, & Atun, 2016). In 2010, the updated WHO report showed that 12% of the global burden of diseases was attributable to mental disorders, and that estimate is expected to reach 15% by 2020 (World Health Organization, 2011). The cumulative economic loss associated with mental disorders is projected to US$ 16.3 trillion worldwide between 2011 and 2030, making the economic loss related to mental disorders higher than that of cancer, chronic respiratory diseases, and diabetes (Trautmann, Rehm, & Wittchen, 2016). The long-term socio-economic effects of childhood maltreatment in later-on life may be due to the occurrence of mental disorders (Barrett, Kamiya, & O'Sullivan, 2014). Those with childhood maltreatment reported lower family incomes and reduced labor force participation (Goodman, Joyce, & Smith, 2011; Stith et al., 2009).

Recent studies of childhood maltreatment have suggested that the deleterious sequela of childhood maltreatment may be transmitted from one generation to the next (Buss et al., 2017). A strong link has been documented between a maternal history of childhood maltreatment and mental health problems in offspring, including depression, anxiety, autism, suicide attempts, and poorer behavioral trajectories across the time (Brent et al., 2004; Brodsky et al., 2008; Collishaw et al., 2007; Plant, Barker, Waters, Pawlby, & Pariante, 2013; Roberts, Lyall, Rich-Edwards, Ascherio, & Weisskopf, 2013). The offspring of victimized mothers, even without suffering any childhood maltreatment themselves, may experience an increased risk of psychiatric disorders (Plant, Barker, Waters, Pawlby, & Pariante, 2013; Rijlaarsdam et al., 2014). Noteworthy, the association between a history of maternal maltreatment and offspring's mental disorders appears to be particularly pronounced when mothers suffered the abuse during their childhood compared to the later stage of their lives (Thompson, 2007).

Several theoretical frameworks have been proposed to explain the intergenerational transmission of maternal childhood maltreatment to their children's mental illness. One theory explores how the environmental effect of maternal childhood maltreatment could potentially influence the normal development of offspring. Caregiving patterns are the putative mediating mechanism that has been postulated to explain the link (Collishaw et al., 2007; Plant, Pariante, Sharp, & Pawlby, 2015). Mothers, who had a history of maltreatment, are less likely to provide adequate opportunities to observe healthy caregiving behaviors, leading to intrusiveness, hostility towards children, increased use of harsh and intensive discipline and rejection, decreased sensitivity to children's need, decreased mother-children involvement (Bert, Guner, Lanzi, & Centers for Prevention of Child Neglect, 2009; Bosquet Enlow, Englund, & Egeland, 2018; Lomanowska, Boivin, Hertzman, & Fleming, 2017). These negative environmental factors could influence normal fetal programming to produce a less emotionally labile offspring temperament, which may increase the offspring's vulnerability of being maltreated, thus increasing the risk for mental illness (Madigan et al., 2019; Pariante, 2014). From an environmental perspective, disadvantaged caregiving, inability to protect children and aggregated domestic risks may directly put children at higher risk of mental illness (Plant, Pariante, Sharp, & Pawlby, 2015). Epigenetic vulnerability is also theorized as an explanation of the intergenerational transmission of vulnerability to psychopathology. In animal studies, maternal care (grooming) was found to alter the expression of genes that govern behavior and stress responses (Meaney, 2001). Maternal care has also been shown to affect the subsequent maternal care exhibited by offspring (Meaney, 2001). More recently, in mice studies, Dias and Ressler (2014) demonstrated how a behaviorally induced trauma experience was inherited biologically through the offspring's parental gametes. They observed changes in RNA being passed down through sperm so that the offspring mice inherited what was initially a behavioral trauma fear through their fathers. Subsequent studies showed that with extinction based behavioral strategies this fear could be reversed both behaviorally and biologically in offspring and in the parental germline (Aoued et al., 2019). In human studies, an interdisciplinary framework proposed by Buss and colleagues suggested that the primary model of intergenerational transmission is biological (Buss et al., 2017). Genetic predispositions of the corticotropin-releasing hormone (CRH) receptor 1 Gene and FKBP Prolyl Isomerase 5 (FKBP5) DNA demethylation have been found to render children to be more vulnerable to negative consequences of maternal maltreatment when these genes were passed

onto offspring (Buss et al., 2017; Heim et al., 2009; Klengel et al., 2013). Therefore, adverse environmental factors might have more than one pathway linking maternal childhood maltreatment and offspring's mental health.

Given the importance of childhood maltreatment in the development of psychiatric disorders and the possible link between maternal childhood maltreatment and offspring's psychopathology, it is important to understand to what extent maternal childhood maltreatment may impact upon their children's psychopathology (Miranda, Osa, Granero, & Ezpeleta, 2013; Plant, Jones, Pariante, & Pawlby, 2017). Even though the knowledge about the role of intergenerational transmission effect of maternal childhood maltreatment on offspring's mental health is increasing (Collishaw et al., 2007), few intergenerational studies have been conducted to explore the consequences of maternal maltreatment on the offspring's physical and mental health outcomes. We were not aware of any systematic review being conducted to summarize the impact of maternal childhood maltreatment on offspring's psychopathology. There is one narrative review conducted by Plant et al. (2018) covering the literature to October 2015 that reported an association of maternal childhood maltreatment with the risk of next generation's psychological wellbeing, in addition to not being a systematic review, the review was not specific to studies on depression/internalizing disorder - common adolescent psychiatric disorders. The epidemiological evidence provided in the review did not provide a basis for a firm conclusion on the intergenerational effect of maternal childhood maltreatment.

This present systematic review and meta-analysis aimed to 1) quantitatively synthesize the intergenerational effect of maternal childhood maltreatment on offspring's psychopathology; and 2) to improve inferences about the temporal order (cause) and reduce selection bias. The current review only included prospective studies thus dealing with the issue of temporal order. A pooled effect size was calculated to indicate the magnitude and overall strength of the association. We also examined a range of covariates, factors potentially moderating the relationship between maternal childhood maltreatment and offspring's psychopathology.

6.3 Methods

This systematic review and meta-analysis are guided by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklists. MOOSE is an evidence-based tool consisting of a checklist of 35 items, which is designed to respond to the issue of increasing diversity and

variability of meta-analyses of observational studies by standardizing a reporting checklist thus improving the usefulness of research (Stroup et al., 2000) (see Appendix A). The MOOSE checklist is one of several guidelines that are part of a larger initiative to improve the reliability and value of published research by using standardized guidelines to promote accurate and transparent reporting of research (see https://www.equator-network.org).

6.3.1 Search strategy and inclusion criteria

Eligible studies were identified by computerized and manual searches. Five bibliographic databases were searched: MEDLINE, PubMed, Web of Science, EMBASE, and Cochrane Library. The literature search comprised articles published between January 1980 and January 2019. The detailed search strategies for each database are fully described in Appendix B. The 'published after 1980' criterion was used because the first research on the impact of childhood adversity on mental health was published during the 1980s. Figure 6-1 presents a flowchart of the literature search and screening based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher, Liberati, Tetzlaff, & Altman, 2009).

The inclusion criteria were if the study: 1) used a prospective cohort study design; 2) assessed maternal childhood maltreatment exposure prior to the age of 18 with clear information defining the abuse as physical, sexual or emotional abuse, physical or emotional neglect and exposure to domestic violence; 3) had a measure on either depression or internalizing behaviors (which comprise anxious/depressed, withdrawn-depressed, and somatic complaints) among offspring prior to the age of 18; 4) used generally accepted diagnostic criteria for the presence of depression and internalizing behaviors; and, 5) was published in English. Exclusion criteria were if the study:1) only included relatively common punishments (e.g., spanking, or yelling), which may or may not be considered as maltreatment exposures due to cultural variability; 2) did not provide sufficient information to extract necessary data to calculate the results on any type of childhood maltreatment and the mental health outcomes.

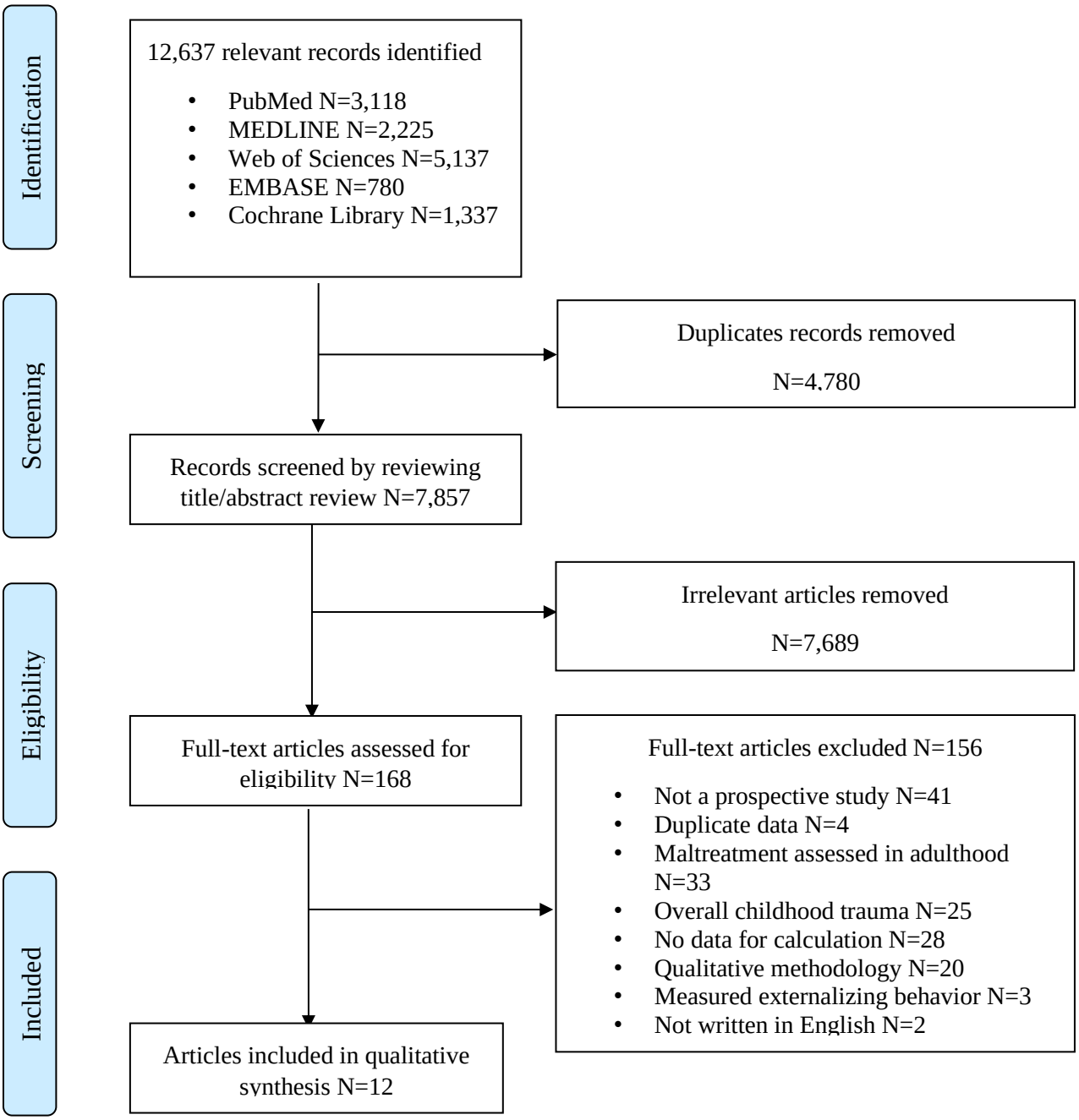

Figure 6-1 A summary of the literature search in this systematic review.

6.3.2 Data extraction and quality assessment

Two reviewers (YS and XM) independently assessed articles to analyze eligible titles, abstracts, and full-text articles, with differences resolved by group discussions. A standardized data extraction sheet was used to collect data from eligible studies. The following study characteristics were extracted from those selected studies: authors(s); year of publication; age of offspring; study site (coded as North America, Europe, and Asia); sample size; source of the study sample (clinical samples vs. community samples); sex of offspring (% of females); ethnicity (% Caucasian); type of abuse (physical abuse, sexual abuse, emotional abuse, and neglect); measures of maternal childhood maltreatment exposures; type of mental health outcomes (diagnoses); psychopathology measures (questionnaires or scales used for offspring's mental health outcomes). To enable a comparison of results from the diverse studies, zero-order correlation coefficients were extracted to indicate the correlation between maternal childhood maltreatment and the offspring's mental outcome. Articles that met the inclusion criteria were then assessed for their methodological quality and potential bias based on the Newcastle-Ottawa Scale (NOS) (Wells, 2001), a widely used scale consisting of eight questions, with a maximum of ten possible points for each type of study. The NOS scores were categorized into two groups based on the mean score of all included studies: above the mean score-high risk of bias, and below the mean score-low risk of bias (Lo, Mertz, & Loeb, 2014).

6.3.3 Meta-analysis

Calculation of effect sizes. To achieve comparable effect sizes for analyses, we used the zero-order correlation coefficient as the common effect size measure in the present study. Effect size coefficients were either directly obtained from studies or first computed and transformed from the reviewed articles (Lipsey & Wilson, 2001). Coefficients (rs) were then converted with Fisher's Z transformation to avoid the standard error skew in correlational analyses. Effect sizes were weighted by their inverse variance, subsequently, the Z-values were converted back to coefficients for the interpretation of results (Fischer, 1944; Hedges & Olkin, 2014; Lipsey & Wilson, 2001). A positive effect size indicates a positive association with r values of 0.10, 0.30 and 0.50 representing small, moderate, and large effects, respectively (Cohen, 1992). Individual studies could generate multiple effect sizes concerning the relationships between different subtypes of maternal maltreatment and outcomes; therefore, these within-study effects were

dependent on each other. Cheung and Chan have suggested a sample wise approach to handle dependent correlations, simply analyzing them by within-sample mean procedures (Cheung & Chan, 2008). This sample wise method can generate an average effect size based on each set of dependent effect sizes from the same sample (Hunter & Schmidt, 2004).

Statistical analyses and moderators. Random-effect models were performed to synthesize overall effect sizes given the amount of variances produced by differences between and within studies and taking the heterogeneity test results into account. Further, effect sizes could vary across studies as a function of potential moderators. The random variance component was determined by using maximum-likelihood estimation (Lipsey & Wilson, 2001). Cochrane's Q statistic was used to test the heterogeneity (Higgins & Thompson, 2002). Heterogeneity of results was assumed if Q was significant at $p<0.05$, allowing for testing of potential moderators. Categorical factors, including (age of offspring, study site, source of the study sample, type of maltreatment, measures of maltreatment exposure, and type of outcome), were tested by using procedures analogous to analysis of variance (ANOVA) with a between-group test of homogeneity ($Q_{between}$) (Lipsey & Wilson, 2001). Significant results indicated that effect sizes significantly differed across the categories of the moderator. The impact of continuous variables (publication year, sex, ethnicity, and maternal depression) on results was assessed by meta-regression. We considered the above four variables as continuous due to the availability of data and the feasibility of explanation. A significant slope indicated the moderation effect on the overall effect. Sensitivity analyses were also performed to test the effect of individual studies on overall effect sizes. Finally, publication bias was assessed by funnel plots and quantitatively evaluated by Egger's regression and Begg's correlation (Begg & Mazumdar, 1994; Sterne, Egger, & Smith, 2001). Trim and Fill test was performed to estimate the unbiased pooled effect size while taking publication bias into account (Duval & Tweedie, 2000).

All analyses were conducted using the Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood, NJ, USA) and IBM SPSS Statistical Version 21 (IBM Corp, NY, USA) and the macros statistical program written by Lipsey and Wilson to calculate effect sizes from different measures of statistical association (Lipsey & Wilson, 2001). A p-value less than 0.05 is considered statistically significant.

6.4 Results

A total of 12 articles covering 29,682 subjects were included in this meta-analytic review. Figure 6-1 presents the selection process of the literature search. Table 6-1 summarizes the study characteristics of these selected studies. All studies were published within the last 20 years. All studies but one were from developed countries with that exception being from China. Overall, the quality of these studies was moderate as assessed by the Newcastle-Ottawa scale with a mean score of 6.75 (range from 4 to 8) (see Appendix C in supplement). These studies targeted a wide age range of offspring varying from 1 year to 16 years but most of them focused on age from 8 to 14 years of old. The offspring cohort had about half females (50.1%) and Caucasian (48.8%).

6.4.1 Overall effects for maternal childhood maltreatment and offspring psychopathology

A composite effect size of maternal childhood maltreatment on offspring's psychopathology was calculated using 12 mean effect sizes weighted by the study's sample sizes. As shown in Figure 6-2, the pooled effect size from the selected studies was in the small but significant range ($r=0.14$, 95%CI 0.09-0.19, $p<0.001$). However, it should be noted that 4 of the 12 studies reported significant moderate effect sizes in the 0.30 range. The heterogeneity test was significant across the studies ($Q=117.45$, $p<0.001$). Therefore, a random-effect model was used in the meta-analysis. Sensitivity analyses were used to assess the influence of each study on the pooled effect size by omitting one study at a time. The overall correlation between maternal childhood maltreatment and the offspring's psychopathology was not influenced by the inclusion or exclusion of any specific study ($r=0.15$, 95%CI 0.04-0.26, $p=0.006$).

Both funnel plot (Appendix D) and Egger's test ($Tau=0.12$, $p=0.58$) and Begg's test ($t=0.76$, $p=0.47$) did not show publication bias. In addition, the Trim-and-fill test was conducted to estimate a pooled effect size after adjusting the potential missing publications that might exist in the meta-analysis. After considering the potential missing publications, a small, but significant effect size was found ($r=0.12$, 95% CI: 0.11-0.14).

Study name	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Plant et al, 2013	0.010	-0.166	0.185	0.110	0.912
Roberts et al, 2015	0.090	0.072	0.108	9.635	0.000
Min et al, 2013	0.120	-0.009	0.245	1.821	0.069
Plant et al, 2018	0.110	0.090	0.130	10.705	0.000
Linde-Krieger & Yates, 2018	-0.140	-0.266	-0.009	-2.100	0.036
Rijlaarsdam et al, 2014	0.150	0.121	0.179	10.065	0.000
Koverola et al, 2005	0.420	0.300	0.527	6.331	0.000
Letourneau et al, 2019	0.040	-0.025	0.105	1.203	0.229
Liu et al, 2019	0.053	-0.084	0.188	0.758	0.449
Choi et al, 2019	0.270	0.229	0.310	12.471	0.000
Dubowitz et al, 2001	0.260	0.168	0.347	5.428	0.000
Pereira et al, 2018	0.320	0.128	0.489	3.198	0.001
	0.142	0.093	0.190	5.657	0.000

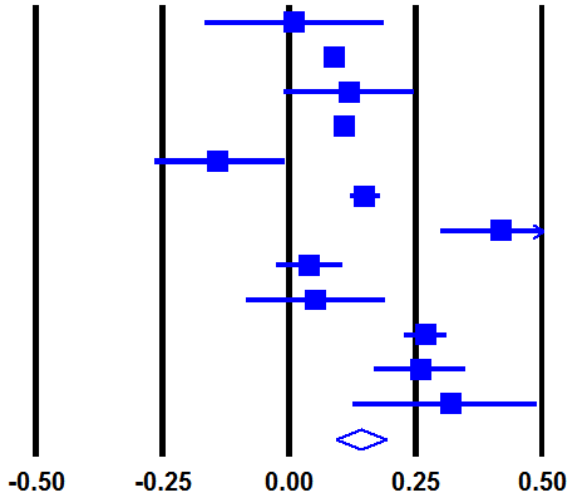

Figure 6-2 Pooled effect sizes for the association between maternal childhood maltreatment and the offspring's psychopathology.

Table 6-1 Study characteristics of the selected studies in this systematic review.

Authors	Year	Offspring Age	Study site	Sample size	Sample source	Sex No.(% of female)	Ethnicity No.(% of Caucasian)	Type of abuse	Maternal childhood maltreatment measurements	Offspring psychopathology measures	Type of outcome
Plant et al.	2013	11- and 16-year	United Kingdom	125 mother-child dyads	Clinical	68/125 (54.0)	90/125 (72.0)	PA/SA/EN/ PN	Maternal self-report questionnaire	DSM-IV symptoms of depression	Depression
Roberts et al.	2015	9- to 14-year	United States	mothers = 8,882; children = 11,402	Clinical	6,462/11,402 (56.7)	10,645/11,402 (93.4)	PA/EA/SA	Childhood Trauma Questionnaire (CTQ)	Center for Epidemiological Studies Depression Scale–10 (CESD-10)	Depressive Symptoms
Min et al.	2013	9 years	United States	231 mother-child dyads	Clinical	120/231 (51.9)	NA	PA/SA/EA/ EN/PN	Childhood Trauma Questionnaire (CTQ)	Child Behavior Checklist for ages 6-18 (CBCL)	Internalizing behaviors
Plant et al.	2018	11 years	United Kingdom	9,397 mother-child dyads	Community	4,558/9,397 (48.5)	9,087/9,397 (96.7)	PA/SA/EA/ EN/PN	Maternal self-report questionnaire	Strengths and difficulties questionnaire(SDQ); DSM-IV	Internalizing behaviors
Liu et al.	2019	14 months	China	207 mother-child dyads	Clinical	102/207 (49.3)	0/207 (0.0)	PA/EA/SA	Childhood Trauma Questionnaire Short Form (CTQ-SF)	Infant-Toddler Social and Emotional Assessment (ITSEA)	Internalizing behaviors
Linde-Krieger & Yates	2018	4 -and 8-year	United States	225 mother-child dyads	Community	108/225 (48.0)	45/225 (20.0)	SA	A verbal administration of the Early	Test Observation Form (TOF)	Internalizing behaviors

									Trauma Inventory		
Pereira et al.	2018	5 years	Canada	96 mother-child dyads	Community	45/96 (47.0)	79/96 (82.3)	PA/SA/EA/EN/PN	Childhood Trauma Questionnaire Short Form (CTQ-SF)	Child Behavior Checklist for ages 1.5–5 (CBCL)	Internalizing behaviors
Choi et al.	2019	12 years	United Kingdom	mothers=1,016; children=2,032	Community	1,036/2,032 (51.0)	NA	PA/SA/EA/EN/PN	Childhood Trauma Questionnaire (CTQ)	Child Behavior Checklist (CBCL)	Internalizing behaviors
Rijlaarsdam et al.	2014	6 years	Netherlands	4,438 mother-child dyads	Community	2,241/4,438 (50.5)	3,333/4,438 (75.1)	PA/SA/EA/EN/PN	Childhood Trauma Questionnaire (CTQ)	Child Behavior Checklist (CBCL)	Internalizing behaviors
Dubowitz et al.	2001	6- to 7-year	United States	419 mother-child dyads	Clinical	207/419 (49.4)	NA	PA/SA	Study-developed measure	Child Behavior Checklist (CBCL)	Internalizing behaviors
Koverola et al.	2005	8 years	United States	203 mother-child dyads	Clinical	98/203 (48.3)	NA	PA/SA	Study-developed measure	Child Behavior Checklist (CBCL)	Internalizing behaviors
Letourneau et al.	2019	2 years	Canada	907 mother-child dyads	Community	423/907 (46.6)	788/907 (86.9)	PA/SA/EN/PN	Adverse Childhood Experiences Questionnaire (ACE)	Child Behavior Checklist (CBCL)	Internalizing behaviors

Abbreviations: PA, physical abuse; SA, sexual abuse; EA, emotional abuse; EN, emotional neglect; PN, physical neglect; NA, not available.

6.4.2 Moderator analyses

Table 6-2 presents results on the moderation analyses. We found two variables had significant moderation effects: ethnicity (% Caucasian) and maternal depression. Meta-regression analyses showed that ethnicity significantly moderated the relationship between maternal childhood maltreatment and offspring's psychopathology ($p=0.001$). The correlation between maternal childhood maltreatment and offspring outcomes was much stronger among studies with higher proportions of non-Caucasians than those with more Caucasians. We also found a significant moderating effect for maternal depression ($p=0.001$). Maternal depression reduced the correlation between maternal childhood maltreatment and the offspring's disease outcome. No significant moderating effect was found for the rest of the categorical variables (child age, study site, source of study subjects, type of maltreatment, maltreatment assessment, and type of outcome) ($p>0.05$). Similarly, publication year and sex of offspring did not have a moderating effect in this association ($p>0.05$).

Table 6-2 Potential moderators of the meta-analytic association between maternal childhood maltreatment and offspring psychopathology.

				Effect size estimate		Test of homogeneity		
Moderator	k	Number of participants	Fisher's Z	r(95%CI)	p value	Cochran's Q	p value	Slope(p value)
All studies	12	29,682	5.71	0.14(0.09-0.19)	<0.001	117.45	<0.001	
Categorical moderator								
Age								
0-8 years	7	6,495	2.89	0.15(0.05-0.25)	0.004	0.09	0.76	
9-16 years	5	23,187	2.14	0.13(0.01-0.24)	0.032			
Study site								
North America	7	13,483	2.90	0.15(0.05-0.25)	0.004	0.42	0.81	
Europe	4	15,992	2.27	0.15(0.02-0.27)	0.023			
Asia	1	207	0.38	0.05(-0.22-0.33)	0.703			
Source of sample								
Clinical	5	12,462	3.13	0.18(0.07-0.30)	0.002	0.93	0.23	
Community	7	17,220	2.23	0.11(0.01-0.21)	0.026			
Type of maltreatment								
Abuse only	5	12,456	2.24	0.14(0.02-0.26)	0.025	0.01	0.93	
Abuse and neglect	7	17,226	2.81	0.14(0.04-0.24)	0.005			
Maltreatment assessment								
Self-report	8	15,792	3.46	0.16(0.07-0.26)	<0.001	0.75	0.39	
Interview	4	13,890	1.47	0.09(-0.03-0.22)	0.143			
Type of outcome								
Depression	2	11,527	0.63	0.06(-0.12-0.24)	0.529			
Internalizing behavior	10	18,155	3.78	0.16(0.08-2.34)	<0.001	0.92	0.34	
Continuous moderator								

Publication year	12	29,682	1.51	0.031(0.130)
Gender	12	29,682	0.74	0.004(0.460)
Ethnicity(Caucasian)	9	26,797	-3.33	-0.002(0.001)
Maternal depression	6	23,959	-3.22	-0.006(0.001)

6.5 Discussion

This systematic review and meta-analysis quantitatively summarized the relationship between maternal childhood maltreatment and the offspring's depression and internalizing behaviors. A maternal history of maltreatment in childhood was found to have a small but significant detrimental impact on the offspring's mental health with four of the twelve studies reporting negative impact in the moderate effect size range. Because this systematic review included studies with high heterogeneity, findings of this review should be carefully interpreted. The findings of this current review are generally in line with previous literature, suggesting maternal child maltreatment has a small, but negative consequence on offspring's mental health outcomes (Bosquet Enlow, Englund, & Egeland, 2018; Collishaw et al., 2007; Plant, Pawlby, Pariante, & Jones, 2018).

We found both ethnicity and maternal depression moderated the relationship between maternal childhood maltreatment and offspring's psychopathology. Children of non-Caucasians were more susceptible to their mother's exposures of child maltreatment. Considering the etiological nature of depression and internalizing disorders, these differences might result from multiple factors, including biological factors, environmental exposures and gene-environment interplay. Caucasians and non-Caucasians may have different genetic susceptibilities and psychosocial risk factors. The implication for genotypes is that psychiatric disorders may have varying levels of heritability for different ethnic groups, which determines the offspring's susceptibility to mental health outcomes (Gatt, Burton, Williams, & Schofield, 2015; Hernandez, Plant, Sachs-Ericsson, & Joiner Jr, 2005). Compared to Caucasians, non-Caucasians were more likely to have lower socioeconomic status, higher rates of unemployment and other social stressors (e.g., exposure to crime). All these factors expose offspring to highly stressful and stigmatized environments (Turner & Lloyd, 2004; Ulbrich, Warheit & Zimmerman, 1989). Also, maternal depression moderated the relationship between maternal childhood maltreatment and offspring's psychopathology. As expected, maternal depression reduced the effect size of maternal maltreatment on offspring's depression and internalizing disorders. Clearly, maternal depression and maternal childhood maltreatment were competing risk factors for offspring's psychopathology. The association between maternal depression and adverse child outcomes could be explained by intergenerational epigenetic transmission, effects of environmental

mechanisms, and/or gene-environment interactions and the effects of depression treatment interventions (Goodman & Gotlib, 1999; Wilson & Durbin, 2010). The treatment of maternal depression may increase awareness of factors contributing to depression and thus increase awareness of the possibility of the intergenerational transmission of depression and trigger clinical interventions to ameliorate these effects. What this review adds to the literature is that it emphasizes the importance of maternal depression in offspring's mental health outcomes. Meng et al. in their systematic review alluded to the point that the influence of maltreatment on mental health might become less important as more proximal competing factors come into place (Meng, Fleury, Xiang, Li, & D'Arcy, 2018).

There are several hypotheses proposed to explain the intergenerational transmission of maternal childhood maltreatment on offspring's psychopathology. First, the transmission effect could be inherited through epigenetic alterations in genes encoding for proteins that regulate the process, such as the serotonin-transporter polymorphism (5-HTTLPR), which moderates the effects of environmental factors on the risk of childhood expression of endophenotypes that are associated with depression (Bouvette-Turcot et al., 2015). Second, the transmission may be mediated through gestational biology, with the developing feto-placental unit sensing and responding to biological cues in the maternal compartment (Buss et al., 2017). Third, exposure to negative social/psychological environment may increase the risk of developing mental disorders. Mothers with a history of childhood maltreatment have been found to be more likely to demonstrate depressive behaviors, especially at the earliest two generations intersection points, this may fundamentally contribute to maltreatment in the next generation (Plant, Barker, Waters, Pawlby, & Pariante, 2013). Fourth, maternal childhood maltreatment is often related to marital discord, parenting styles, and tense interpersonal relationships (Dixon, Hamilton-Giachritsis, & Browne, 2005; Fleming, Mullen, Sibthorpe, & Bammer, 1999; Ornduff, 2000). These negative environmental influences may lead to disruptions in stress regulation abilities and change the brain structures and functioning (Bosquet Enlow, Englund, & Egeland, 2018). Fifth, findings from clinical samples indicated that the relationship between parental childhood abuse and offspring psychopathology was mediated by the experience of abuse in the offspring generation (Brent et al., 2004). Children of abused mothers were more likely to experience maltreatment via mechanisms such as inadequate maternal care, dysfunctional mother-child relationships, and

family instability (Collishaw et al., 2007). Intergenerational continuities in offspring abuse combined with these adverse conditions can culminate in elevated vulnerability in offspring to psychiatric illness (Plant, Pariante, Sharp, & Pawlby, 2015). Sixth, offspring with victimized mothers were more likely to be exposed to an accumulation of stressors and psychosocial adversities associated with their mental health problems, for example, unstable housing, acquisition of new friends' figures, which may contribute to the transmission of risk for psychopathology associated with maternal childhood abuse (Wickrama, Conger, & Abraham, 2005). Finally, the intergenerational transmission may also be seen as a result of the complex interplay between genetic and psychosocial environmental factors binding parents to their children (Mason, Chmelka, Trudeau, & Spoth, 2017).

Strengths and Limitations

This systematic review and meta-analysis comprehensively synthesized and provided the first estimation of the negative consequence of maternal childhood maltreatment on the offspring's psychopathology, specifically, depression and internalizing behaviors. The findings of this review suggest that future research and prevention efforts on childhood maltreatment should be extended, if possible, to two generations or more generations.

There are several study limitations to be noted. First, there are a relatively small number of studies in this emerging research field with few studies being eligible for this review. The meta-analysis was limited in terms of its statistical power which may increase the chance of having a false positive effect (Dumas-Mallet, Button, Boraud, Gonon, & Munafò, 2017). The review was also restricted in its ability to explore potential moderators. Second, the generalizability of findings warrants careful interpretation, as most of the included studies measured general childhood maltreatment rather than individual subtypes of maltreatment. It remains unclear how individual subtype of maltreatment during maternal childhood would predict offspring's psychopathology. Third, the variables in the studies reviewed were limited which in turn limited what characteristics could be examined for their potential roles as moderators. Fourth, this review included mostly studies from developed countries. Findings may not apply to developing countries. Finally, this review had high heterogeneity across studies. These selected studies included a mix of moderators, used both self-report and in-person interviews to collect

information on child maltreatment, as well as symptoms and diagnostic measures. Interpretations of these results should be made cautiously.

6.6 Conclusion

This systematic review demonstrates that the experience of maternal childhood maltreatment has a small but significant impact in increasing the risk of psychopathology among those mothers' children. Improving maternal mental health may help reduce the offspring's risk of depression and internalizing behaviors. This review further informs research examining the long-term consequences of childhood maltreatment and exploring its potential moderators. It is encouraging to know that not all maternal childhood abuse leads to negative mental health outcomes for their children. So, the question arises as to what contributes to the transmission of negative mental health experiences from one generation to the next and conversely what interrupts or mitigates against such transmission? In addition, what is the impact of paternal childhood abuse? How does it affect their children's mental health? Unfortunately, research is scarce on this topic, much more is required. The role of parent-child gender symmetry and asymmetry and type of abuse and how it impacts offspring's' mental health needs further exploration. Finally, a wider range of mental health outcomes needs to be explored.

6.7 References

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Appendix A. MOOSE checklist for meta-analyses of observational studies.

Item No	Recommendation	Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
1	Problem definition	The importance of the possible link between maternal childhood maltreatment and offspring's psychopathology increased, but no systematic review has been conducted to synthesize findings on this research topic.
2	Hypothesis statement	The maternal experience of childhood maltreatment may pass onto offspring's psychopathology.
3	Description of study outcome(s)	Offspring's psychopathology
4	Type of exposure or intervention used	Maternal experience of childhood maltreatment
5	Type of study designs used	Prospective cohort study
6	Study population	Children who have mothers with childhood maltreatment experience
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	The affiliations of the investigators are provided in the title page.
8	Search strategy, including time period included in the synthesis and key words	MEDLINE, PubMed, Web of Science, EMBASE and Cochrane Library. Articles published between January 1980 and January 2019. Also see Appendix B in the supplement.
9	Effort to include all available studies, including contact with authors	Grey literature was also searched to find potentially relevant studies.
10	Databases and registries searched	MEDLINE, PubMed, Web of Science, EMBASE and Cochrane Library
11	Search software used, name and version, including special features used (eg, explosion)	No special search software was used in this study.
12	Use of hand searching (eg, reference lists of obtained articles)	Grey literature was searched for relevant articles.
13	List of citations located and those excluded, including justification	Inclusive and exclusive studies are outlined and detailed in the flow chart (Figure 6-1) and also in the Methods section.
14	Method of addressing articles published in languages other than English	We only included original empirical studies published in English.

15	Method of handling abstracts and unpublished studies	Abstracts and unpublished studies were excluded.
16	Description of any contact with authors	We contacted all the corresponding authors or first author to request additional data when needed.
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	The inclusion criteria and exclusion criteria are presented in the Methods section.
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Data extracted and coded were relevant to the study characteristics, exposure, outcome, and potential moderators. Detailed information is listed in the "Coding of Studies and Quality Assessment" section.
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	Data were extracted and analyzed by two reviewers independently.
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Because different studies controlled for different confounders, we used zero order effect sizes to make included studies' results more comparable. Zero order effect sizes do not control for confounders.
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	The quality of studies was assessed with Newcastle-Ottawa Scale.
22	Assessment of heterogeneity	Cochrane's Q statistic was used to test the heterogeneity.
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Random-effect models were used to calculate the overall point estimate. Categorical factors were tested with a between-group test of homogeneity, and the impact of continuous variables on results were assessed by meta-regression. All analyses were conducted using the Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood, NJ, USA) and IBM SPSS Statistical Version 21 (IBM Corp, NY, USA) and the macros statistical program written by Lipsey and Wilson.
24	Provision of appropriate tables and graphics	Two tables and two supplementary tables are provided. PRISMA flow-chart, one Forest Plot

		and a Funnel Plot are also provided in the main text.
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures are appended in the main text. Figure 6-2-3.
26	Table giving descriptive information for each study included	Table 6-1.
27	Results of sensitivity testing (eg, subgroup analysis)	Sensitivity analyses were used to assess the influence of each individual study on the pooled effect size.
28	Indication of statistical uncertainty of findings	95% confidence intervals were provided with overall effect estimates.
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Details on the publication bias are provided in the Result section.
30	Justification for exclusion (eg, exclusion of non-English language citations)	Articles were excluded if: (1) only included relatively common punishments (e.g. spanking, or yelling), which might not be consider as maltreatment exposures due to cultural variability; (2) did not provide sufficient information to extract effect size or data to calculate the results on any type of childhood maltreatment and the psychiatric disorder outcomes.
31	Assessment of quality of included studies	The quality of these studies was moderate as assessed by the Newcastle-Ottawa scale with a mean score of 6.75 (range from 4 to 8) (details see Appendix C in the Supplement).
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	We fully discussed the possible explanations and mechanisms of the results in the Discussion section.
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	We discussed the need for future research on this topic among developing countries in the Discussion section.
34	Guidelines for future research	Given that the negative effects of the maternal experience childhood maltreatment is not automatically passed on to the next generation future studies should examine the mechanisms that link maternal childhood maltreatment with offspring's mental health as well as how

		moderators interrupt this intergenerational transmission.
35	Disclosure of funding source	Disclosed in the relevant section.

Appendix B. Search strategies

PubMed

((((((((depressive disorder[MeSH Terms]) OR major depressive disorder[Text Word]) OR major depression[Text Word]) OR unipolar depression[Text Word]) OR depression[Text Word]) OR depressed[Text Word]) OR depressive[Text Word])) AND (child* AND (abus* OR maltreat* OR neglect OR abandon* OR illtreat* OR ill-treat* OR mal-treat* OR advers* OR trauma* OR ACE*)) AND (maternal* OR parental* OR parents OR intergenerational* OR inter-generational*) Filters: Humans

MEDLINE

(mesh (depressive disorder) OR (major depressive disorder) OR (major depression) OR (unipolar depression) OR depression OR depressed OR depressive) AND (child* AND (abus* OR maltreat* OR neglect OR abandon* OR illtreat* OR ill-treat* OR mal-treat* OR advers* OR trauma* OR ACE*)) AND (maternal* OR parental* OR parent* OR intergenerational* OR inter-generational*)

Web of Sciences

#1 TS= "child*" OR "youth" OR "adolescent*"

#2 TS="abus*" OR "maltreat*" OR "neglect" OR "abandon*" OR "illtreat*" OR "ill-treat*" OR "mal-treat*" OR "advers*" OR "trauma*" OR "ACE*"

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

#3 TS="depressive disorder" OR TS="major depressive disorder" OR TS="major depression" OR TS="unipolar depression" OR TS=depression OR TS=depressed OR TS=depressive

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

#4 #2 AND #1

#5 #3 AND #4

#6 TS= "maternal*" OR "parental*" OR "parent*" OR “intergenerational” OR"inter-generational*"

#5 #5 AND #6

EMBASE

#1 TS= "child*" OR "youth" OR "adolescent*"

#2 TS="abus*" OR "maltreat*" OR "neglect" OR "abandon*" OR "illtreat*" OR "ill-treat*" OR "mal-treat*" OR "advers*" OR "trauma*" OR "ACE*"

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

#3 TS="depressive disorder" OR TS="major depressive disorder" OR TS="major depression" OR TS="unipolar depression" OR TS=depression OR TS=depressed OR TS=depressive

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

#4 #2 AND #1

#5 #3 AND #4

#6 TS= "maternal*" OR "parental*" OR "parent*" OR “intergenerational” OR"inter-generational*"

#5 #5 AND #6

Cochrane Library

#1 MeSH descriptor: [Depressive Disorder] explode all trees

#2 "major depressive disorder" or "major depression" or "unipolar depression" or "depressed" or "depression" (Word variations have been searched)

#3 #2 or #1 or "depressive" (Word variations have been searched)

#4 MeSH descriptor: [child maltreatment] explode all trees

#5 abus* OR maltreat* OR neglect OR abandon* OR illtreat* OR ill-treat* OR mal-treat* OR advers* OR trauma* OR ACE (Word variations have been searched)

#6 #4 OR #5

#7 #3 AND #6

#8 maternal* OR parental* OR parent* OR intergenerational* OR inter-generational* (Word variations have been searched)

#9 #8 AND #7

Appendix C. A summary of the Newcastle-Ottawa Scale (NOS) quality assessment for included studies.

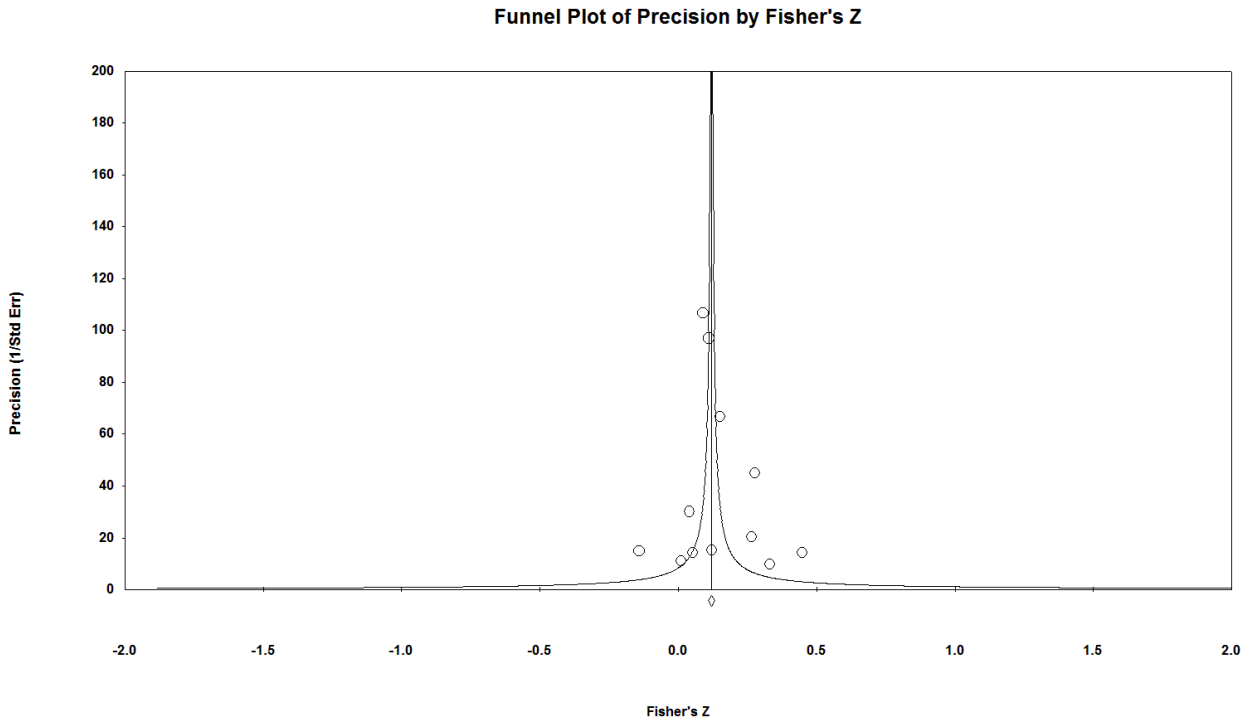
Assessment item	Study											
	Plant et al. (2013)	Roberts et al. (2015)	Min et al. (2013)	Plant et al. (2018)	Liu et al. (2019)	Linde-Krieger & Yates (2018)	Pereira et al. (2018)	Choi et al. (2019)	Rijlaarsdam et al. (2014)	Dubowitz et al. (2001)	Koverola et al. (2005)	Letourneau et al. (2019)
Selection												
1. Representativeness of the intervention cohort												
a) truly representative of the average, elderly, community-dwelling resident	0	0	0	1	0	0	0	0	1	0	0	0
b) somewhat representative of the average, elderly, community-dwelling resident	1	1	0	0	1	1	1	1	0	0	0	1
c) selected group of patients, e.g. only certain socio-economic groups/areas	0	0	0	0	0	0	0	0	0	0	0	0

d) no description of the derivation of the cohort	0	0	0	0	0	0	0	0	0	0	0	0
2. Selection of the non-intervention cohort												
a) drawn from the same community as the intervention cohort	1	1	1	1	1	1	1	1	1	1	0	1
b) drawn from a different source	0	0	0	0	0	0	0	0	0	0	0	0
c) no description of the derivation of the non-intervention cohort	0	0	0	0	0	0	0	0	0	0	0	0
3. Ascertainment of intervention (exposure)												
a) secure record (e.g. health care record)	0	0	0	0	0	0	0	0	0	0	0	0
b) structured interview	0	1	1	0	0	1	0	1	1	0	0	0
c) written self-report	0	0	0	0	0	0	0	0	0	0	0	0
d) other / no description	0	0	0	0	0	0	0	0	0	0	0	0
4. Demonstration that outcome of interest was not												

present at start of study												
a) yes	1	1	1	1	1	1	1	0	1	0	0	1
b) no	0	0	0	0	0	0	0	0	0	0	0	0
Comparability												
1. Comparability of cohorts on the basis of the design or analysis												
a) study controls for age, sex, marital status	0	0	0	0	0	0	0	0	0	0	0	0
b) study controls for any additional factors (e.g. socio-economic status, education)	1	1	1	1	0	1	1	1	1	1	1	1
Outcome												
1. Assessment of outcome												
a) independent blind assessment	1	1	1	1	1	1	1	1	1	1	1	1
b) record linkage	0	0	0	0	0	0	0	0	0	0	0	0
c) self-report	0	0	0	0	0	0	0	0	0	0	0	0
d) other / no description	0	0	0	0	0	0	0	0	0	0	0	0

2. Was follow up long enough for outcomes to occur												
a) yes, if median duration of follow-up >= 6 month	1	1	1	1	1	1	1	1	1	1	1	1
b) no, if median duration of follow-up < 6 months	0	0	0	0	0	0	0	0	0	0	0	0
3. Adequacy of follow up of cohorts												
a) complete follow up: all subjects accounted for	1	1	1	1	1	0	0	0	0	1	1	1
b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, or description of those lost suggesting no different from those followed	0	0	0	0	0	1	1	1	1	0	0	0
c) follow up rate < 80% (select an adequate %) and no description of those lost	0	0	0	0	0	0	0	0	0	0	0	0
d) no statement	0	0	0	0	0	0	0	0	0	0	0	0

Overall	7	8	7	7	6	8	7	7	8	5	4	7



Appendix D. The publication bias test by the funnel plot (N=12).

CHAPTER 7. DEVELOPMENTAL ORIGINS OF DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

A version of this chapter has been published as: “Su, Y., D’Arcy, C., & Meng, X. (2020). Developmental origins of depression: a systematic review and meta-analysis. Journal of Child Psychology and Psychiatry. In press, published online.” My contributions to this study included study design, data analysis, results interpretation, and manuscript writing as well as editing.

7.1 Abstract

Background: Many observational studies have found a direct association between adverse in-utero, perinatal and postnatal exposures and offspring's depression. These findings are consistent with the "developmental origins of disease hypothesis". But no review has comprehensively summarized the roles of these exposures. This review aims to systematically scrutinize the strength of associations between individual prenatal, perinatal, and postnatal exposures and subsequent depression in offspring.

Methods: We conducted a systematic review and meta-analysis to synthesize the literature from the EMBASE, HealthStar, PsychoInfo, and Medline databases since their inception to September 1, 2019. English language articles on population-based prospective cohort studies examining the associations between in-utero, perinatal and postnatal exposures and offspring's depression were searched. Random-effects models were used to calculate pooled estimates and heterogeneity and sensitivity tests were conducted to explore potential confounders in the relationships of depression and early life factors. Qualitative analysis was also conducted.

Results: Sixty-four prospective cohort studies with 28 exposures studied in the relationships to offspring's depression met inclusion criteria. The meta-analysis found 12 prenatal, perinatal and postnatal characteristics were associated with an increased risk of depression in offspring: low birth-weight, premature birth, small gestational age, maternal education, socioeconomic status, having younger parents (<20 years), having older parents (≥ 35 years), maternal smoking, paternal smoking, maternal stress, maternal anxiety, and prenatal depression. Heterogeneity and sensitivity tests supported the findings. By and large, study characteristics had no effects on conclusions. Qualitative analyses generally supported the findings of meta-analysis and reported on additional risk factors.

Conclusions: This review provides a robust and comprehensive overview of the lasting psychopathological effects of in-utero, perinatal, and postnatal exposures. The findings highlight the need for clinical and public health interventions focusing on the identified risk factors. Large prospective cohort studies are warranted to investigate the combined effects of multiple co-existing early life exposures.

7.2 Introduction

Major depression is a public health problem internationally, especially in high- and upper-middle-income countries (Rehm & Shield, 2019). It is estimated that major depression was one of the five leading causes (out of 328) of years lived with disability (YLDs) in 195 countries and territories from 1990 to 2016, contributing 34.1 million years to the total YLDs (Vos et al., 2015). Accumulating evidence shows adverse conditions in pregnancy and early life are associated with later negative neuropsychiatric outcomes (Hazel, Hammen, Brennan, & Najman, 2008; Newman et al., 2016; Strüber, Strüber, & Roth, 2014). Adverse in-utero and perinatal exposures were associated with mental health status in adolescence and adulthood. The association between adverse in-utero and perinatal exposures and mental health outcomes in later adulthood could involve alternations in cellular aging (Entringer et al., 2011). The alternations of cellular aging could then trigger epigenetic modifications and increase the susceptibility of mental disorders among affected individuals (Vaiserman & Koliada, 2017). Although there is evidence that adverse in-utero and perinatal exposures are associated with subsequent health outcomes in adolescence and adulthood, the underlying mechanisms of the 'biological embedding' of early life experiences are not sufficiently understood. Empirical studies on fetal programming effects have shown that maternal stress or undernutrition leads to fetal growth retardation, which compromises in fetal development and growth linking with early onset of adult diseases (Calkins & Devaskar, 2011). The developmental origins of health and disease (DOHaD) model highlights the roles for in-utero, perinatal and postnatal factors in the development of major depression during the life course (O'Donnell & Meaney, 2017). However, as mental disorders are complex diseases involved multiple risk factors, the causal conclusions between the in-utero and perinatal exposures and adolescent and adult mental health status warrant further investigation.

The following mechanisms have been proposed to understand the associations between prenatal and perinatal factors and subsequent psychopathology, including 1) intergenerational transmission of maternal stress (Hentges, Graham, Plamondon, Tough, & Madigan, 2019), 2) low birth-weight has been associated with impaired executive function, educational achievements, and an elevated risk of major depression (Aizer & Currie, 2014), 3) antenatal maternal emotional wellbeing has been closely linked with offspring's neurodevelopmental

outcomes (Glover, 2014; Pearson et al., 2013), 4) glucocorticoids have been shown to mediate the association between maternal adversities and offspring development (Desplats, 2015; Meaney, Szyf, & Seckl, 2007), and, 5) the integration of genetic and prenatal environmental factors on DNA methylation is seen to have enduring influences on normal development and health (Czamara et al., 2019).

While an increasing number of observational studies has found that several prenatal, perinatal, and postnatal factors increased the risk of depression across the lifespan, most of these studies were cross-sectional leaving them open to the criticism that cross-sectional designs increase the likelihood of contributing spurious associations between these factors and depression (Betts, Williams, Najman, & Alati, 2015; Fryer, McGee, Matt, Riley, & Mattson, 2007; Owens & Hinshaw, 2013; Quarini et al., 2016; Richardson et al., 2016; Whelan, Leibenluft, Stringaris, & Barker, 2015). There is lack of systematic evidence that comprehensively summarizes the factors during early life that contribute to the development of depression. A critical review of these in-utero, perinatal and postnatal conditions not only stimulates possible etiological explanations of the reported associations in depression but also suggests directions for care and prevention services to provide adequate and appropriate support to those with identified risk factors. We are not aware of any systematic review of in-utero, perinatal and postnatal factors on *depression* that comprehensively synthesizes those attributes associated with the risk of depression. This present review aims to objectively evaluate the role of each early life exposure (occurring after conception, before or after birth (up to 1 year old), or characteristics of the perinatal environment) in major depression or depressive symptoms across the life span. The exposures were grouped into biological, psychological, and sociological factors based on the biopsychosocial model proposed by Engel (Engel, 1977) which provides a fundamental framework to systematically consider the roles of biological, psychological, and sociological factors in the process of disease and health. This model endorsed a holistic approach, linking normality to abnormality through biological and psychosocial mechanisms (Frazier, 2020). Findings of this review could add new knowledge to the DOHaD hypothesis by clearly showing the factors that are robustly associated with depression and draw attention to these identified factors noting their importance and the necessity for high quality maternal and childcare to address them.

7.3 Methods

7.3.1 Search strategy

This systematic review and meta-analysis are guided by the Preferred Reporting Items for Systematic Reviews (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklists (Appendix A.1) (Moher, Liberati, Tetzlaff, Altman, & The, 2009; Stroup et al., 2000). The protocol of this study was registered in PROSPERO, number CRD42019147074. We searched for prospective longitudinal studies on in-utero, perinatal/postnatal exposures. These exposures included birth weight, baby's length at birth, birth order, gestational age (GA), small gestational age (SGA), socioeconomic status at birth, maternal education, teen parents, parental age greater than 35 years of age, single mother, maternal stress, maternal anxiety, maternal pre- and postnatal depression, exposure to maternal drinking, maternal smoking and paternal smoking, and exposure to bisphenol A, fetal antiepileptic drug, selective serotonin reuptake inhibitors, antibiotics, organic pollutants, elemental carbon attributable to traffic (ECAT), marijuana, cocaine, famine, maternal infection, and maternal chronic disorders. We first conducted a computerized search for bibliographic databases, including EMBASE, HealthStar, PsychoInfo, and Medline from their inception until September 1st, 2019 for published articles on the above-mentioned maternal and child conditions and major depression. The detailed search strategies for each database are fully described in Appendix A. We then applied a snowball technique to search the reference lists of all relevant studies for further potential studies. In addition, we manually searched other resources to maximize the relevant studies. The reference lists of selected articles, review articles on relevant topic, and the gray literature were all screened. Only articles published in English were included.

7.3.2 Eligibility criteria

Articles that met the following criteria were included in this systematic review: 1) population: had a clear diagnosis for major depression or depressive symptoms, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) and its updates, International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) or other generally accepted criteria; 2) phenomenon of interest: provided the information on in-utero, perinatal, or early life exposures; 3) comparison: had a comparison group(s) without the exposure(s); 4) outcome: provided statistical indicators to examine the impact of in-utero and

perinatal factors on major depression across the lifespan; and, 5) study design: were longitudinal cohort studies, including population-based cohort studies and registry-based studies.

7.3.3 Selection of the studies

Two researchers (YS and XM) independently screened and selected the retrieved articles by titles and abstracts, followed by full texts. An article was discarded if both reviewers agreed that the article did not meet the inclusion criteria. Inconsistencies in interpretation were resolved through group discussions among the authors. Endnote and RefWorks were used as bibliographic software.

7.3.4 Data extraction, synthesis, and quality assessment

Data on first author(s), year of publication, study site, sample size, age of offspring at enrolment, length of follow-up, type of depression, prenatal, perinatal, and postnatal factors, measures of major depression or depressive symptoms, other covariates, and major results were extracted independently. If there were multiple reports from a single cohort, only the record with more complete information was extracted. If there were any discrepancies in reports, we contacted the study authors for clarification. Any disagreements were solved by group discussions. For those articles which did not have the data to calculate the pooled estimates, we provided a narrative description instead and kept the results for qualitative analysis. And if several studies were from the same cohort study with the same exposures, the one with the longest follow-up time was chosen for analysis.

The reviewers endeavored to contact the original authors of the studies with missing information to gather complete information. We offered open-ended questions to prevent the skewness of responses. The methodological quality of the included studies was assessed by the Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort studies (Wells, 2001). The NOS rating is composed of eight items covering three domains: selection of study groups, comparability of case and comparison groups, and ascertainment of outcome or exposure. The total score of the NOS ranges between 0 and 9. The scores of good quality studies ranged from 7 to 9, studies scoring 6 were judged fair, and those scoring <5 were considered poor.

This review included both quantitative and qualitative analyses for the selected articles. For the quantitative analysis only original studies with the necessary data to calculate an odds ratio

were included, whereas the qualitative synthesis included the rest of the studies for which odd ratios could not be calculated or could not be synthesized by meta-analysis due to high heterogeneity. These later studies had diverse categorizations of variables, or statistical indicators that could not be translated into odds ratios. Or they were included in the qualitative analysis because of the limited number of available studies on a given risk factor. A total of 64 articles were included in this review. Of the included studies 29 reported only quantitative results, 31 reported only qualitatively analyzed results and four reported both quantitative and qualitative results. As a result, 33 studies were used in the meta-analysis and 35 studies were qualitatively synthesized. We report results of both the quantitative and qualitative syntheses based on the studied exposure.

7.3.5 Meta-analysis

DerSimonian and Laird I^2 statistics were used to test heterogeneity across studies. We used both funnel plots and Egger/Begg tests to examine publication bias. Compared to funnel plots, the Egger test provides a more objective way to estimate the reliability of the results. We then applied the trim and fill method to explore potential publication bias. Based on the results of heterogeneity tests, random-effects model was used to calculate pooled estimates, which is more conservative compared to fixed-effects model. Meta-regression analysis was conducted to identify possible explanations for the heterogeneity. Sensitivity analysis was also performed to explore the effects of the potential confounders. We did subgroup analysis for different prenatal and perinatal/postnatal factors. Analyses were conducted using RevMan version 5.3 and Stata version 15.0.

7.4 Results

We started with a total of 9,418 titles from the four bibliographic databases. 4,293 duplicates were then removed. A total of 1,392 articles were identified as eligible studies for full-text review with 1,328 being subsequently excluded for detailed reasons. After applying the inclusion criteria 64 studies remained for this systematic review and meta-analysis. A flow chart of the study selection process is presented in Figure 7-1.

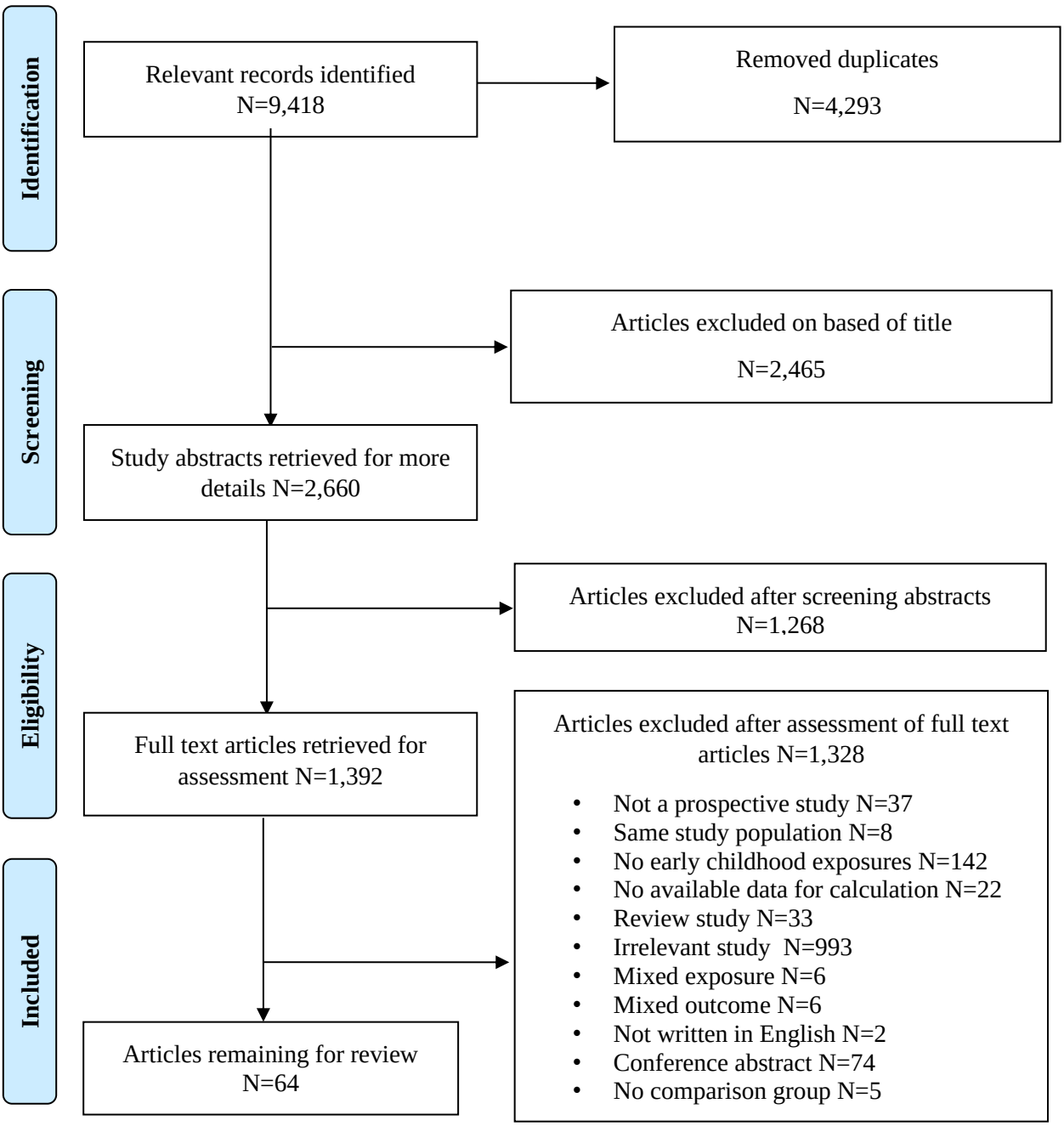


Figure 7- 1 A summary of study selection process.

Appendix A.2 presents a summary of the characteristics of 64 studies reviewed (Alati et al., 2007; Barker, Copeland, Maughan, Jaffee, & Uher, 2012; Betts, Salom, Williams, Najman, & Alati, 2015; Biederman, Martelon, Woodworth, Spencer, & Faraone, 2017; Buizer-Voskamp et al., 2011; Butler, 2014; Chiu et al., 2019; Cohen et al., 2013; Colman, Ataullahjan, Naicker, & Van Lieshout, 2012; Elmasry, Goodwin, Terry, & Tehranifar, 2014; Fan & Eaton, 2001; Fergusson, Woodward, & Horwood, 1998; Gale & Martyn, 2004; Geoffroy, Gunnell, Clark, & Power, 2018; Gray, Day, Leech, & Richardson, 2005; Harley et al., 2013; Herva et al., 2008; Johnson, O'Reilly, Ni, Wolke, & Marlow, 2019; Joinson, Kounali, & Lewis, 2017; Kiff et al., 2012; Kingsbury et al., 2016; Leung, Leung, & Schooling, 2015; Levine, 2014; Levy-Shiff et al., 1994; Li et al., 2018; Liu et al., 2011; Loret de Mola et al., 2015; Malm et al., 2016; Meier et al., 2017; Menezes et al., 2013; Murphy et al., 2017; Nomura, Brooks-Gunn, Davey, Ham, & Fifer, 2007; Nomura, Wickramaratne, et al., 2007; O'Connor & Kasari, 2000; Pawlby, Hay, Sharp, Waters, & O'Keane, 2009; Pearson et al., 2013; Pereira et al., 2012; Perera et al., 2016; Perquier, Lasfargues, Mesrine, Clavel-Chapelon, & Fagherazzi, 2014; Phillips, Hammen, Brennan, Najman, & Bor, 2005; Pitzer, Jennen-Steinmetz, Esser, Schmidt, & Laucht, 2011; Plant, Pariante, Sharp, & Pawlby, 2015; Power et al., 2007; Ramchandani et al., 2008; Raposa, Hammen, Brennan, & Najman, 2014; Richardson, Goldschmidt, Larkby, & Day, 2013; Saigal, Pinelli, Hoult, Kim, & Boyle, 2003; Slykerman et al., 2015; Slykerman et al., 2017; Sonon, Richardson, Cornelius, Kim, & Day, 2016; Strom et al., 2014; Taka-Eilola Nee Riekki, Veijola, Murray, Koskela, & Maki, 2019; Taylor et al., 2017; Tearne et al., 2016; Tracy, Salo, Slopen, Udo, & Appleton, 2019; Tuovinen et al., 2014; Van Lieshout & Boylan, 2010; Wang, Leung, Lam, & Schooling, 2015; Westrupp, Northam, Doyle, Callanan, & Anderson, 2011; Yamasaki et al., 2019; Yolton et al., 2019; Zohsel et al., 2017). Of the 64 studies, 18 studies were conducted in the United States, 13 in United Kingdom, 6 in Australia, 3 in Canada, 4 in Finland, 1 in France, 4 in China, 2 in Denmark, 2 in Germany, 4 in Brazil, 1 in Japan, 3 in New Zealand, 1 in Netherlands, 1 in Norway, and 1 in Israeli. The NOS score of study quality for the included studies ranged from 4 to 9 with the median score of 6.9. This review includes mostly good quality studies. Thirty-eight of the studies were judged to be good quality studies and 25 were rated as being of fair quality with one study rated as poor. Details of study quality can be found in Appendix A.3 in the supporting information. Of the studies reporting quantitative results 17

were judged as good quality studies, 16 were judged as being of fair quality. Of the studies reporting qualitatively synthesized results 21 were judged to be good quality, nine were judged fair, and one was poor quality.

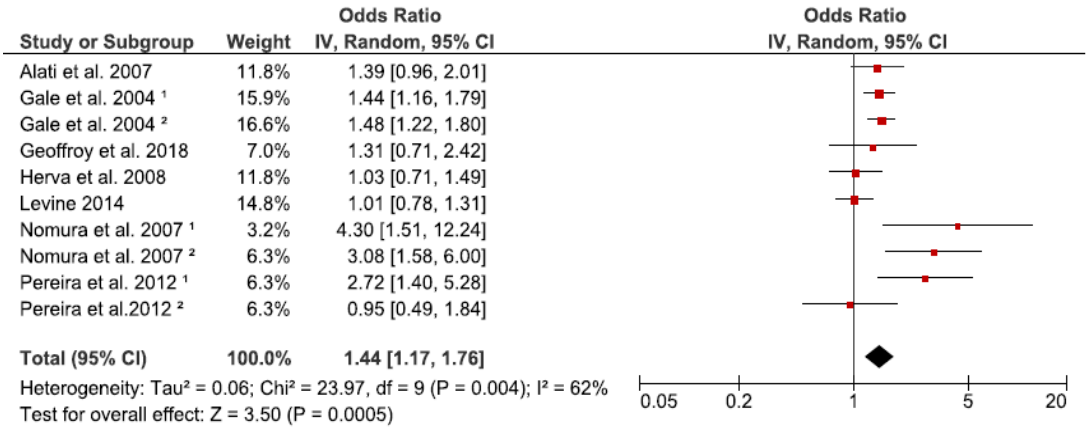
Table 7-1 provides a concise summary of the meta-analysis's findings. Of the 28 early life exposures studied a total of 12 prenatal and perinatal/postnatal factors were significantly associated with offspring's depression, namely: low birth-weight, premature birth, SGA, maternal education, socioeconomic position, having younger parents (<20 years old), having older parents (≥35 years), maternal smoking, paternal smoking, maternal stress, maternal anxiety, and prenatal depression. Forest plots of the studied individual and pooled odds ratios are presented in Figure 7-2. Heterogeneity tests for most of the studied variables were not significant (P>0.05) with exceptions being socioeconomic status (SES), maternal smoking, maternal prenatal depression, low birth-weight, and GA. Since high heterogeneity was found for the pooled estimates for some risk factors, we used meta-regression analyses to explore if age onset of depression (≤17 and >18 year of old) could explain the heterogeneity across the selected studies. The univariate meta-regression showed that age of onset had a significant impact on the heterogeneity across studies. Appendix A.4 (supporting information) displays the results of the meta-regression models.

Because some exposures only had one publication in the selected studies, we then applied qualitative approach to synthesize these exposures instead. Additionally, studies with either diverse categorization or statistical indicators that could not be converted into odds ratios were also summarized as qualitatively analyzed studies. Noteworthy, although some studies presented the findings with odds ratios, their categorizations of exposures could not be harmonized thus these studies were described qualitatively. Detailed results from these qualitatively analyzed studies are reported in Table Appendix A.5 (Supporting information). These qualitatively analyzed studies are also noted by the # symbol in Appendix A.2. Although there are some overlapped risk factors between qualitatively and quantitatively analyzed studies, there are some risk factors that are unique to the qualitatively analyzed studies. All qualitatively analyzed results are summarized in Table 7-2. We grouped in-utero, perinatal and postnatal exposures into biological, psychological and sociological factors following the biopsychosocial model of mental illness.

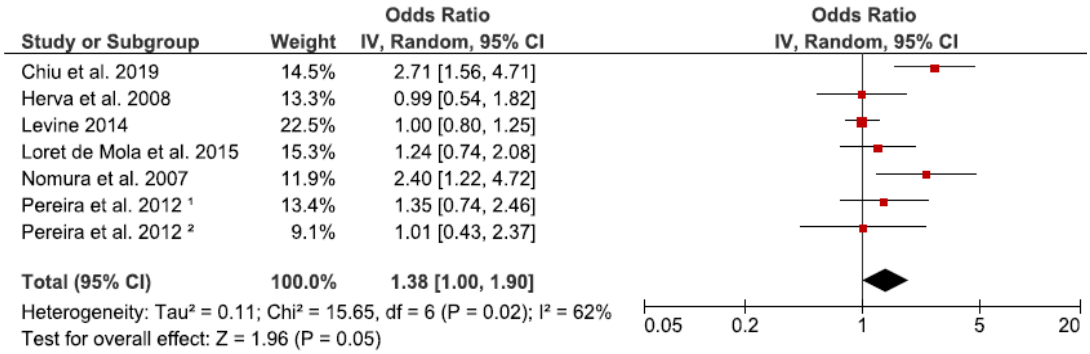
Table 7- 1 A summary table of the meta-analysis findings.

Factors	Number of studies	Odds Ratio	95%CI	Find significant association
Biological Factors				
Low birth-weight (<2500 grams)	10	1.44	1.17, 1.76	Yes
Gestational age (Premature children <37 weeks)	7	1.38	1.00, 1.90	Yes
Small gestational age	3	1.46	1.11, 1.94	Yes
Birth order	5	1.08	0.91, 1.29	No
Teen parents (<20 years old)	9	1.46	1.22, 1.74	Yes
Parents' age >35 years	6	1.13	1.07, 1.20	Yes
Psychological Factors				
Maternal stress	4	1.12	1.04, 1.22	Yes
Maternal anxiety	2	1.09	1.02, 1.17	Yes
Maternal prenatal depression	8	1.36	1.07, 1.72	Yes
Maternal postnatal depression	3	1.52	0.92, 2.50	No
Sociological Factors				
Maternal education (<9 years of study)	9	1.37	1.19, 1.57	Yes
Socioeconomic status (Low)	6	1.29	1.10, 1.52	Yes
Single mother	2	1.20	0.64, 2.25	No
Maternal smoking	13	1.45	1.28, 1.63	Yes
Paternal smoking	4	1.28	1.11, 1.48	Yes
Maternal drinking	2	1.09	0.96, 1.24	No

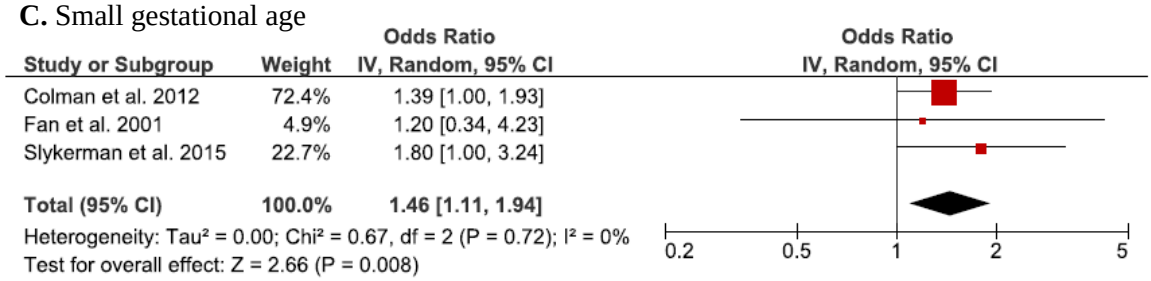
A. Birth weight



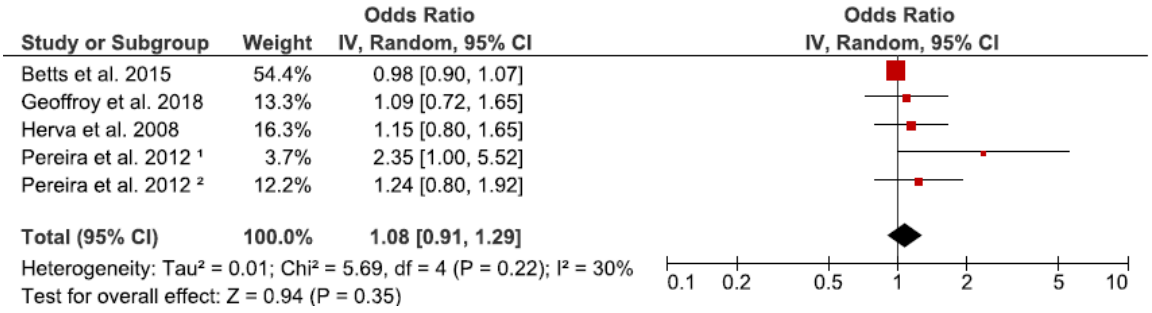
B. Preterm birth



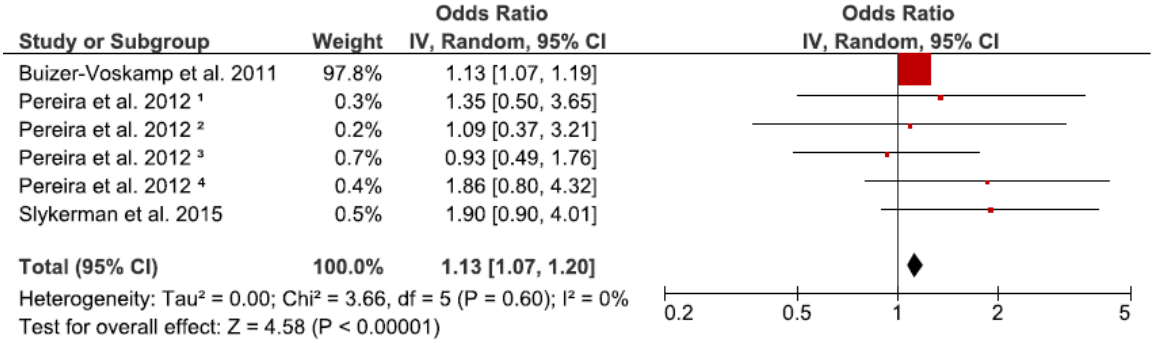
C. Small gestational age



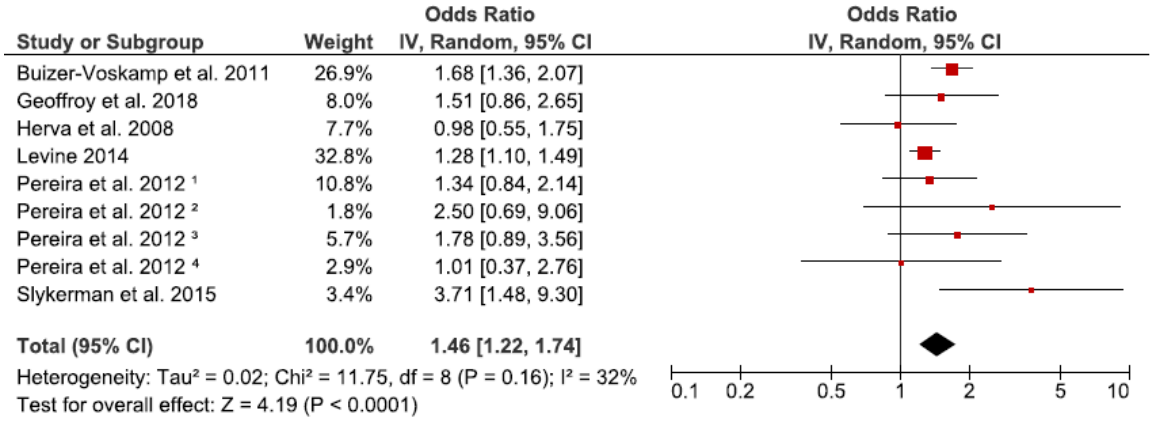
D. Birth order



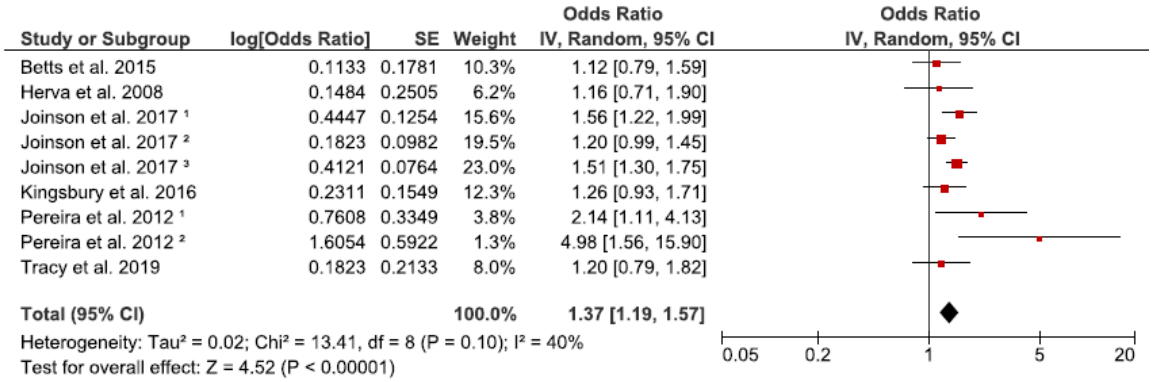
E. Teen parents



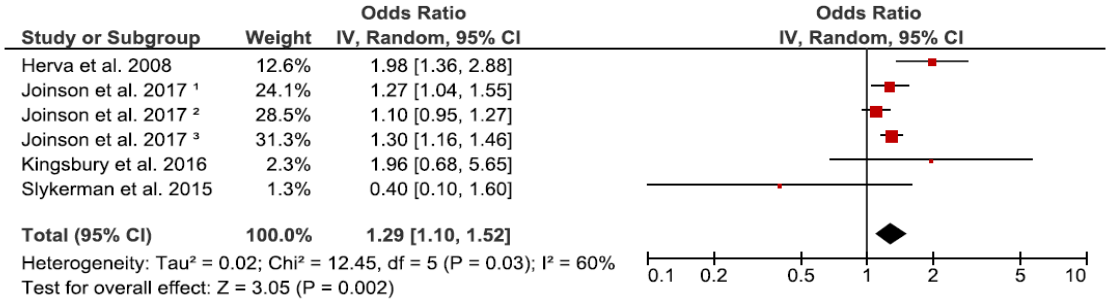
F. Parental age greater than 35 years



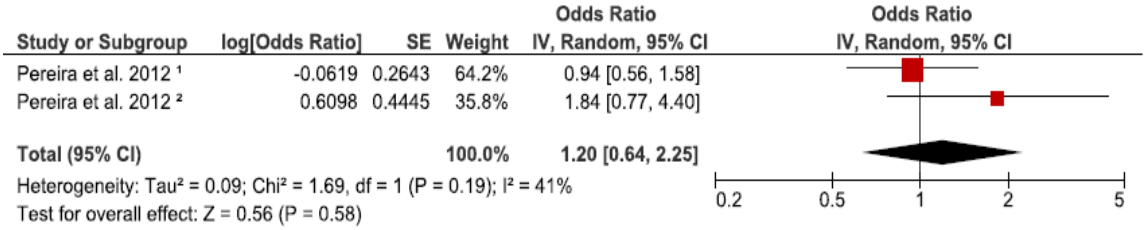
G. Maternal education



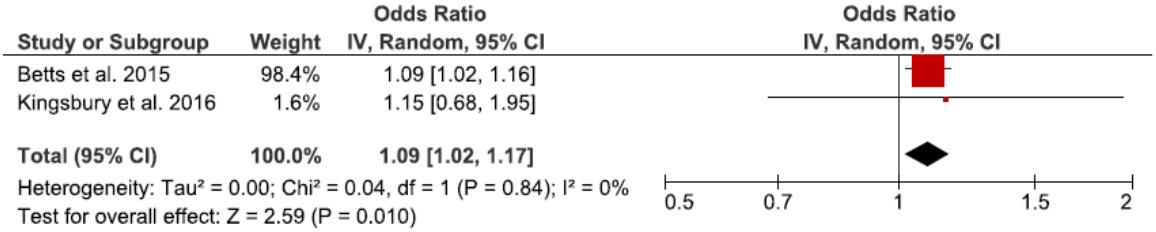
H. Socioeconomic status



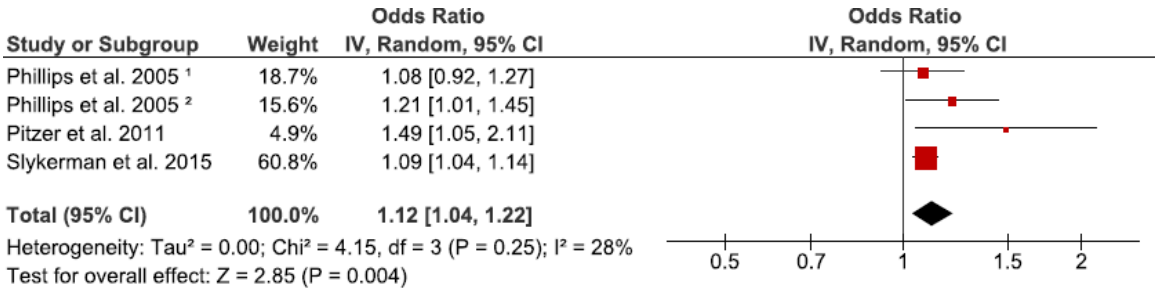
I. Single mother



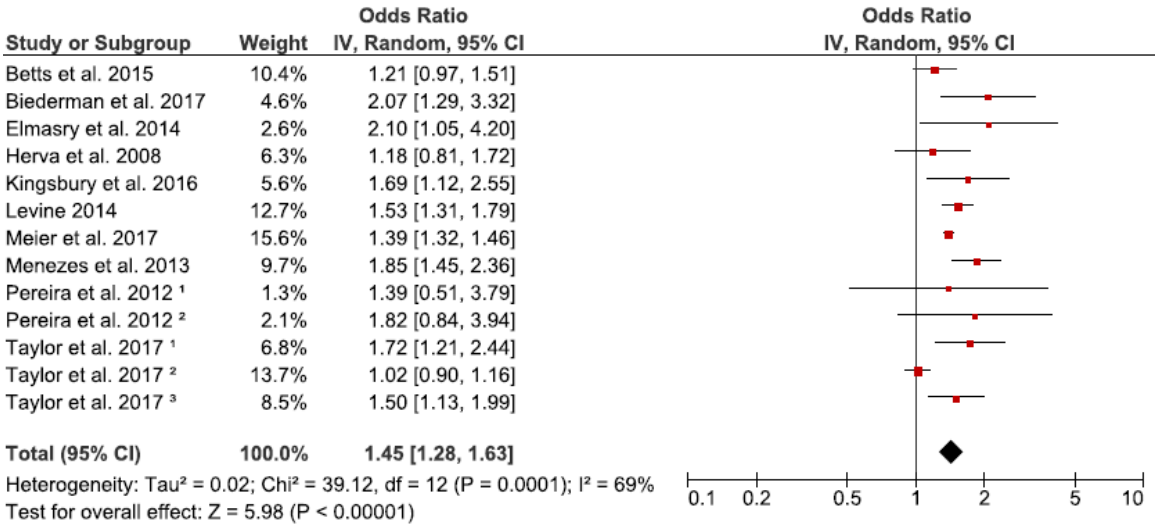
J. Maternal anxiety



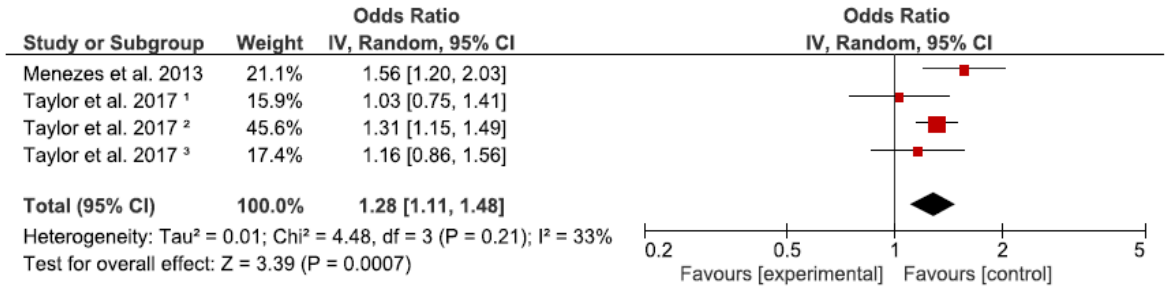
K. Maternal stress



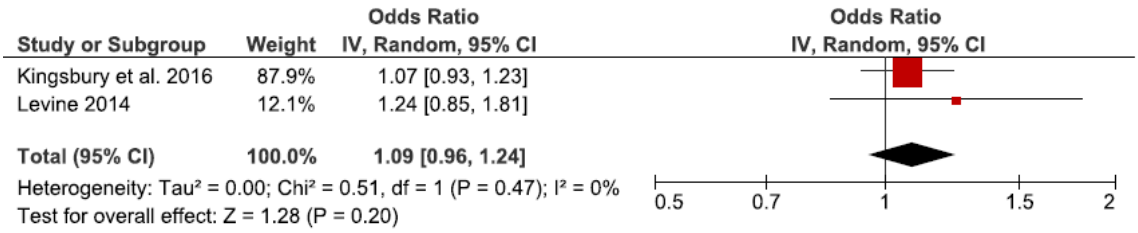
L. Maternal smoking



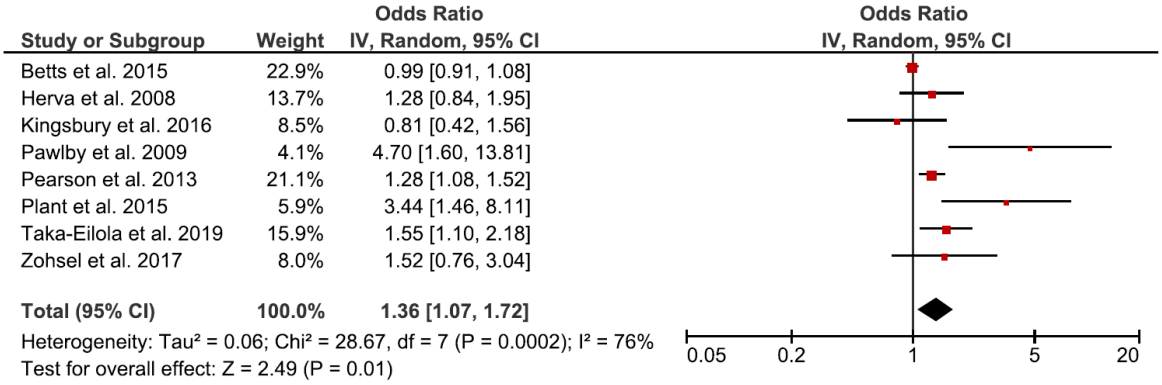
M. Paternal smoking



N. Maternal drinking



O. Maternal prenatal depression



P. Maternal postnatal depression

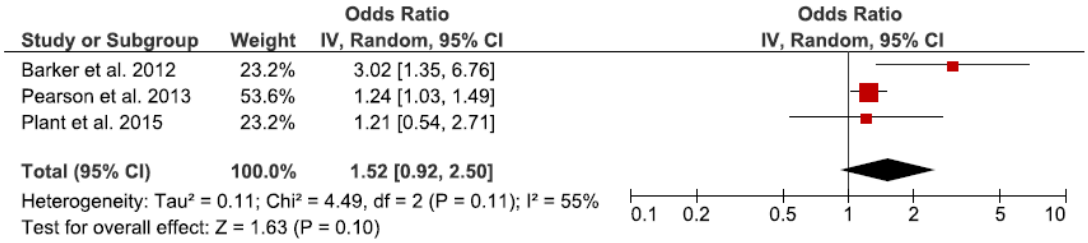


Figure 7- 2 Pooled ORs for the association between prenatal, perinatal and postnatal factors and depression risk.

Gale[1] is the study among females, Gale[2] is the study among males; Nomura[1] is the New York State Psychiatric Institute/Columbia University study, Nomura[2] is the National Collaborative Perinatal Project (NCPP) study; Pereira[1] study compares depression in children 7-9 years with maternal factors, Pereira[2] study compares depression in children 10-11 years with maternal factors, Pereira[3] study compares depression in children 7-9 years with paternal factors, Pereira[4] study compares depression in children 10-11 years with paternal factors; Joinson[1] study compares depression in children less than 12 years old, Joinson[2] study compares depression in children at 12-16 years old, Joinson[3] study compares depression in children at 12-17 years old; Phillips[1] is the study on prenatal stress, Phillips[2] is

the study on postnatal stress; Taylor[1] is the ALSPAC study, Taylor[2] is the HUNT study, Taylor[3] is the Pelotas 1982 study.

Table 7- 2 A summary of the qualitative analyzed findings.

Factors	Number of studies	Results	Major findings
Biological Factors			
Low birth-weight *	7	Negative (4) Positive (3)	Three studies reported an association between low birth-weight and depression in offspring, while four studies reported null association.
Gestational age *	4	Negative (3) Positive (1)	One study reported an association between preterm birth and depression in offspring, while three studies reported null association.
Small gestational age *	1	Positive	One study reported an association between small gestational age and depression in offspring in adolescence.
Baby's length at Birth	1	Negative	One study reported null association between birth length and depression in offspring.
Teen parents *	4	Positive (3) Negative (1)	Three studies reported an association between having teen parents and depression in offspring, while one study reported null association.
Parents' age >35 years *	1	Positive	One study reported an association between having elderly parents and depression in male offspring.
Maternal infections	2	Mixed	One study reported an association between maternal infections and depression in offspring, while one study reported null association.
Chronic diseases	2	Positive	Two studies reported that maternal hypertensive disorder and diabetes were associated with an elevated risk of depression in offspring, respectively.
Bisphenol A	2	Positive	Two studies reported an association between Bisphenol A and depression in offspring.
Fetal antiepileptic drug	1	Negative	One study reported null association between fetal antiepileptic drug and depression.
SSRI	1	Positive	One study reported an association between SSRI and depression in offspring.
Antibiotics	1	Positive	One study reported an association between antibiotics use and depression in offspring.
Organic pollutants	1	Negative	One study reported null association between fetal exposure to persistent organic pollutants and depression.
ECAT	1	Positive	One study reported an association between prenatal ECAT exposure and depression in offspring.

Marijuana exposure	2	Positive	Two studies reported an association between maternal marijuana exposure and depression in offspring.
Cocaine exposure	1	Negative	One study reported null association between cocaine exposure and depression.
Psychological Factors			
Maternal stress *	2	Mixed	One study reported an association between maternal stress and depression in offspring, while one study reported null association.
Maternal prenatal depression *	2	Mixed	One study reported an association between maternal prenatal depression and depression in offspring, while one study reported null association.
Paternal postnatal depression	1	Negative	One study reported null association between paternal postnatal depression and depression in offspring.
Sociological Factors			
Socioeconomic status *	2	Mixed	One study reported an association between low socioeconomic status and depression in offspring, while one study reported null association.
Maternal smoking *	4	Negative (3) Positive (1)	One study reported an association between maternal smoking and depression in offspring, while three studies reported null association.
Maternal drinking	3	Positive (2) Negative (1)	Two studies reported an association between maternal drinking and depression in offspring, while one study reported null association.
Famine	1	Positive	One study reported null association between famine in-utero and depression in offspring.

Notes: *Indicates risk factors found to be significantly associated with offspring's depression in the meta-analysis.

SSRI: Selective serotonin reuptake inhibitors; ECAT: Elemental carbon attributable to traffic.

7.4.1 Biological factors

Low birth-weight

Ten studies were included in the meta-analysis (Alati et al., 2007; Gale & Martyn, 2004; Geoffroy, Gunnell, Clark, & Power, 2018; Herva et al., 2008; Levine, 2014; Nomura, Brooks-Gunn, Davey, Ham, & Fifer, 2007; Nomura, Wickramaratne, et al., 2007; Pereira et al., 2012). The findings indicated that low birth-weight (<2500 grams) was associated with an elevated risk of depression, with a pooled OR of 1.44 (95%CI, 1.17-1.76, k=10, N=27,574). There was a high degree of heterogeneity between studies (I^2=62%, *P*<0.01). Visual assessment of a funnel plot, and Egger as well as Begg test provided no evidence of obvious publication bias.

However, the findings in the qualitative analysis were mixed (k=7). Three of seven studies reported an association between low birth-weight and depression (Levy-Shiff et al., 1994; Loret de Mola et al., 2015; Van Lieshout & Boylan, 2010). In contrast, two studies found *no* association between birth weight and major depression (OR=0.91; 95%CI, 0.82-1.01; OR=1.15; 95%CI, 0.96-1.36) (Betts, Salom, Williams, Najman, & Alati, 2015; Perquier, Lasfargues, Mesrine, Clavel-Chapelon, & Fagherazzi, 2014). Two additional studies, one on very low birth-weight (<1500 grams) and the other on extremely low birth-weight (<1000 grams) did not find any association between low birth-weight and depression (Saigal, Pinelli, Hoult, Kim, & Boyle, 2003; Westrupp, Northam, Doyle, Callanan, & Anderson, 2011) (Details could be found in Table S5).

Gestational age

In the meta-analysis of seven studies (Chiu et al., 2019; Herva et al., 2008; Levine, 2014; Loret de Mola et al., 2015; Nomura, Brooks-Gunn, Davey, Ham, & Fifer, 2007; Pereira et al., 2012), premature children (<37 weeks) were found at an elevated risk of depression (OR=1.38; 95%CI, 1.00-1.90, k=7, N=128,001) and there was a high degree of heterogeneity between studies (I^2=62%, *P*=0.02). No obvious publication bias was observed from visual assessment of a funnel plot nor Egger/Begg test.

In contrast, the findings of qualitatively analyzed studies (k=4) on the relationship between gestational age and depression were generally negative. One study reported that gestational age was linked with a higher risk of offspring's depression (r=0.82, p<0.001) (Levy-Shiff et al.,

1994), whereas three studies found no statistical evidence of such association including one study on extremely preterm children (<26 weeks) (Cohen et al., 2013; Johnson, O'Reilly, Ni, Wolke, & Marlow, 2019; Wang, Leung, Lam, & Schooling, 2015).

Small gestational age at birth

The meta-analysis of three studies suggested that being small for gestational age at birth was more likely to lead to major depression (OR=1.46; 95%CI, 1.11-1.94, k=3, N=6,165) (Colman, Ataullahjan, Naicker, & Van Lieshout, 2012; Fan & Eaton, 2001; Slykerman et al., 2015). There was no evidence of heterogeneity between studies (I^2=0%, *P*=0.72). Visual inspection of a funnel plot, and Egger as well as Begg test provided no evidence of obvious publication bias.

In the qualitative analysis, one study found small gestational age was associated with an increased risk of depression onset only in adolescence but not in childhood ($t_{adolescence}$=2.70, p < 0.01; $t_{childhood}$ =0.15, p < 0.88) (Van Lieshout & Boylan, 2010). It supported our significant findings with a pooled OR of 1.46.

Birth order

The meta-analysis of five studies found that there was no statistical association between birth order and depression (OR=1.08; 95%CI, 0.91-1.29, k=5, N=21,246), when comparing individuals who were second born or later to those who were first born individuals (Betts, Salom, Williams, Najman, & Alati, 2015; Geoffroy, Gunnell, Clark, & Power, 2018; Herva et al., 2008; Pereira et al., 2012). There was no evidence of heterogeneity between studies (I^2=30%, *P*=0.22). The visual inspection of the funnel plot and Begg test did not indicate any evidence of publication bias. However, the result of Egger test found significant publication bias (*P*=0.031).

Baby's length at birth

One qualitative study reported null association between baby's birth length and depression (Perquier, Lasfargues, Mesrine, Clavel-Chapelon, & Fagherazzi, 2014). There were no comparable meta-analysis findings.

Age of parents

There were nine studies exploring the association between having teen parents (<20 years old) and depression in offspring in the meta-analysis (Buizer-Voskamp et al., 2011; Geoffroy,

Gunnell, Clark, & Power, 2018; Herva et al., 2008; Levine, 2014; Pereira et al., 2012; Slykerman et al., 2015). The findings showed that having teen parents elevated the risk of offspring's depression (OR=1.46; 95 % CI, 1.22-1.74, k=9, N=93,850) and there was no evidence of heterogeneity between studies (I^2=32%, *P*=0.16).

Likewise, in the meta-analysis of six studies (Buizer-Voskamp et al., 2011; Pereira et al., 2012; Slykerman et al., 2015), we found that offspring who had parents 35 years of age and older also reported a higher risk of depression (OR=1.13; 95% CI, 1.07-1.20, k=6, N=73,208). There was no evidence of heterogeneity between studies (I^2=0%, *P*=0.60). No obvious publication bias was observed from the visual assessment of a funnel plot nor Egger/Begg test for both of the exposures.

A total of four qualitatively analyzed studies explored the relationship between having teen parents and the risk of depression in offspring, with 3 of 4 studies reported a positive association (Kiff et al., 2012; Slykerman et al., 2015; Tracy, Salo, Slopen, Udo, & Appleton, 2019). One study reported non-significant findings (Tearne et al., 2016).

Additionally, the only qualitatively analyzed study reported that parental age greater than 35 years increased the risk of depression for girls but not for boys (Tearne et al., 2016).

Physical health problems

There was no meta-analysis on the exposure of physical health problems due to the limited number of eligible studies.

Qualitatively analyzed findings (k=4) on maternal infections were inconsistent, including one study reporting an elevated risk of depression among offspring (Murphy et al., 2017), and non-significant findings in another study (Betts, Salom, Williams, Najman, & Alati, 2015). Two studies reported that maternal hypertensive disorder and diabetes were associated with an elevated risk of depression among offspring, respectively (Tuovinen et al., 2014; Yamasaki et al., 2019).

Chemical, and drug exposures

There is only qualitative synthesis available for the chemical and drug exposures. We did not perform a meta-analysis for these factors because of limitations in available studies and high

heterogeneity in the measurement of these exposures. A total of eight chemical or drug exposures have been studied to explore their effects on offspring's depression, including bisphenol A (BPA), fetal antiepileptic drug, selective serotonin reuptake inhibitors, antibiotics, organic pollutants, elemental carbon attributable to traffic (ECAT), marijuana exposure, and cocaine exposure. Prenatal BPA exposure was consistently found to be associated with an elevated risk of depressive symptoms and depression in boys (Harley et al., 2013; Perera et al., 2016). In terms of drugs, prenatal SSRI exposure (Malm et al., 2016), antibiotics use (Slykerman et al., 2017), prenatal or early life exposure to elemental carbon attributable to traffic (ECAT) (Yolton et al., 2019), and maternal marijuana exposure (Gray, Day, Leech, & Richardson, 2005; Sonon, Richardson, Cornelius, Kim, & Day, 2016), were associated with an elevated risk of depression. There were no statistical associations between offspring's depression and exposure to fetal antiepileptic drug (Cohen et al., 2013), persistent organic pollutants (Strom et al., 2014), and maternal cocaine use (Richardson, Goldschmidt, Larkby, & Day, 2013).

7.4.2 Psychological factors

Maternal stress

The meta-analysis of four studies found that: 1) maternal stress was associated with offspring's depression (OR=1.12; 95% CI, 1.04-1.22, k=4, N=2,582) (Phillips, Hammen, Brennan, Najman, & Bor, 2005; Pitzer, Jennen-Steinmetz, Esser, Schmidt, & Laucht, 2011; Slykerman et al., 2015). There was no evidence of heterogeneity between studies (I^2=28%, *P*=0.25); 2) prenatal maternal stress (two studies) was associated with the increased risk for depression with the pooled odds ratio of 1.09 (95%CI, 1.04-1.14, k=2, N=1,157) and there was no evidence of heterogeneity between studies (I^2=0%, *P*=0.91); and, 3) maternal postnatal stress (two studies), was similarly reported to elevate the risk of depression among offspring (OR=1.27; 95%CI, 1.07-1.51, k=2, N=1,425). No evidence of heterogeneity between studies was found (I^2=7%, *P*=0.30). Visual inspection of funnel plots, and Egger as well as Begg tests provided no evidence of obvious publication bias.

The qualitative analyzed findings (k=2) on the relationship between maternal stress and offspring's depression risk are mixed, with one study finding a positive relationship whereas another did not (Gray, Day, Leech, & Richardson, 2005; Murphy et al., 2017).

Maternal anxiety

The meta-analysis of two studies found that maternal anxiety increased the risk of depression (OR=1.09; 95% CI, 1.02-1.17, k=2, N=13,127) and there was no evidence of heterogeneity between studies (I^2=0%, *P*=0.84) (Betts, Salom, Williams, Najman, & Alati, 2015; Kingsbury et al., 2016). There was no evidence of obvious publication bias based on the visual assessment of a funnel plot and the Egger/Begg test.

Maternal prenatal depression

In the quantitative analyses of eight studies, maternal prenatal depression increased the risk of depression among offspring (OR=1.36; 95% CI 1.07-1.72, k=8, N=36,985) (Betts, Salom, Williams, Najman, & Alati, 2015; Herva et al., 2008; Kingsbury et al., 2016; Pawlby, Hay, Sharp, Waters, & O'Keane, 2009; Pearson et al., 2013; Plant, Pariante, Sharp, & Pawlby, 2015; Taka-Eilola Nee Riekki, Veijola, Murray, Koskela, & Maki, 2019; Zohsel et al., 2017). There was statistically significant heterogeneity (I^2=76%, *P*<0.01). The visual inspection of the funnel plot and Begg test did not indicate any evidence of publication bias. However, the result of Egger test found significant publication bias (*P*=0.032).

In the two qualitatively analyzed studies (k=2), maternal prenatal depression was significantly associated with depressive symptoms in one study (Gray, Day, Leech, & Richardson, 2005), but not in another (Raposa, Hammen, Brennan, & Najman, 2014).

Parental postnatal depression

Our meta-analysis of three studies found no statistically significant association between maternal postnatal depression and offspring's depression (OR=1.52; 95%CI, 0.92-2.50, k=3, N=10,379) (Barker, Copeland, Maughan, Jaffee, & Uher, 2012; Pearson et al., 2013; Plant, Pariante, Sharp, & Pawlby, 2015). There was no evidence of heterogeneity between studies (I^2=55%, *P*=0.11). Visual inspection of a funnel plot, and Egger as well as Begg test provided no evidence of obvious publication bias.

In the qualitative study, one study reported a null association between paternal postnatal depression and depression in their offspring (Ramchandani et al., 2008), which is consistent with other findings in this systematic review.

7.4.3 Sociological factors

Education

Our meta-analysis of nine studies found that low maternal education (<9 years of study) was associated with the elevated risk of depression (OR= 1.37; 95% CI, 1.19-1.57, k=9, N=41,768) (Betts, Salom, Williams, Najman, & Alati, 2015; Herva et al., 2008; Joinson, Kounali, & Lewis, 2017; Kingsbury et al., 2016; Pereira et al., 2012; Tracy, Salo, Slopen, Udo, & Appleton, 2019). There was no evidence of heterogeneity between studies (I^2=40%, *P*=0.10). No evidence of obvious publication bias was observed based on the visual assessment of a funnel plot and the Egger/Begg test.

SES

Six studies were included in the meta-analysis investigating the relationship between SES and depression in offspring (Herva et al., 2008; Joinson, Kounali, & Lewis, 2017; Kingsbury et al., 2016; Slykerman et al., 2015). The results suggested that low SES was associated with a higher risk of depression (OR=1.29; 95% CI, 1.10-1.52, k=6, N=28,710). There was statistically significant heterogeneity (I^2=60%, *P*=0.03). No obvious publication bias was found from visual inspection of a funnel plot, and Egger as well as Begg test.

Two other qualitatively analyzed studies (k=2) had mixed findings, with one study reported a significant relationship between low SES and an increased risk of depression and the other found no association (Butler, 2014; Power et al., 2007).

Having a single mother

The meta-analysis including two studies found that having a single mother did not increase a child's risk of depression (OR=1.20; 95% CI, 0.64-2.25, k=2, N=1,444) (Pereira et al., 2012). There was no evidence of heterogeneity between studies (I^2=41%, *P*=0.19). No obvious publication bias was observed from visual inspection of a funnel plot, and Egger as well as Begg test.

Parental smoking

There were 13 studies exploring the association between maternal smoking and depression risk in offspring (Betts, Salom, Williams, Najman, & Alati, 2015; Biederman, Martelon,

Woodworth, Spencer, & Faraone, 2017; Elmasry, Goodwin, Terry, & Tehranifar, 2014; Herva et al., 2008; Kingsbury et al., 2016; Levine, 2014; Meier et al., 2017; Menezes et al., 2013; Pereira et al., 2012; Taylor et al., 2017). Maternal smoking was associated with the increased risk of depression in the meta-analysis (OR=1.45; 95%CI: 1.28-1.63, k=13, N=823,532). There was statistically significant heterogeneity (I^2=69%, *P*<0.01).

Likewise, paternal smoking was also associated with the increased risk of depression in the meta-analysis of four studies (OR =1.28; 95%CI: 1.11-1.48, k=4, N=26,237) (Menezes et al., 2013; Taylor et al., 2017). There was no evidence of heterogeneity between studies (I^2=33%, *P*=0.21). Visual assessment of funnel plots, and Egger as well as Begg tests provided no evidence of obvious publication bias for maternal smoking exposure and paternal smoking exposure.

In contrast, the qualitatively analyzed studies (k=4) were largely unsupportive of a relationship between maternal smoking and offspring depression. One study reported significant associations across all trimesters ($r_{1st\ trimester}$=0.07, p <0.10; $r_{2nd\ trimester}$=0.07, p <0.10; $r_{3rd\ trimester}$=0.06, p <0.10) (Gray, Day, Leech, & Richardson, 2005), but three other studies found no association (Fergusson, Woodward, & Horwood, 1998; Leung, Leung, & Schooling, 2015; Liu et al., 2011).

Maternal drinking

The meta-analysis did not find a statistically significant association between mothers' drinking habits and depression among two studies (OR=1.09; 95%CI, 0.96-1.24, k=2, N=13,976) (Kingsbury et al., 2016; Levine, 2014), and there was no evidence of heterogeneity between studies (I^2=0%, *P*=0.47). No obvious publication bias was observed from visual assessment of a funnel plot nor Egger/Begg test.

Qualitatively analyzed studies (k=3) suggest a potential link between maternal drinking and offspring depression, with two qualitatively analyzed studies reporting that exposure to maternal drinking increased the risk of depression and depressive symptoms in offspring (Gray, Day, Leech, & Richardson, 2005; O'Connor & Kasari, 2000), however another study reported no association between maternal drinking (defined as >1 drink per day) and offspring depression (Betts, Salom, Williams, Najman, & Alati, 2015).

Famine

One Chinese study found that exposure to famine in-utero increased the risk of depression among offspring (Li et al., 2018).

For the meta-analysis

7.4.4 Publication bias

We used Begg and Egger tests to explore publication bias. Most of the studied variables did not have publication bias. The shapes of the funnel plots did not indicate any evidence of obvious asymmetry (see Appendix B, supporting information). Although Begg test found no significant publication bias for all the exposures, the results of Egger test suggested that two variables (birth order and maternal prenatal depression) had publication bias (Appendix A.6, supporting information). The trim and fill method was then used to recalculate the pooled results for these two variables. The adjusted pooled effect of birth order exhibited a similar trend (OR=0.99; 95 % CI 0.84-1.18) with three potential studies were filled. For prenatal depression, the adjusted pooled effect became non-significant (OR=1.21; 95 % CI 0.90-1.55) after two additional studies were added.

7.4.5 Sensitivity analysis

Each study was excluded at one time to test the stability of the pooled results. We found that findings of three variables (SGA, parental age greater than 35 years, and paternal smoking) changed when we removed one study at a time. The rest of the results remained unchanged (see Appendix C, supporting information). Subgroup analyses were also utilized for prenatal, perinatal and postnatal exposures. Subgroup analyses supported that the effects of prenatal, perinatal, and postnatal exposures on depression all remained significant (see Appendix D1 and D2, supporting information).

7.5 Discussion

This review provides the first comprehensive overview of prenatal, perinatal, and postnatal exposures related to offspring's depression. These early-life exposures cover biological, psychological and sociological characteristics that are pertinent for depression. A total of 28 prenatal, perinatal, and postnatal exposures had been reported on in the 64 prospective cohort

studies, we provide both quantitative and qualitative syntheses. For the quantitative synthesis, our meta-analysis identified that a total of 12 prenatal and perinatal/postnatal factors were associated with an increased risk of depression. These factors were low birth-weight, premature birth, small gestational age, having teen birth parents (<20 years old), having birth parents older than 35 years, maternal education, SES, maternal smoking, paternal smoking, maternal stress, maternal anxiety, and maternal prenatal depression. The qualitative syntheses identified a total of 23 factors (some overlapped with quantitative analysis) and were generally supportive of the relationships between some of the risk factors identified in the meta-analysis and offspring's depression. The qualitative analysis also provided additional information on other risk factors that may influence offspring's depression. Together these studies provided solid evidence for a developmental origin of depression hypothesis.

For the biological factors that are studied in this review, our findings are generally consistent with previous reviews on specific biological factors. For example, a previous systematic review of 14 studies reported a positive association between low birth-weight and depression, but not for premature birth and SGA (Loret de Mola, de França, Quevedo Lde, & Horta, 2014). They noted that conservative analytical approaches and publication bias might confound the relationships between premature birth, SGA and depression. Our findings on low birth-weight and depression are consistent with the literature. Another meta-analysis also reported a small but significant effect of low birth-weight on depression (Wojcik, Lee, Colman, Hardy, & Hotopf, 2013). These associations of birth outcome measures (low birth-weight, SGA, and premature birth) can be potentially explained by the glucocorticoid programming of the hypothalamic-pituitary-adrenal axis (HPAA) (Seckl & Meaney, 2004). Preterm and SGA births were linked with altered HPAA activity in an early acquired and persisting neurophysiological vulnerability (Patton, Coffey, Carlin, Olsson, & Morley, 2004), which then becomes involved in the development of depression due to an increased sensitivity to adversity (Räikkönen et al., 2008). Low birth-weight may be related to an elevated level of circulating glucocorticoids. Other hormonal systems like growth hormone - insulin-like growth factor system can synergize HPAA to regulate the fetal growth and brain development and may contribute to the pathogenesis of depression (Russo, Gluckman, Feldman, & Werther, 2005). These birth measures are also related to the activity of placental enzymes, which regulate maternal-fetal glucocorticoid and serotonin transfer. These enzymes are known as key modulators of fetal programming in adult mental disorders (Bonnin &

Levitt, 2011). Neurological damage caused by preterm births, such as cerebellar hemorrhagic injury, has been related to internalizing behavioral problems (Limperopoulos et al., 2007). We found no association between birth order and subsequent depression. The literature on birth order and depression is mixed (Carballo et al., 2013; Hardt, Weyer, Dragan, & Laubach, 2017). The relationship between birth order and depression needs to consider the presence of different family sizes, spacing between offspring, the underlying perceptions adolescents had of their older sibling, or support levels within the sibling dyads (Finan, Ohannessian, & Gordon, 2018).

There has been an increasing interest in the relationship between parental age and psychiatric disorders (Chudal et al., 2014; D'Onofrio et al., 2014). We found both younger parents (<20 years) and older parents (>35 years) were more likely to have depressed children. This is consistent with prior reviews on autism and psychotic disorder (Lopez-Castroman et al., 2010; Sandin et al., 2012). Younger parents are more likely to be challenged by unplanned parenting, stress, marital discord, lack of parenting experience, and economic circumstances, which in turn affect the trajectory of normal development of their children (Kessler et al., 2010). Older parents may be also unprepared for the relationship and life changes brought by the advent of a child.

Our review found that the studied psychosocial factors (maternal stress, anxiety, and prenatal depression) were related to depression in offspring. Depression, stress, and anxiety during pregnancy can trigger increased levels of maternal glucocorticoids, which have been considered as the key connection linking maternal adversity to the fetus (McGowan & Matthews, 2018; Stroud et al., 2016). Evidence has also shown that maternal glucocorticoids increase the risk of children psychopathology (Buss, Davis, et al., 2012). Also, depression is somewhat heritable (Agrawal, Jacobson, Gardner, Prescott, & Kendler, 2004). Maternal stress and prenatal anxiety may be associated with less optimal development trajectory for offspring (Pesonen, Räikkönen, Strandberg, & Järvenpää, 2005). Genetic susceptibilities combine with early life environmental adversities can posit a threat to a normal growth and development.

Empirical psychological and social studies have stressed the importance of the timing of exposures, that is, the period of development in which the infant may be more susceptible to the effects of these exposures (Michel & Tyler, 2005; Sanger, Iles, Andrew, & Ramchandani, 2015). For example, studies have shown that the activation of the maternal stress response especially

during the second and third trimesters, including glucocorticoid signaling and the immune response, could damage offspring's brain development (Wang, Kloth, & Badura, 2014). Maternal depression in the early postnatal months has been found to be closely related to child development (Rigato, Stets, Bonneville-Roussy, & Holmboe, 2020). Maternal depression may not have a single sensitive period but instead has a cascading influence and cumulative impact across the whole pregnancy period and into early childhood (Bagner, Pettit, Lewinsohn, & Seeley, 2010).

Although prenatal depression was seen as the strongest predictor of postnatal depression and may persist into the postnatal period (Heron et al., 2004), in this present review we also observed that maternal prenatal depression was an independent risk factor for offspring's depression and the contributing role of maternal postnatal depression in offspring's depression was diminished. Therefore, we could propose that the effect of prenatal depression in offspring's depression is independent from the effect of postnatal maternal depression in offspring's depression. Some supporting evidence has been found which demonstrated that there is generally no effect of change in maternal depression from the prenatal to postnatal period with the effect of postnatal depression limited to mothers with lower education (Pearson et al., 2013). These findings suggest that prenatal and postnatal maternal depression may affect offspring via different pathways. Prenatal depression might exert a detrimental effect on utero through biological mechanisms (Srinivasan, Pearson, Johnson, Lewis, & Lewis, 2020). A great deal of physiological changes of depressed mothers during pregnancy posit an adverse intrauterine environment which can alternate fetal developmental programming (Wen et al., 2017). In contrast, postnatal depression impacts offspring possibly through environmental factors such as parental discipline and social engagement which predict increased vulnerability to psychopathology in offspring (Murray, 2009). Depressed mothers have been found to be less sensitive in responding to and interacting with their children, and more likely to have unpredictable parenting styles (Milgrom, Westley, & Gemmill, 2004). Therefore, it is suggested there is no *direct* effect of postnatal depression on offspring, but its effect is possibly mediated through the pathways of the home environment (Pearson et al., 2013).

For sociological characteristics, lower SES and lower maternal education were associated with an increased risk in subsequent depression in children. Consistent with our findings, a

previous systematic review of 55 studies reported that children from socioeconomically disadvantaged families were at a higher risk of mental health problems. This meta-analysis also found that low parental education was the strongest risk factor for mental disorders among children and adolescents (Reiss, 2013). Children from low SES families, especially for those with parents of having lower levels of education, have limited access to the material, psychological and social resources that model important contributions to the development of positive mental health (McLaughlin et al., 2011).

Maternal smoking and paternal smoking were associated with an increased risk of offspring's depression in the current meta-analysis. One of the explanations is the "fetal programming hypothesis", which hypothesizes that the developmental origin of psychiatric disorders might be a result of prenatal exposure to adverse intrauterine conditions such as infection, pollution, smoking, and other substance use, altering the body's organs and systems (Buss, Entringer, & Wadhwa, 2012). Stroud and his colleague highlighted an important role of placental serotonin signaling in modulating prenatal programming of the fetal HPA axis by maternal adversity (Stroud et al., 2016). More importantly, we observed a slightly stronger maternal-offspring association compared to paternal-offspring association for smoking exposures during pregnancy. We anticipate that there is a causal intra-uterine effect between smoking and depression in offspring rather than a link due to genetic and shared environmental confounders. If the genetic and shared environmental confounders account for this association, the magnitude of the association between maternal and paternal smoking and depression in offspring would be similar (Langley, Heron, Smith & Thapar, 2012; Richmond, Al-Amin, Smith & Relton, 2014). The possible explanations to account for the differential effects of maternal and/or paternal smoking on the fetus are the unique maternal utero effects come through causal pathways affecting fetal programming (Taylor et al. 2017). Future studies (e. g. family-based sibling control studies), which partially account for genetic and environmental confounders, are needed to reveal the nature of the relationship between parental smoking and offspring's depression.

This review provides the first comprehensive overview of prenatal, perinatal, and postnatal factors associated with offspring's subsequent depression. This review used a comprehensive search and followed the recommended guidelines for reporting of results and methodological quality assessment to ensure the findings objectively summarize the literature on the DOHaD in

depression. This review only included prospective cohort studies, good quality studies, studies with large sample sizes, with relatively long and adequate follow-up periods, with reliable measurements of exposures and outcomes to deliver robust evidence on developmental origins of depression.

However, several potential limitations should be noted. First, 2 of the 16 factors in the meta-analysis (birth order and prenatal depression) have publication bias. The pooled estimate of prenatal depression became non-significant after taking two additional studies (as suggested by trim and fill tests) into account. Interpretation of the relationship between prenatal depression and offspring's depression warrants attention. Second, we observed high heterogeneity for a few exposures and the limited number of studies in some exposures precluded the detailed subgroup analyses. Also, even though 33 studies were included in the overall meta-analysis, for some exposures, there were generally fewer than six studies included, thus limiting the statistical power to detect heterogeneity and to assess potential effect modification resulting from study characteristics. Third, although we used subgroup analysis, sensitivity analysis, and meta-regression analysis to explore potential confounders involved in the relationship between prenatal, perinatal, and postnatal factors and depression, there are still other unknown and unobserved confounders that might also be involved in this relationship. Both measured and unmeasured familial confounders can influence the parent-child relationship. Kingsbury et al. (2016) reported that neither maternal drinking nor maternal prenatal depression was associated with offspring depression after controlling for sex, ethnicity, maternal teen status, maternal education, maternal history of depression, prenatal smoking or alcohol use, prenatal depression or anxiety, high maternal stress at 8 months postpartum, and maternal depression at 8 years postpartum. A Swedish study found that there was no clear evidence to support the association between maternal smoking during pregnancy and offspring depression in a sibling-controlled analysis with the same family context and genetic predisposition (Taylor et al., 2017), though there are limitations in using sibling controls. Fourth, meta-analysis cannot take all studied covariates from original studies into account because of variations in what were measured across the included studies. We used sensitivity and subgroup analysis instead to explore potential confounders that might be involved in the relationship between offspring's depression and prenatal, perinatal, and postnatal exposures.

7.6 Conclusion

This systematic review provides a robust and comprehensive overview of prenatal, perinatal, and postnatal factors associated with the risk of offspring's depression. Within the framework of the biopsychosocial model, a total of 12 prenatal and perinatal/postnatal factors among 28 studied factors were significantly associated with offspring's depression in the meta-analysis. The findings of the review highlight the need for clinical and public health interventions to focus on these identified risk factors. Large prospective cohort studies are warranted to investigate the combined effects of *co-existing* early life exposures.

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Appendix A. Search strategies

OVID

EMBASE, MEDLINE, PSYCHOINFO, HEALTHSTAR

from inception until Sep 1, 2019.

1. Depression OR Depressive OR Depressed OR SAD OR mood

2. “birth order” OR “parity” OR “multiparity” OR “family size” OR “sibship size” OR “number of siblings” OR “birth weight” OR “underweight” OR “maternal age” OR “mother age” OR “paternal age” OR “father age” OR “parent* age” OR “foetal fetal growth” OR “fetal growth” OR “early life” OR “early-life” OR “perinatal” OR “prenatal” OR “Alcohol” OR “Drinking” OR “Smoking” OR “Tabacco”)

AND (“longitudinal” OR “population-based” OR “cohort” OR “observational” OR “prospective” OR “registry” OR “register-based”).

Cohort studies:

3.cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.

1 and 2 and 3

4. offspring.ti,ab.

5. child*.ti,ab.

6. 4 and 5

1 and 2 and 3 and 6

Appendix A.1. MOOSE checklist for meta-analyses of observational studies.

Item No	Recommendation	Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
1	Problem definition	The literature has ample of evidence on the association between adverse in-utero and perinatal exposures and depression. However, there is no comprehensive overview of these adverse conditions.
2	Hypothesis statement	Adverse in-utero and perinatal exposures associated with risk of later-on depression.
3	Description of study outcome(s)	Offspring's depression
4	Type of exposure or intervention used	Prenatal, perinatal, and postnatal factors
5	Type of study designs used	Prospective cohort study
6	Study population	Children who have exposed during in-utero and perinatal period
Reporting of search strategy should include		
7	Qualifications of searchers (e.g., librarians and investigators)	The affiliations of the investigators are provided in the title page.
8	Search strategy, including time period included in the synthesis and key words	EMBASE, HealthStar, PsychoInfo, and Medline. Articles published from their inception to September 1, 2019. Also see Appendix S1 in the supplement.
9	Effort to include all available studies, including contact with authors	Grey literature was also searched to find potentially relevant studies.
10	Databases and registries searched	EMBASE, HealthStar, PsychoInfo, and Medline
11	Search software used, name and version, including special features used (e.g., explosion)	No special search software was used in this study.
12	Use of hand searching (e.g., reference lists of obtained articles)	Grey literature was searched for relevant articles.
13	List of citations located and those excluded, including justification	Inclusive and exclusive studies are outlined and detailed in the flow chart (Figure 7-1) and also in the Methods section.
14	Method of addressing articles published in languages other than English	We only included original empirical studies published in English.
15	Method of handling abstracts and unpublished studies	Abstracts and unpublished studies were excluded.
16	Description of any contact with authors	We contacted all the corresponding authors or first author to request additional data when needed.
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	The inclusion criteria and exclusion criteria are presented in the Methods section.
18	Rationale for the selection and coding of data (eg., sound clinical principles or convenience)	Data extracted and coded were relevant to the study characteristics, exposure, and outcome. Detailed information is listed in Methods section.
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	Data were extracted and analyzed by two reviewers independently.

20	Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	Because different studies controlled for different confounders, this meta-analysis did not take covariates from original studies into account to make included studies' results more comparable.
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	The quality of studies was assessed with Newcastle-Ottawa Scale.
22	Assessment of heterogeneity	Cochrane's Q statistic was used to test the heterogeneity.
23	Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Based on the results of heterogeneity tests, we used random-effects model to calculate pooled estimates, which are more conservative compared to fixed-effects model. Meta-regression analysis was conducted to identify possible explanations for the heterogeneity. Sensitivity analysis was also performed to explore the effects of the potential confounders.
24	Provision of appropriate tables and graphics	Two tables, three supplementary figures and four supplementary tables are provided. PRISMA flow-chart, and Forest Plots are also provided in the main text.
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures are appended in the main text. Figure 7-2.
26	Table giving descriptive information for each study included	Table A.2.
27	Results of sensitivity testing (e.g., subgroup analysis).	Sensitivity analyses were used to assess the influence of each individual study on the pooled effect size.
28	Indication of statistical uncertainty of findings	95% confidence intervals were provided with overall effect estimates.
Reporting of discussion should include		
29	Quantitative assessment of bias (e.g., publication bias)	Details on the publication bias are provided in the Result section.
30	Justification for exclusion (e.g., exclusion of non-English language citations)	Articles were excluded if did not provide information on available data for calculation or comparison group.
31	Assessment of quality of included studies	The NOS score of study quality for the included studies ranged from 4 to 9 with the median score of 6.9. This review includes most of good quality studies (details see Table A.5 in the Supplement).
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	We fully discussed the possible explanations and mechanisms of the results in the Discussion section.
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	We discussed the need for future research on this topic in the Discussion section.
34	Guidelines for future research	Future research should consider multiple prenatal, perinatal, and postnatal factors in a study to investigate their combined effect on children's depression. It will strengthen our ability to explain the DoHaD hypothesis of depression.
35	Disclosure of funding source	Disclosed in the relevant section.

Appendix A.2. Characteristics of included studies on in-utero, perinatal and postnatal exposures and depression risk.

	First Author	Year	Study site /Country	Sample size	Age of the offspring at enrollment	Year range at cohort/Follow up range	Year of offspring at outcome assessment	Offspring depression measures	Types of depression	In-utero and perinatal exposures	Covariates	Major findings	Quality assessment
USA													
Two identically designed, longitudinal case-control family studies*	Biederman	2017	USA	496	6 to 17 years	10- and 11-year follow-ups for the boys and girls	16-28 years old	Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID) was applied for participants younger than 18 years old, and Affective Disorder and Schizophrenia for Children was for those above18 years old.	Major depression	Maternal smoking	Adjusted for SES	Maternal smoking during pregnancy increased the risk for depression.	Fair quality
New York Women's Birth Cohort*	Elmasry	2014	USA	176	Birth cohort	1959-1963 to 2001	31-37 years old	The Center for Epidemiological Studies Depression Scale (CES-D)	Depressive symptoms	Maternal smoking	Univariate association	Maternal smoking was associated with depressive disorder in their offspring.	Fair quality
New York State Psychiatric Institute/Columbia University*	Nomura	2007	USA	244	NA	20-year follow up	6-17 years old	Schedule for Affective Disorders and Schizophrenia	Major depressive disorders	Birth weight	Univariate association	Low birth weight increased risk of MDD.	Good quality
National Longitudinal Survey	Levine	2014	USA	3,398	Birth cohort	1954-1964 to 2010	15-25 years old	The Center for Epidemiologic Studies Depression	Depression	Maternal depression, maternal	Univariate association	Maternal depression, maternal drinking	Fair quality

of Youth (NLSY) 1979 survey*								Scale Short Form (CES-D-SF)		drinking, maternal age, gestational age, and birth weight.		and maternal age were associated with depression in their offspring.	
National Collaborative Perinatal Project (NCPP)*	Nomura	2007	USA	1,525 mother-child dyads	Birth cohort	1960-1964 to 1992-1994	29 years old	General Health Questionnaire-28 (GHQ-28)	Depression	Birth weight, preterm birth	Univariate association	Birth weight and preterm birth were associated with the depression in the offspring.	Good quality
New York City cohort#	Perera	2016	USA	241	Birth cohort	1998-2006; 12-year follow up	10–12 years old	Children's Depression Rating Scale (CDRS)	Depression	Bisphenol A exposure	Univariate association	No association between maternal Bisphenol A exposure and offspring's depression has been found.	Fair quality
Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS)#	Harley	2013	USA	292	Birth cohort	1999-2000; 9-year old follow up	9 years old	Assessment System for Children 2 (BASC-2)	Depression	Bisphenol A exposure	Univariate association	Maternal Bisphenol A exposure was associated with the depression in the offspring among boys.	Good quality
Magee-Womens Hospital (MWH)#	Richardson	2013	USA	226	Birth cohort	1988-1992; 10-year follow up	10 years old	Children's Depression Inventory (CDI)	Depression	Cocaine exposure	Univariate association	No association between maternal cocaine exposure and offspring's depression has been found.	Good quality
Neurodevelopmental Effects of	Cohen	2013	USA and UK	195	Birth cohort	1999-2004; 6-year follow up	6 years old	Assessment System for Children (BASC)	Depression	Fetal antiepileptic drug,	NA	No association between fetal antiepileptic drug and offspring's	Good quality

Antiepileptic Drugs (NEAD) study#										gestational age		depression has been found.	
Child Health and Development Studies (CHDS)#	Murphy	2017	USA	1,711	Birth cohort	1959-1966 to 1976	15-17 years old	Adolescent depression symptoms scale	Depression	Maternal infection	Univariate association	Maternal infection in the second trimester was associated with the depression in the offspring.	Good quality
Maternal Health Practices and Child Development Project (MHPCD)#	Gray	2005	USA	1,360	Birth cohort	1982 and 1985; 10-year follow-up	10 years old	Children's Depression Inventory (CDI)	Depressive symptoms	Maternal Marijuana exposure, maternal depression, maternal anxiety, maternal smoking and maternal drinking.	Univariate association	Maternal Marijuana exposure, maternal stress, and maternal smoking were associated with depressive symptoms in their offspring. Maternal depression in 2nd and 3rd trimester were associated with depressive symptoms in their offspring. Maternal drinking in 1st and 2nd trimester were associated with depressive symptoms in their offspring.	Good quality

UCLA Amniocentesis Clinic#	O'Connor	2000	USA	41 mother-child dyads	I years old	NA	5-6 years old	Pictorial Depression Scale (PDS)	Depressive symptoms	Maternal drinking	Univariate association	Maternal drinking was associated with depressive symptoms in their offspring. No association between maternal drinking and depression has been found.	Fair quality
Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS)#	Yolton	2019	USA	344	Birth cohort	2001-2003; 12-year follow up	12 years old	Children's Depression Inventory-2 (CDI-2)	Depression	Prenatal/early life traffic-related air pollution exposure	Univariate association	Exposure to ECAT was not significantly associated with parent-reported depression.	Fair quality
Seattle Social Development Project (SSDP)#	Kiff	2012	USA	808	10 years	1985 to 2002; 17-year follow up	21, 24, 27 years old	Diagnostic Interview Schedule (DIS)	Major depressive episode	Maternal age	Univariate association	Children with adolescent mothers had higher risk of depression.	Fair quality
Collaborative Perinatal Project (CPP)#	Liu	2011	USA	611	Birth cohort	1959-1966 to 2005-2007	38-48 years old	The Center for Epidemiological Studies Depression Scale (CES-D)	Depression	Maternal smoking	Adjusted for offspring age, gender, education and current smoking status	No association between maternal smoking and offspring's depression has been found.	Good quality
Panel Study of Income Dynamics (PSID)#	Butler	2014	USA	1,056	Birth cohort	1968 to 2007	12-17 years old	Children's Depression Inventory (CDI) and interviews with the primary caregivers	Depressive symptoms	SES	Univariate association	No association between SES and offspring's depression has been found.	Fair quality

Maternal Health Practices and Child Development Study (MHPCD)#	Sonon	2016	USA	590 mother-child pairs	Birth cohort	1982-1985; 22-year follow up	22 years old	Diagnostic Interview Schedule-IV (DIS-IV)	Depressive symptoms	Maternal Marijuana exposure	Univariate association	Maternal Marijuana exposure was associated with depressive symptoms in their offspring.	Good quality
The Johns Hopkins Collaborative Perinatal Study (JHCPS)*	Fan	2001	USA	1,824	Birth cohort	1960-1964 to 1992-1994	27-33 years old	General Health Questionnaire (GHQ)	Depression	Gestational age	Adjusted for mother's age, parity, and education at child's birth, and child's race, sex, household income and education as an adult	No association between small for gestational age and offspring's depression has been found.	Good quality
UK													
1958 British birth-cohort*	Geoffroy	2018	UK	8,905	Birth cohort	1958 to 2002-2004	45 years old	ICD-10 diagnoses	Depressive episode	Birth weight, parity, and maternal age	Adjusted for sex	No association between birth weight, parity, maternal age and depressive episode has been found.	Good quality
Two general practices*	Pawlby	2009	UK	127 mother-child dyads	Birth cohort	17-year follow up	16 years old	Child and Adolescent Psychiatric Assessment	Depressive episode	Maternal prenatal depression	Univariate association	Maternal prenatal depression increased the risk of offspring's depression.	Good quality

1970 British Cohort Study*	Gale	2004	UK	At age16 years: 5,187; At age 26 years: 8,292	Birth cohort	1970 to 1996; 26-year follow up	16 years and 26 years old	12-item General Health Questionnaire at 16 years old and Rutter's 24-item Malaise Inventory at 26 years old	Depression	Birth weight	Univariate association	Birth weight was associated with depression during 16 to 26 years old and 26 years old.	Good quality
ALSPAC#	Ramchandani	2008	UK	4,792	Birth cohort	1991-1992; 7-year follow up	7 years (91 months) old	Structured psychiatric questionnaire (the Development and Well-Being Assessment [DAWBA])	Depressive disorder	Paternal postnatal depression	Univariate association	Depression in fathers in the postnatal period was significantly associated with depressive disorder in their children.	Good quality
ALSPAC*	Joinson	2017	UK	9,193	Birth cohort	1991-1992; 20-year follow up	10–12, 12–16, 16–20 years old	The Short Mood and Feelings Questionnaire (SMFQ) at 10-20 years and Clinical Interview Schedule-Revised (CIS-R) at 18 years	Depressive Symptoms and depression	Maternal education, SES	Univariate association	Maternal education and SES were associated with offspring's depression at less than 12 years and above 16 years.	Good quality
Perinatal Mortality Survey (PMS)#	Power	2007	UK	9,377	Birth cohort	1958 to 2002-2004	45 years old	Revised Clinical Interview Schedule	Depressive episode	SES	Adjusted for sex	Social class in childhood was associated with depressive symptoms.	Good quality
ALSPAC*	Pearson	2013	UK	2,847	Birth cohort	1991-1992; 18-year follow up	18 years old	Clinical Interview Schedule-Revised (CIS-R)	Depression	Maternal prenatal depression and maternal postnatal depression	Univariate association	Maternal prenatal depression and postnatal depression were associated with	Fair quality

												depression in their offspring.	
the EPICure cohort#	Johnson	2019	UK	257	Birth cohort	1995; 10-year follow up	19 years old	Clinical Interview Schedule-Revised (CIS-R)	Depression	Extreme Premature children	Univariate association	No association between preterm and depression has been found.	Fair quality
ALSPAC*	Kingsbury	2016	UK	10,569	Birth cohort	1991-1992; 19-year follow up	17-18 years old	Clinical Interview Schedule-Revised (CIS-R)	Major depression	Maternal education, SES, maternal age, maternal smoking, maternal drinking, maternal depression and maternal anxiety	Fully adjusted	Maternal age and maternal smoking were associated with depression in their offspring.	Fair quality
ALSPAC*	Barker	2012	UK	7,429 mother-child dyads	Birth cohort	1991-1992; 8-year follow up	7.5 years old	Development and Well-Being Assessment (DAWBA)	Depression	Maternal prenatal depression	Univariate association	Maternal depression was associated with depression in their offspring.	Fair quality
ALSPAC*#	Tracy	2019	UK	9,665	Birth cohort	1991-1992; 18-year follow up	18 years old	Clinical Interview Schedule-Revised (CIS-R)	Depressive symptoms	Parental education, maternal age	child sex, parental education, maternal mental health during pregnancy, and maternal age at birth	No association between parental education as well as maternal age and depression has been found.	Fair quality

ALSPAC*	Taylor	2017	UK	2,869	Birth cohort	1991-1992; 17-year follow up	17 years old	Clinical Interview Schedule-Revised (CIS-R)	Depression	Parental smoking	Univariate association	Maternal depression was associated with depression in their offspring.	Good quality
SLCDS*	Plant	2015	UK	103	Birth cohort	1986; 25-year follow up	25 years old	DSM-IV	Major depressive disorders	Maternal depression	Univariate association	Maternal depression was associated with depression in their offspring.	Good quality
Australia													
Two overlapping cohorts born at the Royal Women's Hospital#	Westrupp	2011	Australia	149	Birth cohort	1977-1982 to 2011	24-29 years old	The Symptoms Checklist (SCL-90-R)	Depression	Birth weight	Univariate association	Very low birth weight adults are at greater risk of depression.	Fair quality
Mater University Study of Pregnancy (MUSP)*	Phillips	2005	Australia	816	Birth cohort	1981-1984; 15-year follow up	15 years old	The Schedule for Affective Disorders and Schizophrenia in School-Aged Children (K-SADS-E)	Depressive disorder	Maternal prenatal stress and maternal postnatal stress	Univariate association	Maternal postnatal stress was associated with depressive disorder in their offspring.	Fair quality
Western Australian Pregnancy Cohort (Raine) Study#	Tearne	2016	Australia	2,868	Birth cohort	1989-1991 to 2010-2012	20 years old	Depression Anxiety Stress Scales (DASS-21)	Depression	Maternal age, paternal age.	Adjusted for age of other parent	Maternal age (>35 years old) was associated with the depression in their offspring.	Good quality
Mater Misericordiae Mothers' Hospital-University of Queensland Study of Pregnancy#	Raposa	2014	Australia	815 mother-child pairs	Birth cohort	1981-1984; 20-year follow up	15 years, 22-25 years old	Beck Depression Inventory (BDI)	Depressive symptoms	Maternal depression	Univariate association	No association between maternal depression and depression has been found.	Fair quality

Mater University Study of Pregnancy (MUSP)*#	Betts	2015	Australia	2,558	Birth cohort	1981-1984 to 2002-2005; 21-year follow up	21 years old	Composite International Diagnostic Interview (CIDI-Auto) version 2.1	Major depressive disorders	Maternal infection, antenatal anxiety, antenatal depression, birth weight, parity, maternal smoking, maternal drinking.	Univariate association	Maternal anxiety during pregnancy increased the risk for offspring's depression. But a null association between prenatal infection and depression was found.	Good quality
Mater University Study of Pregnancy (MUSP)*	Alati	2007	Australia	3,493	Birth cohort	1981-1984 to 2002-2005; 21-year follow up	21 years old	The Center for Epidemiologic Studies Depression (CES-D) Scale	Depressive symptoms	Birth weight	Univariate association	No association between birth weight and depressive symptoms has been found.	Good quality
Canada													
National Longitudinal Study of Children and Youth (NLSCY)*	Colman	2012	Canada	3,732	0 to 11 years	1994-1995 to 2006-2007	12-15 years old	7 items derived from the Child Behavior Checklist	Depression	Gestational age	Univariate association	Being born for small for GA but not large for GA was associated with an increased risk of depression in adolescence.	Fair quality
NLSCY#	Van Lieshout	2010	Canada	1,230	Birth cohort	1986-2000	4-7 years and 10-14 years old	Behavior Problems Index	Depressive symptoms	Birth weight, gestational age	NA	Birth weight and gestational age were associated with the depression in the offspring both in the childhood and adolescence.	Good quality

Extremely low birth weight (ELBW) Cohort in Ontario#	Saigal	2003	Canada	263	Birth cohort	1977-1982; 16-year follow up	12-16 years old	Ontario Child Health Study-Revised (OCHS-R)	Depression	Extreme Low birth weight	Univariate association	No association between birth weight and offspring's depression has been found.	Fair quality
Finland													
Two northernmost provinces of Finland*	Herva	2008	Finland	8,339	Birth cohort	1966 to 1997-1998	31 years old	Hopkins Symptom Checklist-25 questionnaire (HSCL-25)	Depression	Maternal depression, birth weight, gestational age, parity, maternal age, social class, maternal education, maternal smoking.	Univariate association	All the in-utero and perinatal exposures are associated with offspring's depression except for the birth weight.	Good quality
Helsinki Birth Cohort#	Tuovinen	2014	Finland	778	Birth cohort	1934-1944 to 2009-2010	69.3±3.1 years old	Diagnostic and Statistical Manual of Mental Disorders (DSM - IV)	Depressive disorder	Maternal hypertensive disorders	Sex, age, gestational age, weight, head circumference, placental weight, occupational status, parity, mother's age, BMI, breastfeeding,	Maternal hypertensive disorders was associated with depression in their offspring.	Good quality

Northern Finland 1966 Birth Cohort (NFBC 1966)*	Taka-Eilola	2019	Finland	12,058	Birth cohort	1966 to 2009; 43-year follow up	16-45 years old	ICD-8 2960, 2980, 3004, 709; ICD-9 2961, 2968, 3004, 2969; ICD-10 F32-F33	Depression	Maternal depression	Univariate association	Maternal depression was associated with depression in their offspring.	Good quality
Finnish National register data#	Malm	2016	Finland	64,754	Birth cohort	1996-2010; 16-year follow up	14 years old	ICD-10 F32–F39	Depression	Selective Serotonin Reuptake Inhibitors	NA	Maternal Selective Serotonin Reuptake Inhibitors exposure was associated with the depression in the offspring.	Good quality
France													
Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale (E3N)#	Perquier	2014	France	41,144	Birth cohort	1925-1950 to 2005	63.9±6.2 years old	The Center for Epidemiologic Studies Depression Scale (CES-D)	Depressive symptoms	Birth weight, birth length	Univariate association	Low birth weights were associated with risk of depression	Good quality
China													
China Health and Retirement Longitudinal Study (CHARLS)#	Li	2018	China	13,005	≥45 years	1959-1961 to 2014-2015	61.5±8.5 years old	The Center for Epidemiological Studies Depression Scale (CES-D)	Depressive Symptoms	Famine	Age, gender, education and childhood location (rural/urban)	Severe famine during fetal was associated with depressive symptoms.	Good quality
National Health Insurance Research Database*	Chiu	2019	Taibei, China	107,381	Birth cohort	2000-2010	9.72; 9.88 years old	ICD-9-CM codes 296.2, 296.3, 300.4, and 311	Depression	Premature children	Univariate association	Preterm children had higher risk of depression than	Good quality

												children born full-term.	
'Children of 1997' birth cohort#	Wang	2015	Hong Kong, China	6,292	Birth cohort	1997-2012	12-15 years old	Patient Health Questionnaire-9 (PHQ-9)	Depressive symptoms	Gestational age	adjusted for sex, age and survey mode	No association between gestational age and offspring's depression has been found.	Good quality
'Children of 1997' birth cohort#	Leung	2015	Hong Kong, China	8,327	Birth cohort	1997-2012	12-15 years old	Patient Health Questionnaire-9 (PHQ-9)	Depressive symptoms	Prenatal smoking and/or postnatal smoking	Adjusted for sex, age of assessment and survey mode (PHQ-9 score)	No association between maternal prenatal smoking and/or postnatal smoking and offspring depression has been found.	Good quality
Denmark													
Six Danish population-based registries*	Meier	2017	Denmark	770,315 siblings nested within 331,396 families	5 years	1991-2007 to 2012	5- years old	ICD-10 codes: F32.00-F33.99 F34.10-F34.90 F38.00-F39.99)	Depression	Maternal smoking	adjusted for calendar year of birth and gender	Maternal smoking was associated with depression in their offspring.	Fair quality
Danish Fetal Origins 1988 (DaFO88) Cohort#	Strom	2014	Denmark	876 mother–child pairs	Birth cohort	1988-1989 to 2011	22-23 years old	At least one prescription for antidepressant medication was registered as an in- or outpatient with a diagnosis of depression (ICD8: 2960, 2962, 2968, 2969, 2980, 3004,	Depression	Organic pollutants	Univariate association	No association for maternal levels of any of the measured pollutants with offspring depression was found.	Good quality

								3011, ICD10: F320–F329)					
Germany													
Mannheim Study of Children at Risk*	Zohsel	2017	Germany	384	Birth cohort	1986-1988; 25-year follow up	25 years old	SCID-I	Depressive disorder	Prenatal maternal depressed mood	adjusted for sex , psychosocial adversity	No association between maternal depressed mood and depressive disorder has been found.	Good quality
Mannheim Study of Children at Risk*	Pitzer	2011	Germany	341	Birth cohort	1986-1988; 11-year follow up	11 years old	The Child Depression Inventory (CDI)	Depressive symptoms	Maternal stress	Univariate association	Maternal distress was associated with depression in their offspring.	Fair quality
Brazil													
A birth cohort study in Pelotas, Brazil*	Menezes	2013	Brazil	5,249	Birth cohort	1993; 18-year follow up	18 years old	Mini-International Neuropsychiatric Interview (MINI)	Depression	Maternal smoking	Univariate association	Maternal smoking and paternal smoking were associated with depression in their offspring.	Fair quality
Two birth cohorts in Brazil*	Pereira	2012	Brazil	1,444	Birth cohort	1994-2004 to 2005; 1997-1998 to 2005-2006	7-9, 10-11 years old	The Childhood Depression Inventory (CDI)	Depressive symptoms	Birth weight, preterm birth, maternal age, paternal age, single mother, maternal education, gestational age, parity, maternal smoking.	Univariate association	Birth weight was associated with the depression in the offspring at 10 to 11 years old.	Fair quality

In 1982, the maternity hospitals in Pelotas, a southern Brazilian city*#	Loret de Mola	2015	Brazil	5,914	Birth cohort	1982 to 2012-2013	30 years old	Mini International Neuropsychiatric Interview (MINI) 5.0	Major depression	Birth weight, gestational age	Univariate association	Birth weight was associated with the depression in the offspring.	Fair quality
Pelotas 1982 Birth Cohort*	Taylor	2017	Brazil	2,626	Birth cohort	1982 to 2012-2013	30 years old	Mini-International Neuropsychiatric Interview (MINI) 5.0	Depression	Parental smoking	Univariate association	Maternal depression was associated with depression in their offspring.	Good quality
Japan													
Tokyo Early Adolescence Survey (EAS)#	Yamasaki	2019	Japan	4,478	Birth cohort	2002-2004 to 2012-2015	10 years old	Short Mood and Feelings Questionnaire (SMFQ)	Depressive symptoms	Maternal diabetes	Univariate association	No association between maternal diabetes and depressive symptoms has been found.	Good quality
New Zealand													
Auckland Birthweight Collaborative Study (ABC)*#	Slykerman	2015	New Zealand	609	Birth cohort	1995-1997; 11-year follow up	11 years old	The Centre for Epidemiological Studies Depression Scale (CES-D)	Depression	Gestational age, SES, maternal age and maternal stress	Univariate association	Gestational age, maternal age and maternal stress were associated with depression in their offspring.	Fair quality
Auckland Birthweight Collaborative Study (ABC study)#	Slykerman	2017	New Zealand	871 mother-child dyads	Birth cohort	1995-1997; 11-year follow up	11 years old	The Centre for Epidemiological Studies Depression Scale (CES-D)	Depression	Antibiotics in the first year of life	Univariate association	Antibiotics use in the first year of life was associated with the depression.	Good quality
Christchurch Health and Development Study#	Fergusson	1998	New Zealand	1,265	Birth cohort	1977; 18-year follow up	16-18 years old	DSM-IV	Major depressive disorders	Maternal smoking	Univariate association	No association between maternal smoking and	Good quality

												offspring's depression has been found.	
Netherlands													
Psychiatric Case Registry Middle Netherlands (PCRMN)*	Buizer-Voskamp	2011	Netherlands	71,155	Birth cohort	NA	36.66 ±9.69; 36.74 ±9.66 years old	DSM-IV code of 296.20 – 296.26, 296.30 – 296.36 or 311.00	Major depressive disorders	Paternal age	Univariate association	Paternal age was associated with offspring's depression.	Fair quality
Norway													
HUNT*	Taylor	2017	Norway	15,493	Above 20 years	1984-1986 to 2006-2008	32 years old	Hospital Anxiety and Depression Scale (HADS)	Depression	Parental smoking	Univariate association	Paternal depression was associated with depression in their offspring.	Good quality
Israeli													
Israeli cohort#	Levy-Shiff	1994	Israeli	180	6-7 years	NA	13-14 years old	The Child Depression Inventory (CDI)	Depression	Birth weight, gestational age	Univariate association	Birth weight and gestational age were associated with the depression in in offspring.	Poor quality

Note: * indicated a quantitative study; # indicated a qualitative study.

Appendix A.3. A summary of the Newcastle-Ottawa Scale (NOS) quality assessment for selected studies.

Assessment item	Study																						
	Taylor 2017	Taylor 2017	Taylor 2017	Biederman 2017	Geoffroy 2018	Pawlby 2009	Betts 2015	Herva 2008	Gale 2004	Colman 2012	Phillips 2005	Elmasry 2014	Meier 2017	Joinson 2017	Zohsel 2017	Menezes 2013	Tuovinen 2014	Nomura 2007	Levine 2014	Pearson 2013	Yamasaki 2019	Slykerman 2014
Selection																							
1. Representativeness of the intervention cohort																							
a) truly representative of the average, elderly, community-dwelling resident	1	1	1	0	1	0	1	1	1	1	0	1	1	1	0	1	0	0	1	0	0	0	
b) somewhat representative of the average, elderly, community-dwelling resident	0	0	0	1	0	1	0	0	0	0	1	0	0	0	1	0	1	1	0	1	1	0	
c) selected group of patients, e.g. only certain socio-economic groups/areas	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
d) no description of the derivation of the cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2. Selection of the non-intervention cohort																							
a) drawn from the same community as the intervention cohort	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
b) drawn from a different source	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
c) no description of the derivation of the non-intervention cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3. Ascertainment of intervention （exposure）																							
a) secure record (e.g. health care record)	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	
b) structured interview	0	0	1	1	0	1	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	1	
c) written self report	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
d) other / no description	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

4. Demonstration that outcome of interest was not present at start of study																							
a) yes	1	1	1	0	1	1	1	1	1	0	0	1	0	1	1	1	1	1	1	1	0	1	
b) no	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Comparability																							
1. Comparability of cohorts on the basis of the design or analysis																							
a) study controls for age, sex, marital status	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	
b) study controls for any additional factors (e.g. socio-economic status, education)	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Outcome																							
1. Assessment of outcome																							
a) independent blind assessment	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	0	
b) record linkage	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	
c) self report	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
d) other / no description	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2. Was follow up long enough for outcomes to occur																							
a) yes, if median duration of follow-up >= 6 month	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
b) no, if median duration of follow-up < 6 months	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3. Adequacy of follow up of cohorts																							
a) complete follow up: all subjects accounted for	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, or description of those lost suggesting no different from those followed	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	0	0	1	0	0	
c) follow up rate < 80% (select an adequate %) and no description of those lost	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

d) no statement	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Overall	7	8	8	6	7	7	8	7	7	6	5	6	6	7	8	7	7	7	6	6	8	5	

Assessment item	**Study**																						
	Buizer Voskamp	Pereira 2012	Pitzer 2011	Plant 2015	Chiu 2010	Taka-Eilola 2010	Kingsbury 2016	Mola 2015	Barker 2012	Nomura 2007	Tracy 2010	Alati 2007	Fan 2001	Westrupp 2011	Perquier 2014	Levy-Shiff 1994	Van [illegible]	Saigal 2002	Cohen 2012	Wang 2015	Johnson 2010	O Connor 2000	
Selection																							
1. Representativeness of the intervention cohort																							
a) truly representative of the average, elderly, community-dwelling resident	0	1	0	1	0	1	1	1	1	0	1	0	0	0	1	0	1	0	0	0	0	0	
b) somewhat representative of the average, elderly, community-dwelling resident	0	0	1	0	0	0	0	0	0	1	0	1	1	0	0	0	0	0	0	1	0	0	
c) selected group of patients, e.g. only certain socio-economic groups/areas	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
d) no description of the derivation of the cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2. Selection of the non-intervention cohort																							
a) drawn from the same community as the intervention cohort	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	
b) drawn from a different source	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
c) no description of the derivation of the non-intervention cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3. Ascertainment of intervention （exposure）																							
a) secure record (e.g. health care record)	1	1	0	0	1	0	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	
b) structured interview	0	0	1	1	0	1	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	

c) written self report	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d) other / no description	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4. Demonstration that outcome of interest was not present at start of study																							
a) yes	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
b) no	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Comparability																							
1. Comparability of cohorts on the basis of the design or analysis																							
a) study controls for age, sex, marital status	0	0	0	0	0	0	0	0	0	1	0	1	1	0	0	0	1	0	0	1	1	0	
b) study controls for any additional factors (e.g. socio-economic status, education)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	0	1	1	1	1	
Outcome																							
1. Assessment of outcome																							
a) independent blind assessment	0	0	0	1	0	0	0	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	
b) record linkage	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
c) self report	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
d) other / no description	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2. Was follow up long enough for outcomes to occur																							
a) yes, if median duration of follow-up >= 6 month	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
b) no, if median duration of follow-up < 6 months	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3. Adequacy of follow up of cohorts																							
a) complete follow up: all subjects accounted for	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	

b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, or description of those lost suggesting no different from those followed	0	0	0	0	0	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	0	0
c) follow up rate < 80% (select an adequate %) and no description of those lost	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d) no statement	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Overall	6	6	6	7	7	8	6	8	6	9	6	9	8	6	7	3	8	5	7	8	6	5

Assessment item	**Study**																					
	Gray 2005	Murphy 2017	Kiff 2012	Tearne 2016	Ramchandani	Raposa 2014	Leung 2015	Liu 2011	Fergusson 1999	Power 2007	Butler 2014	Li 2019	Perera 2016	Harley 2012	Richardson 2012	Malm 2016	Sonon 2016	Slykerman 2017	Yolton 2010	Strom 2014		
Selection																						
1. Representativeness of the intervention cohort																						
a) truly representative of the average, elderly, community-dwelling resident	0	1	0	0	1	0	0	1	0	1	0	0	0	0	0	0	0	1	0	0		
b) somewhat representative of the average, elderly, community-dwelling resident	1	0	1	1	0	1	1	0	1	0	1	1	0	0	1	1	1	0	0	1		
c) selected group of patients, e.g. only certain socio-economic groups/areas	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
d) no description of the derivation of the cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
2. Selection of the non-intervention cohort																						
a) drawn from the same community as the intervention cohort	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
b) drawn from a different source	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
c) no description of the derivation of the non-intervention cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		

3. Ascertainment of intervention （exposure）																							
a) secure record (e.g. health care record)	0	0	0	1	0	0	0	0	0	0	0	1	1	1	0	1	0	0	1	0		
b) structured interview	1	1	0	0	0	0	1	1	0	1	1	0	0	0	1	0	1	1	0	1		
c) written self report	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
d) other / no description	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
4. Demonstration that outcome of interest was not present at start of study																							
a) yes	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1		
b) no	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Comparability																							
1. Comparability of cohorts on the basis of the design or analysis																							
a) study controls for age, sex, marital status	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0		
b) study controls for any additional factors (e.g. socio-economic status, education)	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1		
Outcome																							
1. Assessment of outcome																							
a) independent blind assessment	0	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1		
b) record linkage	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
c) self report	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
d) other / no description	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
2. Was follow up long enough for outcomes to occur																							
a) yes, if median duration of follow-up >= 6 month	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		

b) no, if median duration of follow-up < 6 months	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
3. Adequacy of follow up of cohorts																						
a) complete follow up: all subjects accounted for	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0		
b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, or description of those lost suggesting no different from those followed	1	1	0	0	1	1	1	0	1	0	0	1	0	1	1	1	1	1	1	1		
c) follow up rate < 80% (select an adequate %) and no description of those lost	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
d) no statement	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Overall	7	7	5	7	7	6	8	7	7	7	6	9	6	7	8	8	8	7	6	8		

Appendix A.4. Meta-regression analyses.

Risk factor	Number of study estimates	Meta regression of onset age of depression			
		Coeff.	95%CI	I^2	P value
Low birth-weight	10	0.69	0.31, 1.53	63%	0.320
Maternal education	9	1.14	0.78, 1.68	49%	0.437
Socioeconomic status	6	0.74	0.41, 1.34	54%	0.235
Gestational age	7	1.35	0.57, 3.19	54%	0.413
Small gestational age	3	NA	NA	NA	NA
Parity	5	0.70	0.36, 1.35	0%	0.180
Teen parents	9	1.01	0.58, 1.76	40%	0.977
Parents' age >35	6	0.84	0.50, 1.42	0%	0.417
Single mother	2	NA	NA	NA	NA
Maternal drinking	2	NA	NA	NA	NA
Maternal smoking	13	1.09	0.76, 1.57	70%	0.590
Paternal smoking	4	1.29	1.03, 1.62	34%	**0.038**
Maternal prenatal depression	8	3.72	0.70, 1.74	72%	0.103
Maternal postnatal depression	3	NA	NA	NA	NA
Maternal stress	4	1.11	1.00, 1.22	29%	**0.045**
Maternal anxiety	2	NA	NA	NA	NA

Appendix A.5. Detailed findings from the qualitative studies.

	Study Quality	Exposure Categorization	Statistical Indicator	Effect Size	Covariates
Low birth-weight					
Westrupp (2011)	Fair	<1500 g/ ≥2500g	OR	OR=1.75 (95%CI: 0.65, 4.65)	Univariate association
Betts (2015)	Good	Low birth-weight Z score	OR	OR=0.91(95%CI: 0.82,1.01)	Univariate association
Perquier (2014)	Good	<2500 g/≥2500g-4000g	OR	OR=1.15 (95%CI: 0.96, 1.36)	Univariate association
Loret de Mola (2015)	Fair	<2500 g/≥3500g	PR	PR=1.55 (95%CI: 1.02, 2.37)	Univariate association
Levy-Shiff (1994)	Poor	<1500 g/≥2500g	β	β=-0.34, p<0.01	Univariate association
Van Lieshout (2010)	Good	<2500 g/≥2500g	t	$t_{adolescence}$=4.00, p<0.01; $t_{children}$=0.70, p<0.47	Univariate association
Saigal (2003)	Fair	<1000 g/ ≥2500g	r	r=0.26, p>0.05	Univariate association
Gestational age					
Johnson (2019)	Fair	<26 weeks /≥26 weeks	OR	OR=2.91 (95%CI: 0.81, 10.44)	Univariate association
Levy-Shiff (1994)	Poor	<35 weeks /≥35 weeks	r	r=0.82, p<0.01	Univariate association
Wang (2015)	Good	<37 weeks /≥37 weeks	β	β=0.20, p>0.05	Univariate association
Van Lieshout (2010)	Good	Gestational age	F	F=0.44, p=0.51	Univariate association
Small gestational age					
Van Lieshout (2010)	Good	<10th percentile for gestational age/≥10th percentile	t	$t_{adolescence}$ = 2.70, p<0.01; $t_{children}$ = 0.15, p>0.05	Univariate association
Birth length					
Perquier (2014)	Good	<48 cm/48-51 cm	OR	OR=1.11 (95%CI: 0.95, 1.30)	Univariate association
Teen parents					
Slykerman (2014)	Fair	<24 years/25-34 years	OR	OR=5.80 (95%CI: 2.70, 12.70)	Univariate association
Tearne (2016)	Good	<20 years/25-29 years	RR	$RR_{maternal\ age\text{-}female\ offspring}$=1.17 (95%CI: 0.86, 1.58); $RR_{paternal\ age\text{-}male\ offspring}$=1.15 (95%CI: 0.74, 1.78); $RR_{maternal\ age\text{-}male\ offspring}$=0.68 (95%CI: 0.45, 1.04); $RR_{paternal\ age\text{-}female\ offspring}$=0.71 (95%CI: 0.38, 1.32)	Adjusted for age of other parent
Tracy (2019)	Fair	15-24 years/35-44 years	OR	OR=1.64 (95%CI: 1.12, 2.38)	Univariate association
Kiff (2012)	Fair	<20 years/≥20 years	r	r=0.12, p < 0.05	Univariate association
Parents' age >35 years					

Tearne (2016)	Good	>35 years/25-29 years	RR	RR $_{\text{maternal age-female offspring}}$=1.34 (95%CI: 1.01, 1.77); RR $_{\text{paternal age-male offspring}}$=0.91 (95%CI: 0.65, 1.29)	Adjusted for age of other parent
Socioeconomic status					
Power (2007)	Good	Per increase in social class	OR	OR=1.14 (95%CI: 1.07, 1.21)	Adjusted for sex
Butler (2014)	Fair	Poverty persistence	r	r=0.32, p>0.05	Univariate association
Maternal smoking					
Leung (2015)	Good	Smoking during pregnancy and/or postnatally	β	β=0.79, p<0.05	Univariate association
Liu (2011)	Good	One pack or more cigarettes per day	β	β=-1.7, p>0.05	Univariate association
Fergusson (1998)	Good	Smoking during pregnancy	β	β=0.13, p>0.05	Univariate association
Gray (2005)	Good	Tobacco use during 1st trimester, 2nd trimester and 3rd trimester	r	$r_{\text{1st trimester}}$=0.07, p <0.10; $r_{\text{2nd trimester}}$=0.07, p <0.10; $r_{\text{3rd trimester}}$=0.06, p <0.10	Univariate association
Maternal drinking					
Betts (2015)	Good	>1 drinks/day/Non-drinker	OR	OR=1.42 (95%CI: 0.59, 3.37)	Univariate association
O'Connor (2000)	Fair	Average drinks per drinking occasion	r	r=0.37, p<0.02	Univariate association
Gray (2005)	Good	Three or more drinks per week	r	$r_{\text{1st trimester}}$=0.06, p <0.10; $r_{\text{2nd trimester}}$=0.07, p <0.10; $r_{\text{3rd trimester}}$=0.03, p >0.05	Univariate association
Maternal stress					
Murphy (2017)	Good	Prenatal maternal stress	Cohen's d	Cohen's d=0.09, p>0.05	Univariate association
Gray (2005)	Good	Prenatal maternal stress during 1st trimester, 2nd trimester and 3rd trimester	r	$r_{\text{1st trimester}}$=0.11, p <0.10; $r_{\text{2nd trimester}}$=0.06, p <0.10; $r_{\text{3rd trimester}}$=0.11,p <0.10	Univariate association
Maternal prenatal depression					
Gray (2005)	Good	Maternal prenatal depression during 1st trimester, 2nd trimester and 3rd trimester	r	$r_{\text{1st trimester}}$=0.05, p >0.05; $r_{\text{2nd trimester}}$=0.10, p <0.10; $r_{\text{3rd trimester}}$=0.06,p <0.10	Univariate association
Raposa (2014)	Fair	Maternal prenatal depression	r	r $_{\text{offspring in 15 years old}}$=0.00, p >0.05; r $_{\text{offspring in 22-25 years old}}$=0.09, p >0.05	Univariate association
Paternal postnatal depression					
Ramchandani (2008)	Good	Percentage of depressed offspring in Depressed	PR	PR=1.34 (95%CI: 0.18, 10.02)	Univariate association

		Fathers Group/Percentage of depressed offspring in Non-depressed Group			
Maternal infections					
Betts (2015)	Good	Prenatal maternal major infection /none	OR	OR=1.04 (95%CI: 0.61, 1.75)	Fully adjusted
Murphy (2017)	Good	Prenatal maternal infection	Cohen's d	Cohen's $d_{1st\ trimester}$=-0.05, p >0.05; Cohen's $d_{2nd\ trimester}$=0.14, p <0.10; Cohen's $d_{3rd\ trimester}$=-0.02, p >0.05	Univariate association
Chronic diseases					
Tuovinen (2014)	Good	Hypertension without proteinuria/normotension	OR	OR=1.71 (95%CI: 1.01, 2.89)	Adjusted for sex, year of birth, gestational age, weight for gestational age, head circumference, placental weight, father's occupational status, parity, mother's age, BMI at delivery, breastfeeding, own maximum level of education in adulthood, and age at completion of the questionnaire
Yamasaki (2019)	Good	Maternal diabetes/no maternal diabetes	B	B=1.92, p >0.05	Univariate association
Famine					
Li (2018)	Good	Severe famine exposure during fetal	OR	OR=1.87 (95%CI: 1.36, 2.55)	Univariate association
Bisphenol A					
Perera (2016)	Fair	Prenatal and postnatal Bisphenol A exposure	β	$\beta_{prenatal}$ =1.58, p>0.05; $\beta_{postnatal}$ =0.77, p>0.05	Univariate association
Harley (2013)	Good	Prenatal Bisphenol A exposure	β	$\beta_{male\ offspring}$=1.50, p<0.05; $\beta_{female\ offspring}$=0.10, p>0.05	Univariate association
Fetal antiepileptic drug					

Cohen (2013)	Good	Prenatal epilepsy on antiepileptic drug exposure	F	F=0.21, p>0.05	Univariate association
Selective serotonin reuptake inhibitors					
Malm (2016)	Good	Prenatal Selective Serotonin Reuptake Inhibitors exposure	HR	HR=1.85 (95%CI: 1.15, 2.98)	Univariate association
Antibiotics					
Slykerman (2017)	Good	Antibiotics exposure	β	β=0.20, p<0.05	Adjusted for small gestational age status, sex, maternal school leaving age, maternal smoking in pregnancy, breastfeeding duration and method of delivery.
Organic pollutants					
Strøm (2014)	Good	Maternal serum concentrations of these persistent organic pollutants	HR	HR $_{\text{perfluorooctanoic acid}}$=1.03 (95%CI: 0.61, 1.73); HR $_{\text{perfluorooctane sulfonate}}$=1.16 (95%CI: 0.69, 1.95); HR $_{\text{polychlorinated biphenyls}}$=0.97 (95%CI: 0.57, 1.63); HR $_{\text{hexachlorobenzene}}$=1.01 (95%CI: 0.60, 1.76); HR $_{\text{dichlorodiphenyltrichloroethane}}$=1.19 (95%CI: 0.73, 1.97)	Adjusted for maternal age, pre-pregnancy BMI, parity, maternal smoking during pregnancy, maternal education, maternal cholesterol, maternal triglyceride and offspring sex.
Elemental carbon attributable to traffic					
Yolton (2019)	Fair	Per 0.25 μg/m^3 increase in Elemental carbon attributable to traffic exposure	β	β =3.01, p<0.05	Adjusted for maternal age at delivery, average household income birth to 12 y study visit, maternal BDI-II scores, Relational Frustration T-score, child race, average hair cotinine from samples

					collected at ages 2 and 4 years.
Marijuana exposure					
Sonon (2016)	Good	Prenatal marijuana exposure	β	β=0.15, p<0.05	Univariate association
Gray (2005)	Good	Prenatal marijuana exposure during 1st trimester, 2nd trimester and 3rd trimester	r	$r_{1st\ trimester}$=0.05, p >0.05; $r_{2nd\ trimester}$=0.10, p <0.10; $r_{3rd\ trimester}$=0.13, p <0.10	Univariate association
Cocaine exposure					
Richardson (2013)	Good	Cocaine exposure during 1st trimester	β	β=0.07, p>0.05	Univariate association

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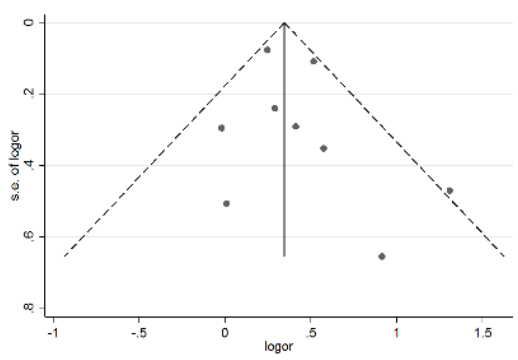
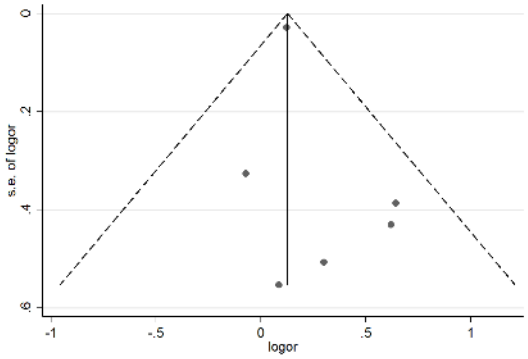
Appendix A.6. Publication bias for the included studies.

Risk factor	Egger test p	Begg test p	Trim-and-Fill Method	
			Adjusted risk estimates (95% CI) [trimmed]	Number of imputed studies
Low birth-weight	0.288	0.371	1.393 (1.126, 1.722)	1
Maternal education	0.620	0.466	1.368 (1.194, 1.567)	0
Socioeconomic status	0.866	1.000	1.289 (1.091, 1.524)	0
Gestational age	0.548	0.764	1.379(1.000, 1.902)	0
Small gestational age	0.909	1.000	1.458 (1.099, 1.933)	0
Parity	**0.031**	0.086	0.995 (0.839, 1.179)	3
Teen parents	0.412	0.348	1.409 (1.151, 1.725)	1
Single mother	NA	NA	0.940 (0.491, 1.798)	1
Parents' age >35	0.299	0.707	1.131 (1.069, 1.197)	1
Maternal drinking	NA	NA	1.090 (0.952, 1.247)	0
Maternal smoking	0.378	0.855	1.351 (1.203, 1.518)	4
Paternal smoking	0.677	0.308	1.281 (1.111, 1.477)	0
Maternal prenatal depression	**0.032**	0.174	1.205 (0.903, 1.548)	2
Maternal postnatal depression	0.533	0.296	1.515 (0.918, 2.500)	0
Maternal stress	0.202	0.089	1.111 (1.004, 1.229)	1
Maternal anxiety	NA	NA	1.090 (1.019, 1.166)	1

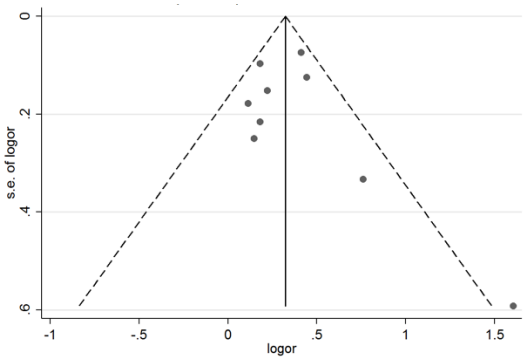
Appendix B. Funnel plot for the analysis of in-utero, perinatal and postnatal factors and depression risk.



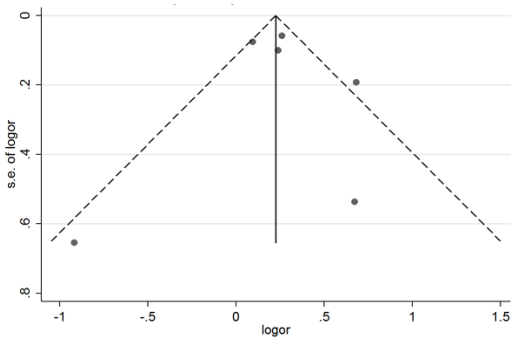
1A. Teen parents



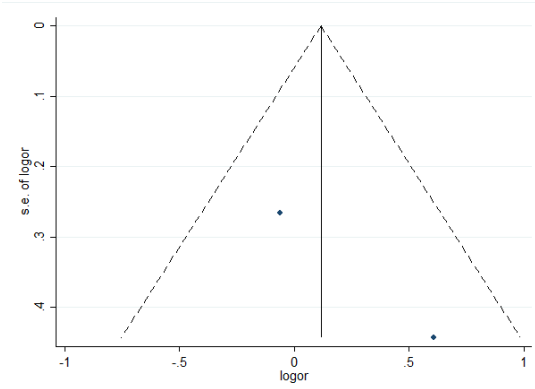
1B. Parental age greater than 35 years



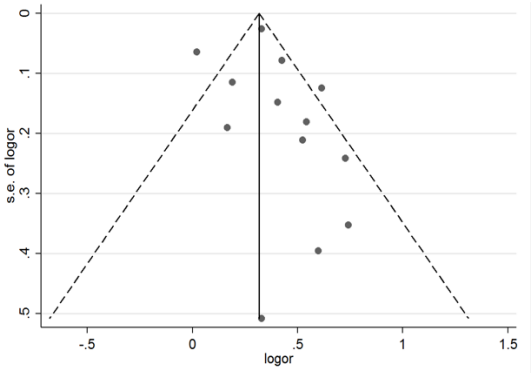
1C. Education



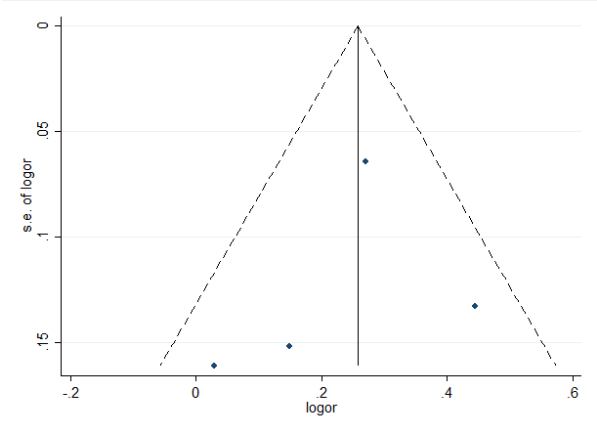
1D. Socioeconomic status



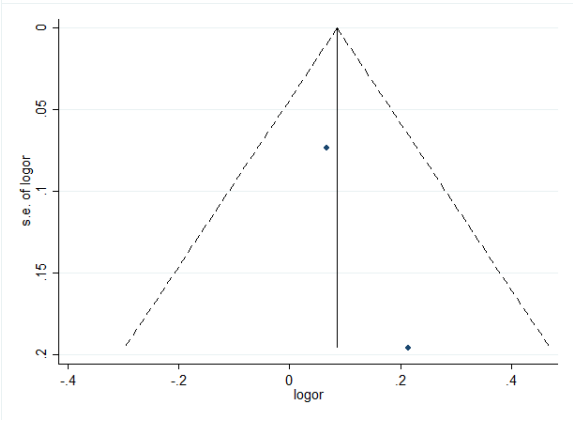
1E. Single mother



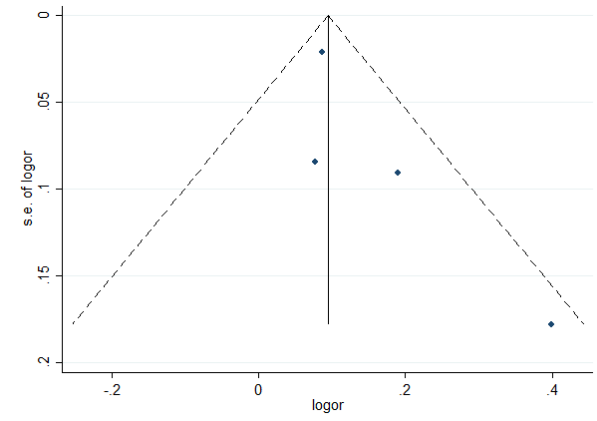
1F. Maternal smoking



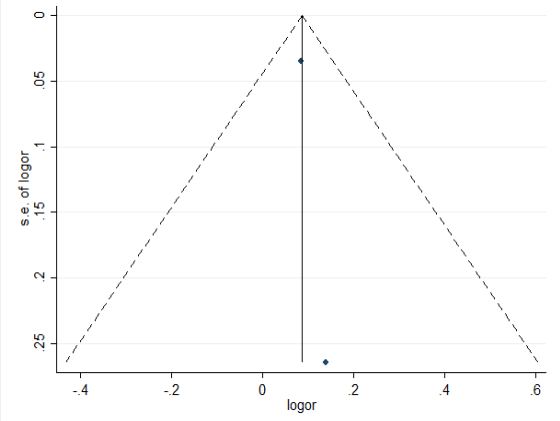
1G. Paternal smoking



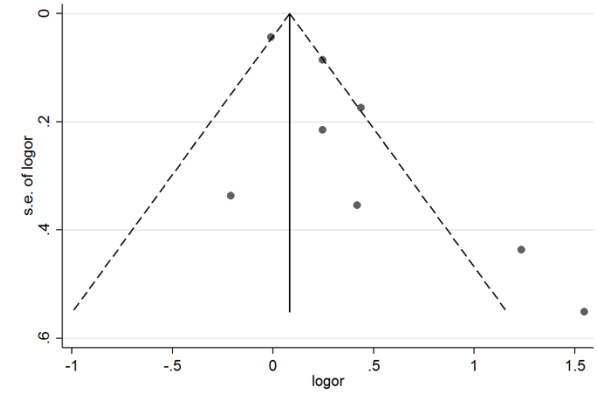
1H. Maternal drinking



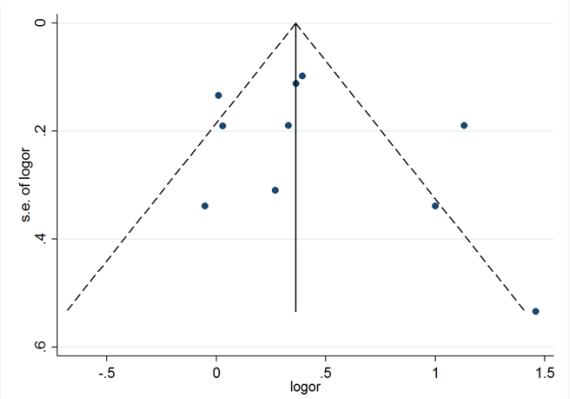
1I. Maternal stress



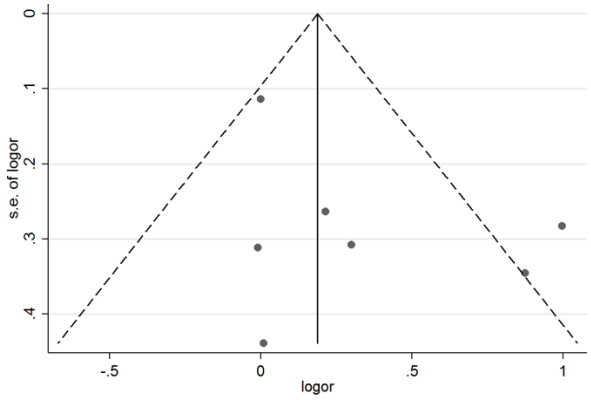
1J. Maternal anxiety



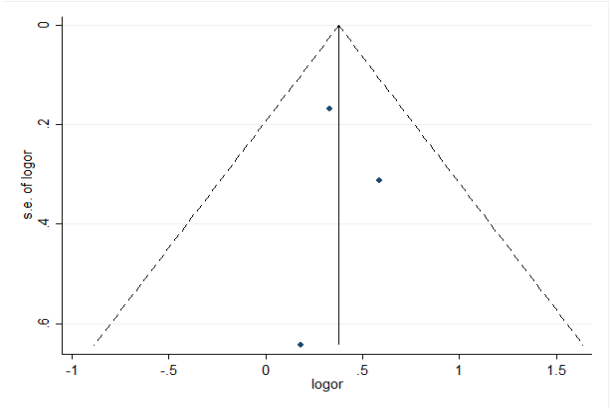
1K. Prenatal depression



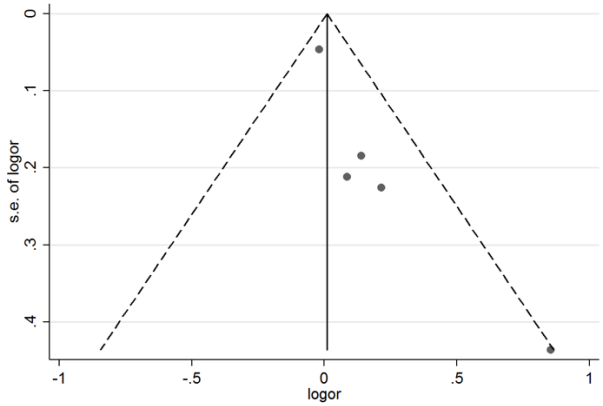
1L. Low birth-weight



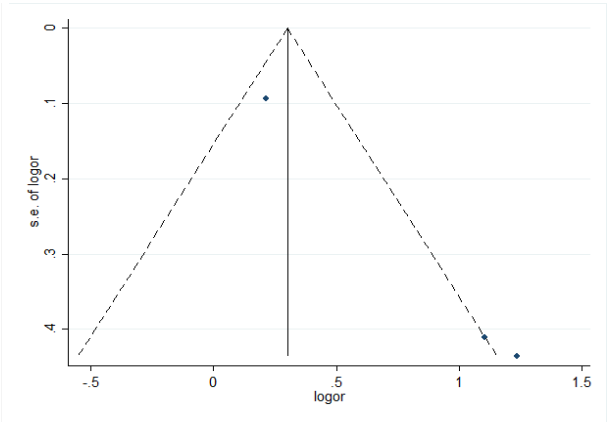
1M. Gestational age



1N. Small gestational age

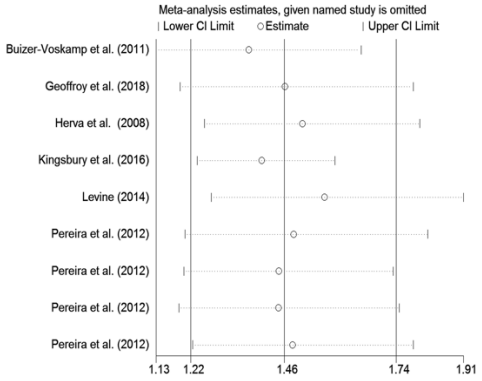


1O. Parity

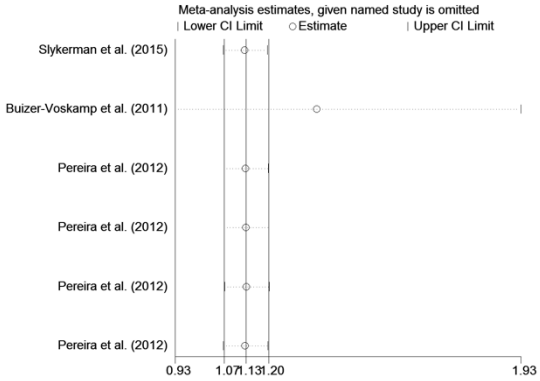


1P. Postnatal depression

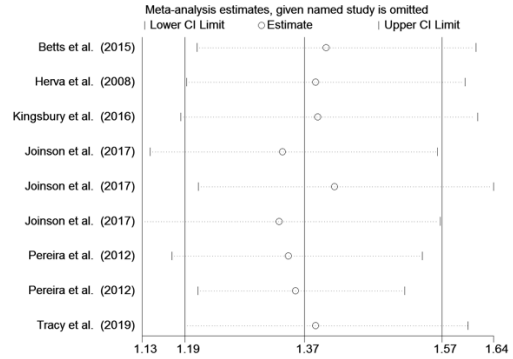
Appendix C. Sensitivity analyses for the association between in-utero, perinatal and postnatal factors and depression risk.



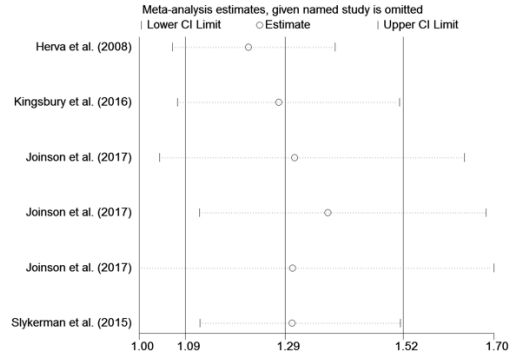
2A. Teen parents



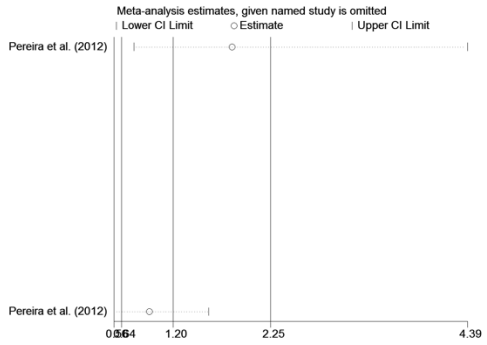
2B. Parental age greater than 35 years



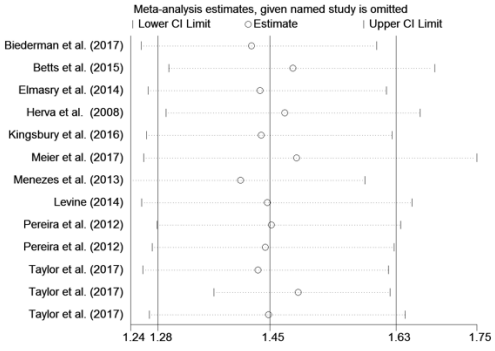
2C. Education



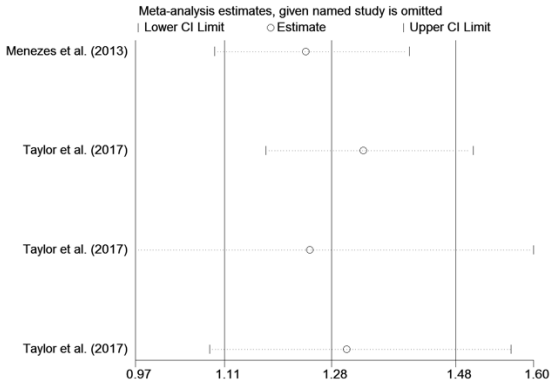
2D. Socioeconomic status



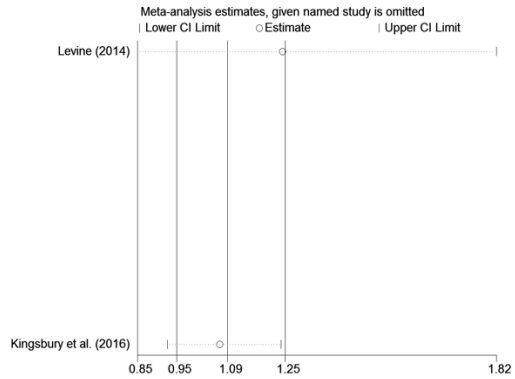
2E. Single mother



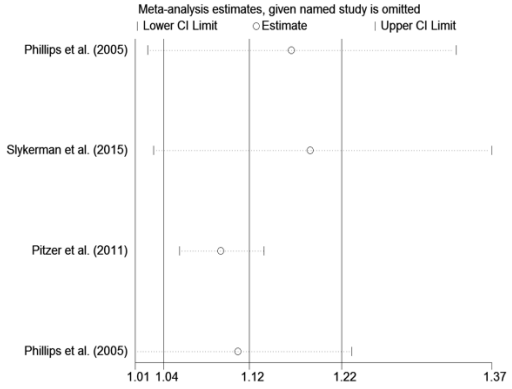
2F. Maternal smoking



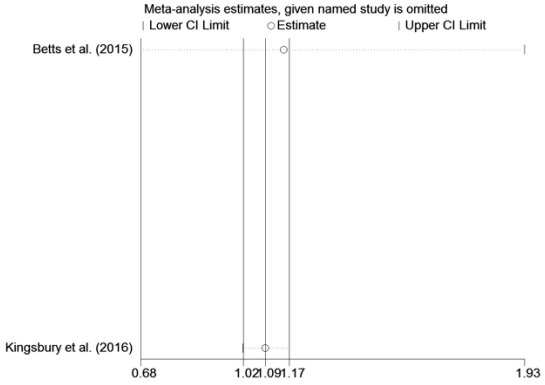
2G. Paternal smoking



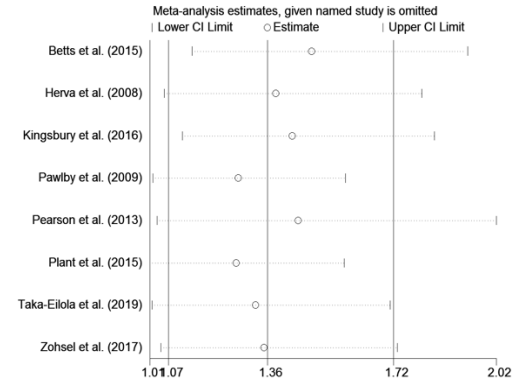
2H. Maternal drinking



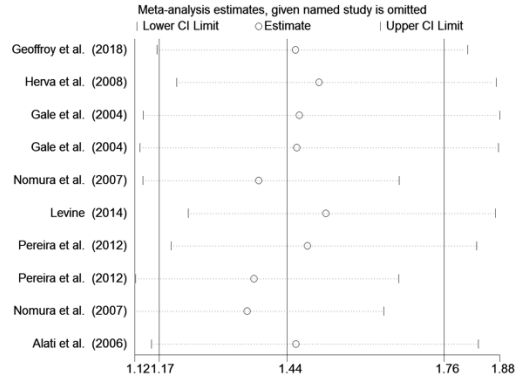
2I. Maternal stress



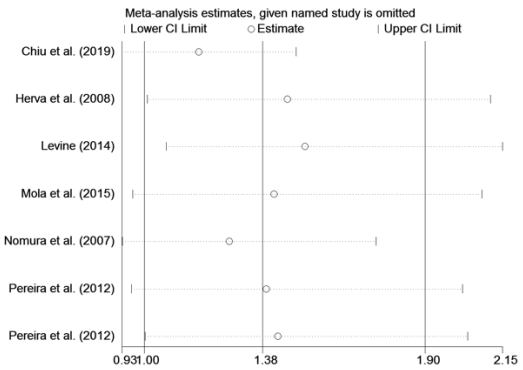
2J. Maternal anxiety



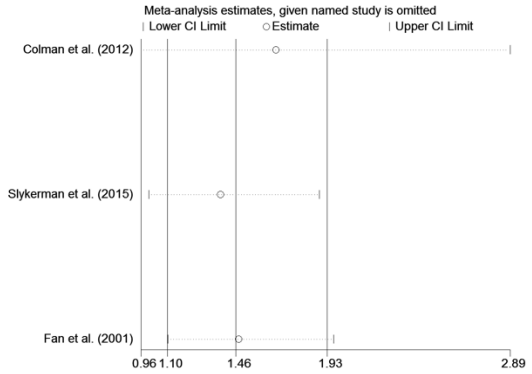
2K. Prenatal depression



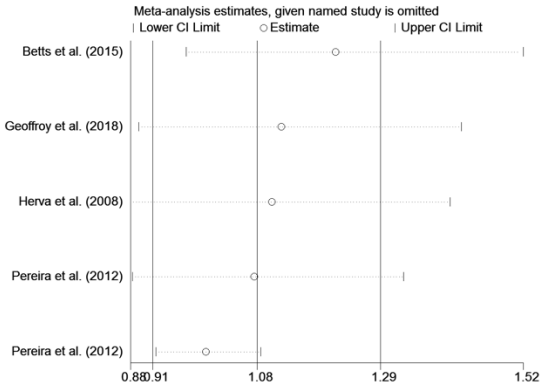
2L. Low birth-weight



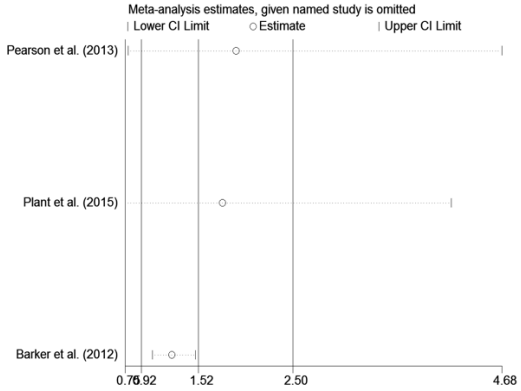
2M. Gestational age



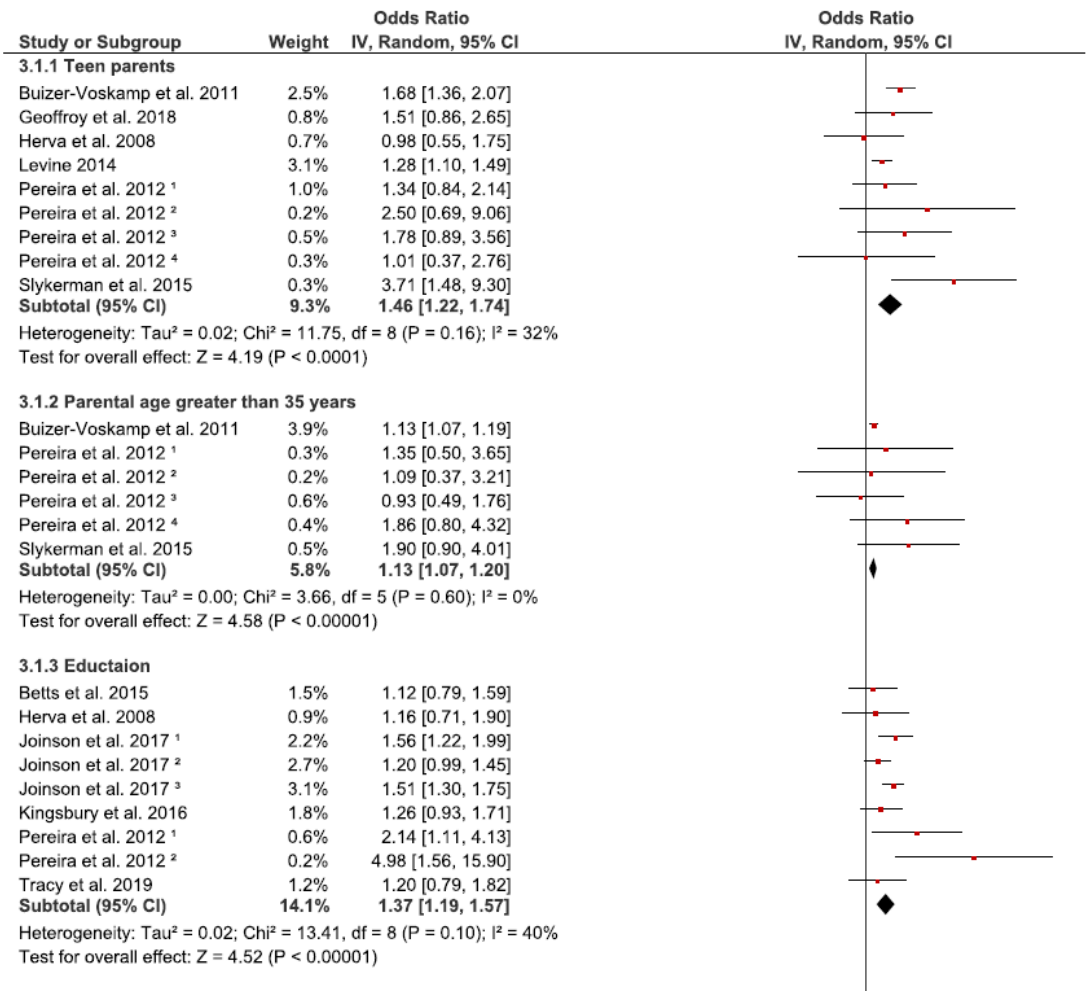
2N. Small gestational age



2O. Parity



2P. Postnatal depression


Odds Ratio
Odds Ratio
Study or Subgroup
Weight
IV, Random, 95% CI
IV, Random, 95% CI
3.1.1 Teen parents
Buizer-Voskamp et al. 2011 2.5% 1.68 [1.36, 2.07]
Geoffroy et al. 2018 0.8% 1.51 [0.86, 2.65]
Herva et al. 2008 0.7% 0.98 [0.55, 1.75]
Levine 2014 3.1% 1.28 [1.10, 1.49]
Pereira et al. 2012 1 1.0% 1.34 [0.84, 2.14]
Pereira et al. 2012 2 0.2% 2.50 [0.69, 9.06]
Pereira et al. 2012 3 0.5% 1.78 [0.89, 3.56]
Pereira et al. 2012 4 0.3% 1.01 [0.37, 2.76]
Slykerman et al. 2015 0.3% 3.71 [1.48, 9.30]
Subtotal (95% CI) 9.3% 1.46 [1.22, 1.74]
Heterogeneity: Tau² = 0.02; Chi² = 11.75, df = 8 (P = 0.16); I² = 32%
Test for overall effect: Z = 4.19 (P < 0.0001)
3.1.2 Parental age greater than 35 years
Buizer-Voskamp et al. 2011 3.9% 1.13 [1.07, 1.19]
Pereira et al. 2012 1 0.3% 1.35 [0.50, 3.65]
Pereira et al. 2012 2 0.2% 1.09 [0.37, 3.21]
Pereira et al. 2012 3 0.6% 0.93 [0.49, 1.76]
Pereira et al. 2012 4 0.4% 1.86 [0.80, 4.32]
Slykerman et al. 2015 0.5% 1.90 [0.90, 4.01]
Subtotal (95% CI) 5.8% 1.13 [1.07, 1.20]
Heterogeneity: Tau² = 0.00; Chi² = 3.66, df = 5 (P = 0.60); I² = 0%
Test for overall effect: Z = 4.58 (P < 0.00001)
3.1.3 Eductaion
Betts et al. 2015 1.5% 1.12 [0.79, 1.59]
Herva et al. 2008 0.9% 1.16 [0.71, 1.90]
Joinson et al. 2017 1 2.2% 1.56 [1.22, 1.99]
Joinson et al. 2017 2 2.7% 1.20 [0.99, 1.45]
Joinson et al. 2017 3 3.1% 1.51 [1.30, 1.75]
Kingsbury et al. 2016 1.8% 1.26 [0.93, 1.71]
Pereira et al. 2012 1 0.6% 2.14 [1.11, 4.13]
Pereira et al. 2012 2 0.2% 4.98 [1.56, 15.90]
Tracy et al. 2019 1.2% 1.20 [0.79, 1.82]
Subtotal (95% CI) 14.1% 1.37 [1.19, 1.57]
Heterogeneity: Tau² = 0.02; Chi² = 13.41, df = 8 (P = 0.10); I² = 40%
Test for overall effect: Z = 4.52 (P < 0.00001)

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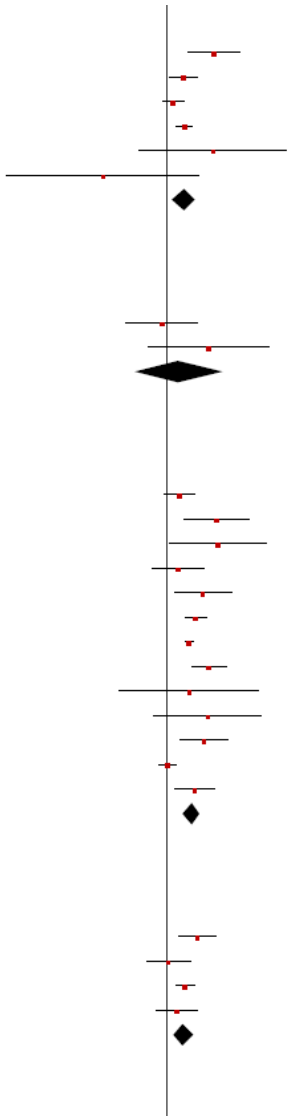

3.1.4 SES

Herva et al. 2008	1.4%	1.98 [1.36, 2.88]
Joinson et al. 2017 [1]	2.6%	1.27 [1.04, 1.55]
Joinson et al. 2017 [2]	3.0%	1.10 [0.94, 1.28]
Joinson et al. 2017 [3]	3.4%	1.30 [1.16, 1.46]
Kingsbury et al. 2016	0.2%	1.96 [0.68, 5.65]
Slykerman et al. 2015	0.1%	0.40 [0.10, 1.60]
Subtotal (95% CI)	**10.8%**	**1.29 [1.10, 1.52]**

Heterogeneity: Tau² = 0.02; Chi² = 12.16, df = 5 (P = 0.03); I² = 59%
Test for overall effect: Z = 3.05 (P = 0.002)

3.1.5 Single mother

Pereira et al. 2012 [1]	0.9%	0.94 [0.56, 1.58]
Pereira et al. 2012 [2]	0.4%	1.84 [0.77, 4.40]
Subtotal (95% CI)	**1.2%**	**1.20 [0.64, 2.25]**

Heterogeneity: Tau² = 0.09; Chi² = 1.69, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 0.56 (P = 0.58)

3.1.6 Maternal smoking

Betts et al. 2015	2.4%	1.21 [0.97, 1.51]
Biederman et al. 2017	1.0%	2.07 [1.29, 3.32]
Elmasry et al. 2014	0.5%	2.10 [1.05, 4.20]
Herva et al. 2008	1.4%	1.18 [0.81, 1.72]
Kingsbury et al. 2016	1.2%	1.69 [1.12, 2.55]
Levine 2014	3.0%	1.53 [1.31, 1.79]
Meier et al. 2017	3.9%	1.39 [1.32, 1.46]
Menezes et al. 2013	2.2%	1.85 [1.45, 2.36]
Pereira et al. 2012 [1]	0.3%	1.39 [0.51, 3.79]
Pereira et al. 2012 [2]	0.4%	1.82 [0.84, 3.94]
Taylor et al. 2017 [1]	1.5%	1.72 [1.21, 2.44]
Taylor et al. 2017 [2]	3.3%	1.02 [0.90, 1.16]
Taylor et al. 2017 [3]	1.9%	1.50 [1.13, 1.99]
Subtotal (95% CI)	**23.0%**	**1.45 [1.28, 1.63]**

Heterogeneity: Tau² = 0.02; Chi² = 39.12, df = 12 (P = 0.0001); I² = 69%
Test for overall effect: Z = 5.98 (P < 0.00001)

3.1.7 Paternal smoking

Menezes et al. 2013	2.1%	1.56 [1.20, 2.03]
Taylor et al. 2017 [1]	1.7%	1.03 [0.75, 1.41]
Taylor et al. 2017 [2]	3.3%	1.31 [1.15, 1.49]
Taylor et al. 2017 [3]	1.8%	1.16 [0.86, 1.56]
Subtotal (95% CI)	**8.8%**	**1.28 [1.11, 1.48]**

Heterogeneity: Tau² = 0.01; Chi² = 4.48, df = 3 (P = 0.21); I² = 33%
Test for overall effect: Z = 3.39 (P = 0.0007)

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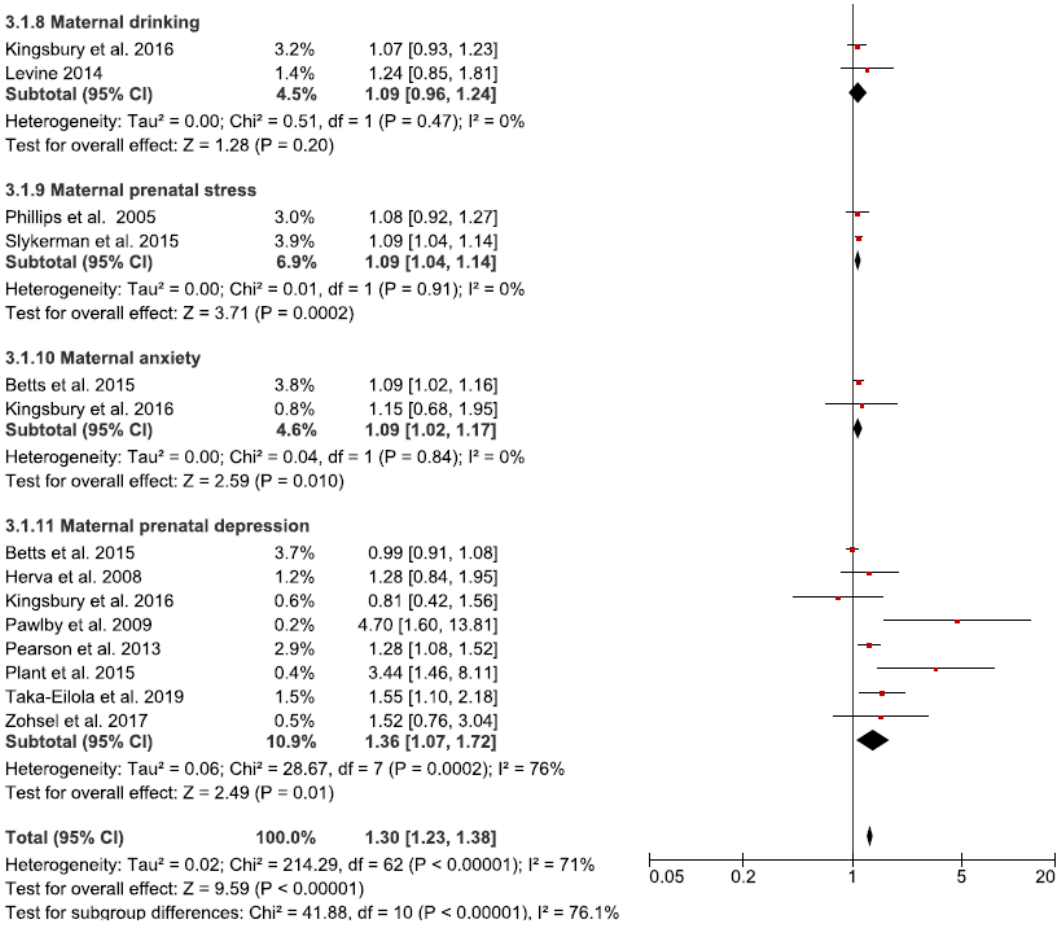
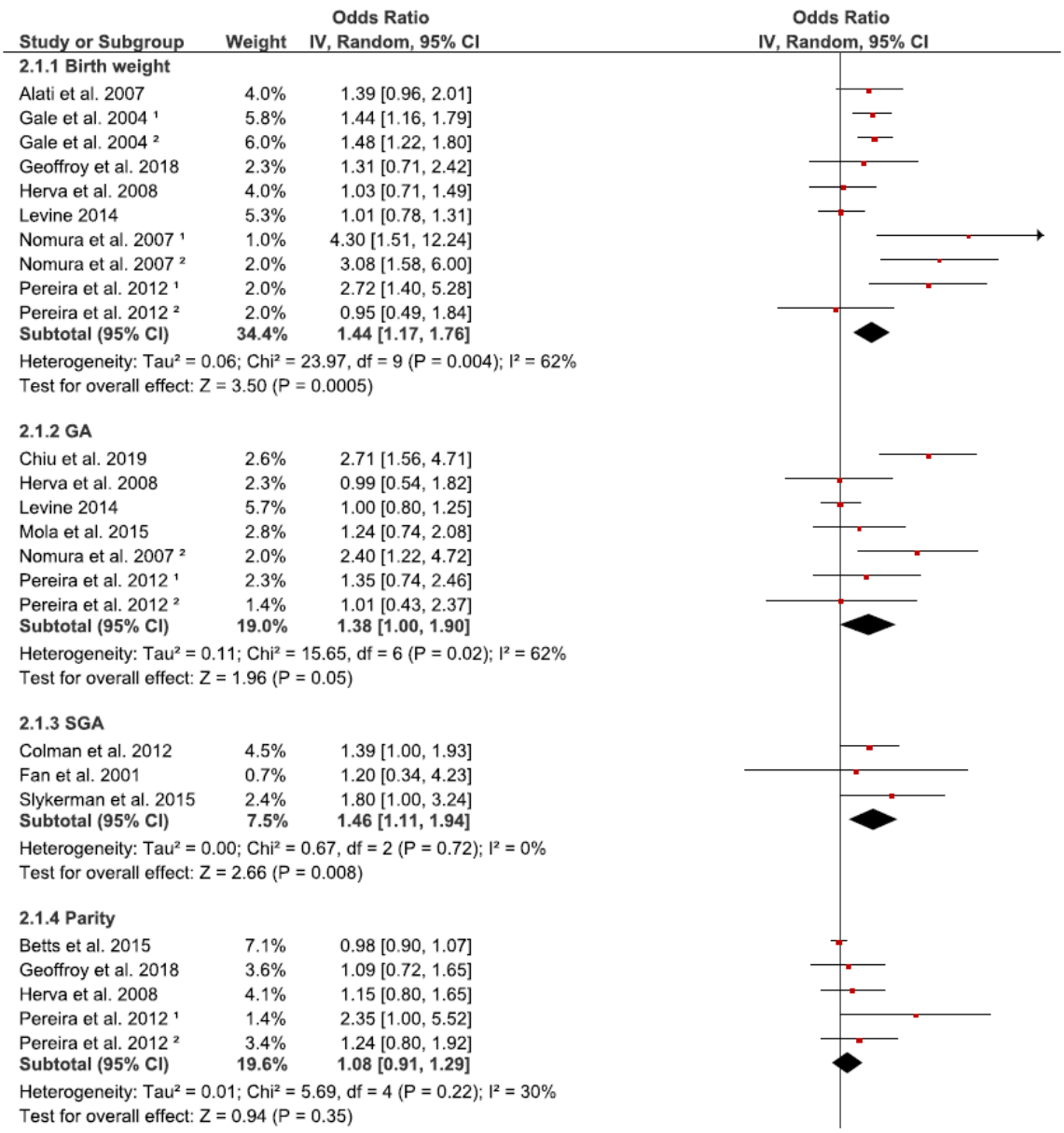


Appendix D1. Subgroup meta-analysis of the relationship between prenatal factors and offspring's depression.

Pereira[1] study compares depression in children 7-9 years with maternal factors, Pereira[2] study compares depression in children 10-11 years with maternal factors, Pereira[3] study compares depression in children 7-9 years with paternal factors, Pereira[4] study compares depression in children 10-11 years with paternal factors; Joinson[1] study compares depression in children less than 12 years old, Joinson[2] study compares depression in children at 12-16 years old, Joinson[3] study compares depression in children at 12-17 years old; Taylor[1] is the ALSPAC study, Taylor[2] is the HUNT study, Taylor[3] is the Pelotas 1982 study.


Odds Ratio
Odds Ratio
Study or Subgroup
Weight
IV, Random, 95% CI
IV, Random, 95% CI
2.1.1 Birth weight
Alati et al. 2007 4.0% 1.39 [0.96, 2.01]
Gale et al. 2004 ¹ 5.8% 1.44 [1.16, 1.79]
Gale et al. 2004 ² 6.0% 1.48 [1.22, 1.80]
Geoffroy et al. 2018 2.3% 1.31 [0.71, 2.42]
Herva et al. 2008 4.0% 1.03 [0.71, 1.49]
Levine 2014 5.3% 1.01 [0.78, 1.31]
Nomura et al. 2007 ¹ 1.0% 4.30 [1.51, 12.24]
Nomura et al. 2007 ² 2.0% 3.08 [1.58, 6.00]
Pereira et al. 2012 ¹ 2.0% 2.72 [1.40, 5.28]
Pereira et al. 2012 ² 2.0% 0.95 [0.49, 1.84]
Subtotal (95% CI) 34.4% 1.44 [1.17, 1.76]
Heterogeneity: Tau² = 0.06; Chi² = 23.97, df = 9 (P = 0.004); I² = 62%
Test for overall effect: Z = 3.50 (P = 0.0005)
2.1.2 GA
Chiu et al. 2019 2.6% 2.71 [1.56, 4.71]
Herva et al. 2008 2.3% 0.99 [0.54, 1.82]
Levine 2014 5.7% 1.00 [0.80, 1.25]
Mola et al. 2015 2.8% 1.24 [0.74, 2.08]
Nomura et al. 2007 ² 2.0% 2.40 [1.22, 4.72]
Pereira et al. 2012 ¹ 2.3% 1.35 [0.74, 2.46]
Pereira et al. 2012 ² 1.4% 1.01 [0.43, 2.37]
Subtotal (95% CI) 19.0% 1.38 [1.00, 1.90]
Heterogeneity: Tau² = 0.11; Chi² = 15.65, df = 6 (P = 0.02); I² = 62%
Test for overall effect: Z = 1.96 (P = 0.05)
2.1.3 SGA
Colman et al. 2012 4.5% 1.39 [1.00, 1.93]
Fan et al. 2001 0.7% 1.20 [0.34, 4.23]
Slykerman et al. 2015 2.4% 1.80 [1.00, 3.24]
Subtotal (95% CI) 7.5% 1.46 [1.11, 1.94]
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 2.66 (P = 0.008)
2.1.4 Parity
Betts et al. 2015 7.1% 0.98 [0.90, 1.07]
Geoffroy et al. 2018 3.6% 1.09 [0.72, 1.65]
Herva et al. 2008 4.1% 1.15 [0.80, 1.65]
Pereira et al. 2012 ¹ 1.4% 2.35 [1.00, 5.52]
Pereira et al. 2012 ² 3.4% 1.24 [0.80, 1.92]
Subtotal (95% CI) 19.6% 1.08 [0.91, 1.29]
Heterogeneity: Tau² = 0.01; Chi² = 5.69, df = 4 (P = 0.22); I² = 30%
Test for overall effect: Z = 0.94 (P = 0.35)

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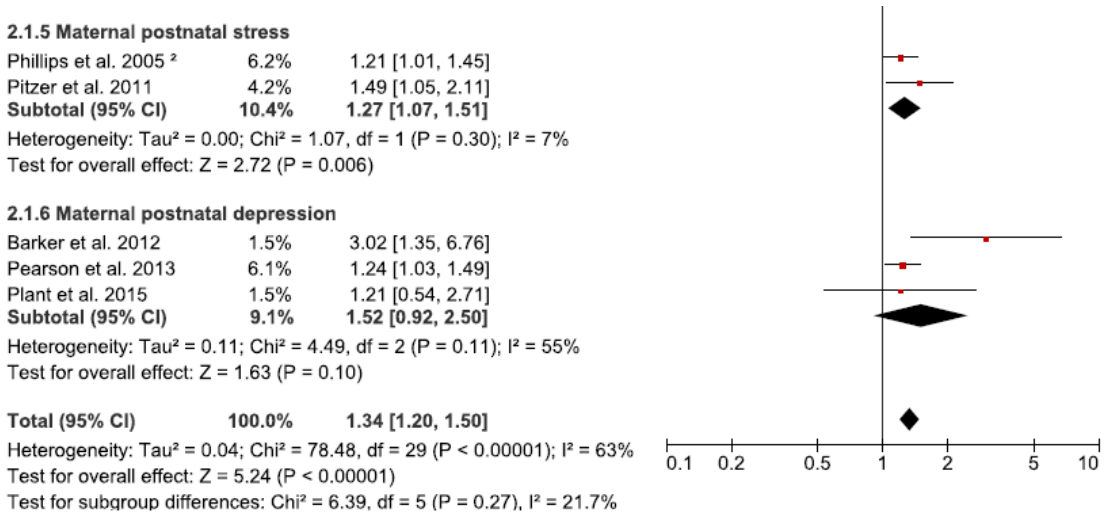

Appendix D2. Subgroup meta-analysis of the relationship between perinatal/postnatal factors and offspring's depression.

Gale[1] is the study among females, Gale[2] is the study among males; Nomura[1] is the New York State Psychiatric Institute/Columbia University study, Nomura[2] is the National Collaborative Perinatal Project (NCPP) study; Pereira[1] study compares depression in children 7-9 years, Pereira[2] study compares depression in children 10-11 years.

CHAPTER 8. CONCLUSIONS AND IMPLICATIONS

This thesis explored the biopsychosocial model of stress and mental disorders. Recognizing the adverse effect of various stressors on the mental health and the role of resilience in mediating (moderating) the stress has important social and mental health implications. It is of great significance to recognize the important roles of different types of resilience in the trajectory of mental health recovery from trauma exposure. Our review of the evidence in the literature reinforces the effect of intergenerational transmission complement and extends research on addressing the link between social stressors and mental illness. Further, the intergenerational effect of maternal child maltreatment warrants special attention, as it not only influences the maltreated mothers but also their children. Health care providers can be aware of the impact of social stress on individual's mental health and interventions need to address it at both the biological and psychosocial levels in order to promote the mental health and well-being of the society as a whole.

8.1 Summary of findings

The primary aim of the chapter 3 of this thesis is to explore maternal and child outcomes of abuse around the time of pregnancy and identify potential modifiable risk factors as well as examine the rural–urban variations in pregnancy abuse at the national level in Canada.

The Maternity Experiences Survey (MES) was used in this study, which was the first and only national survey devoted to pregnancy, labour, birth, and postpartum experiences in Canada. The project was conducted by Statistics Canada and sponsored by the Public Health Agency of Canada's Canadian Perinatal Surveillance System. It was conducted between October 23, 2006, and January 31, 2007. The target population in the study was women aged 15 years who were pregnant in the 12 months prior to the 2006 Canadian census, some of whom had suffered physical or sexual abuse and violence around the time of pregnancy.

The study findings indicated that mothers living in an urban environment had an increased risk of experiencing abuse around the time of pregnancy (OR=1.31, 95% CI: 1.03-1.66). In addition, having aboriginal ancestry, being young, unmarried, a non-immigrant and economically disadvantaged, having more than four pregnancies, with a history of cigarette smoking, alcohol drinking and drug use before the pregnancy were correlated with the increased abuse around the

time of pregnancy. For the whole national sample, abuse experience around the time of pregnancy was significantly associated with an increased number of stressful events (OR = 2.64, 95% CI: 2.09-3.33) and postnatal depression (OR = 2.35, 95% CI: 1.86-2.97). However, no association was found between abuse/violence and adverse birth outcomes, including preterm birth, caesarian delivery, and low birth weight. In the stratification analysis of rural-urban area, the experience of abuse and violence was associated with postnatal depression with 1.92 times increased odds (OR 1.92, 95% CI 1.17-3.18) and 2.50 times increased odds (OR 2.50; 95% CI 11.92-3.25), after adjustment for potential confounders, in rural and urban areas respectively. Additionally, the pregnancy related abuse/violence experience was also associated with increased stressful events in rural areas (OR = 2.45, 95% CI: 1.44-4.17) and in urban areas (OR = 2.66; 95% CI: 2.05-3.45). Whereas there were no instances of low birth weight among abused mothers in comparison with non-abused mothers in either rural or urban areas. Abuse experience was only associated with an increased risk of a preterm birth in rural mothers in both unadjusted and fully adjusted models ($OR_{unadjusted}$ =2.51, 95% CI 1.10-4.19; $OR_{adjusted}$ =2.30, 95% CI 1.09-4.88) but not for urban mothers.

Our findings suggest that the need to improve abuse/violence case detection among pregnant women and more generally promote the health and well-being of pregnant women. Primary care providers should be encouraged to pay attention to women who are potentially at risk of abuse well as to encourage attention to the detection for abuse during pregnancy.

In the chapter 4 of this thesis, structural equation modeling (SEM) was used to investigate the mediation effect of social support and positive coping skills in the multivariate relationships between childhood maltreatment and both psychological distress and positive mental health in a national population survey-the 2012 Canadian Community Health Survey - Mental Health (CCHS-MH, N=25, 113).

We found that childhood maltreatment was negatively correlated with social support, positive coping skills and positive mental health but positively correlated with psychological distress. Social support and positive coping skills were associated with higher levels of positive mental health but lower levels of psychological distress. Social support and positive coping skills clearly partially mediated the negative consequences of childhood maltreatment on mental health. Both separately and together social support and coping skills mediated the negative

impact of childhood maltreatment on mental health. Surprisingly, no sex differences were observed among these associations.

This research clearly demonstrates that social support and positive coping skills mediate the negative effects of childhood maltreatment on mental health and thus suggests avenues for the treatment and prevention of mental health problems among those with the exposure of maltreatment.

Chapter 5 of this thesis explored the longitudinal and bidirectional association between income and self-perceived mental health, and whether the associations vary across sex and age. Four hypotheses were proposed: 1) at population level, does higher income predict better self-perceived mental health over time, or vice versa? 2) what are the effects of age and sex in this relationship at population level; 3) at individual level, does higher income predict better self-perceived mental health over time, or vice versa; 4) what are the effects of age and sex in this relationship at individual level.

Data for this analysis were from a longitudinal, community-based, population cohort study-the Montreal South-West Longitudinal Catchment Area Study-Zone d' Épidémiologie Psychiatrique du Sud-Ouest de Montréal (ZEPSOM). Participants aged between 15 and 65 years old representing 269,720 inhabitants across five neighborhoods. Two types of autoregressive models were conducted to assess the longitudinal associations between income and self-perceived mental health at both population level and individual level: a traditional cross-lagged panel model (CLPM) and a random intercept cross-lagged panel model (RI-CLPM). Multigroup analyses on CLPMs and RI-CLPMs were conducted by comparing the cross-lagged paths and autoregressive paths by sex and age.

We found that the expected significant effect of income on self-perceived mental health at the between-person (population) level, but not vice versa. However, no significant associations emerged at the within-person level. Furthermore, at the between-person (population) level the effects of income on self-perceived mental health were found to be stronger among males and older adults. Thus, this analysis supports the social causation hypothesis that deems low income as a root cause of poor physical and mental health status pointing to a modifiable risk factor of public health importance for improving the health of a population.

Taken together, the current study found a causal link between household income and self-perceived mental health only at the population level but not at the individual level. It suggests that income has a stronger effect on mental health in the population context where one can compare to peers and to a lesser extent when it reflects a change at the personal level. Moreover, it was found that males and older adults are particularly sensitive to these effects. Our findings provide empirical support for strategies targeting improvement of income status as one component of an effective approach for promoting mental health well-being as well as general health.

Chapter 6 examined the effect of maternal childhood maltreatment on the psychopathology of offspring using a systematic review and meta-analysis. MEDLINE, PubMed, Web of Science, EMBASE and Cochrane Library databases and grey literature up to January 2019 were systematically searched for English language with prospective study designs for the research on maternal childhood maltreatment and offspring's psychopathology. Longitudinal studies reporting on either depression or internalizing behaviours among next generation having mothers with clear information on childhood maltreatment were included. Pearson's rs were converted with Fisher's Z transformation effect sizes, and then the Z-values were converted back to r for reporting. Random-effect models were used to calculate the overall point estimates and homogeneity analyses were conducted with Cochrane's Q statistic. Categorical factors were tested with a between-group test of homogeneity, and the impact of continuous variables on results was assessed by meta-regression.

A total of 12 studies met the inclusion criteria for this review (n=29,682). A significant heterogeneity was found across the selected studies. Maternal childhood maltreatment had a small but significant effect on offspring's depression and internalizing behaviors (r=0.14, 95%CI: 0.09-0.19), however, 4 of the studies reported a moderate effect. Ethnicity and maternal depression moderated this relationship. There was no evidence of significant publication bias.

This review supports a small but significant intergenerational effect of maternal childhood maltreatment onto offspring's psychopathology. Future research and prevention efforts should be paid to this intergenerational effect. Special attention should be given to maltreated mothers and their children especially factors that inhibit the transmission of childhood abuse to the next

generation. More research is needed for the neglected topic of the impact of paternal abuse on the next generation.

Finally, Chapter 7 quantitatively and qualitatively summarized the evidence on the effect of early childhood experiences, particularly in-utero and perinatal conditions, on the offspring's depression.

A computerized search of bibliographic databases was conducted, including EMBASE, HealthStar, PsychoInfo, and Medline from their inception until September 1st, 2019 for published longitudinal cohort studies on in-utero, perinatal/postnatal exposures associated with depression in offspring. Random-effect models were used to estimate the pooled odds ratio and investigate the potential sources of heterogeneity. Meta-regression analysis was performed to explore heterogeneity among studies. Additionally, sensitivity analysis was also performed to explore the effects of the potential confounders.

Only prospective cohort studies were selected for inclusion in the review, this allowed us to draw causal inferences. A total of 64 studies with 28 in-utero and perinatal exposures had been studied in the relationship to offspring's depression. Our review shows that low-birth weight, premature birth, small for gestational age, younger parents (<20 years), older parents (≥35 years), maternal education, socioeconomic status, maternal smoking, paternal smoking, maternal stress, maternal anxiety, and maternal prenatal depression, were all associated with an elevated risk for depression in offspring. Heterogeneity and publication bias tests support our conclusions.

To provide comprehensive and best-available evidence for this field, studies with high heterogeneity were also summarized narratively. This review summarizes all the risk factors during the in-utero and perinatal periods and informs further research on the long-term consequences of adverse in-utero and perinatal conditions. Using prospective cohort studies this research provides robust evidence synthesizing the effects of in-utero and perinatal exposures on increasing offspring's depression risk.

8.2 Policy implications and future research

This thesis findings have several policy and program implications. Special attention, from both a clinical and policy perspective, needs to be paid to women's potential to experience abuse or violence during pregnancy because of a wide range of negative health outcomes and

social/psychological consequences both for the women themselves and their children. Identifying women at risk of abuse is crucial as well as developing intervention policies and programs for this vulnerable population. Screening, prevention and treatment opportunities should begin at the very early stage of the pregnancy to preclude the adverse outcomes occurred in both themselves and their next generation.

These findings highlight the importance that policy and program initiatives should focus on developing more women-specific prevention programs which take the barriers experienced by both urban and rural mothers into consideration. These should take place in the context of receiving adequate prenatal and postnatal care.

It is important to understand what factors contribute to the intergeneration transmission and similarly what factors inhibit such transmission. Efforts should be paid into primary prevention of childhood maltreatment, especially to female victims. Improving maternal mental health will reduce offspring's risk of depression and internalizing behaviors. Ethnicity and suffering maternal depression influence the association between maternal childhood maltreatment and offspring's psychopathology. Selective preventive efforts should also consider ethnicity as the intergenerational transmission appears to be stronger in non-Caucasian populations. Even though maternal childhood maltreatment predicted a small but significant risk of offspring's psychopathology, the intergenerational transmission of negative consequences warrants further research in terms of its underlying mechanisms and prevention efforts to effectively intervene mental health problems. These findings support that early detection and intervention for maltreated mothers and their children will positively stimulate the children's development. Future research and prevention efforts should be paid to the intergenerational effect and to the effect of the paternal experience of childhood maltreatment.

Within the framework of the biopsychosocial model, we articulated the roles of in-utero and perinatal factors in the development of major depression during the life course. Twelve prenatal, perinatal, and postnatal risk factors that increase the risk for depression among offspring were identified. This research synthesis provides robust evidence for the developmental origins of health and disease (DOHaD) hypothesis and has important implications for health professionals, policymakers, and researchers to develop prevention and intervention strategies targeted at modifiable early-life risk factors that will reduce the risk of depression in children. And

hopefully set a favorable trajectory for future individual growth and development. The identification of these early-life risk factors for depression has important clinical implications as it reiterates the importance and necessity of quality maternal and childcare. Future large prospective studies should investigate the combined effect of multiple early life exposures.

In addition, based on our findings and literature framework, it was suggested that childhood maltreatment is associated with adverse mental health and wellbeing of children. However, it is important to note that our thesis research also found social support and positive coping strategies can serve as protectors and thus reduce negative effects of maltreatment exposure. In adulthood these two mediators can mediate relationship between childhood abuse and vulnerability to mental disorders. These findings show that the potentially strong protective role of resiliency mechanisms such as the social support and positive coping skills can help abused victims promote psychological adjustment and recovery. Social support and positive coping strategies are teachable and learnable skills. Understanding more about the abuse/mental health associations can provide a solid foundation for further research to investigate the mechanisms that underlying the complex relationship between mental disorders and childhood maltreatment.

Finally, the current study found a causal link between household income and self-perceived mental health at the population level but not at the individual level. It suggested that income has a stronger effect on mental health in the population context when individuals compare themselves to their peers and but has a lesser impact on mental health when it reflects a change at the personal level. Furthermore, the effects of income are stronger among males and older people. Our findings provide empirical support for strategies targeting improvement of income status as one component of an effective approach for promoting mental health well-being. Relative income has a strong perceived effect on mental health. The null results on the within-person level call for further empirical research to apply models that differentiate between between-person (population) differences from within-person changes. An in-depth understanding of directionality of associations between income and self-perceived mental health at both the population and the individual levels could be informative for public health and health policy seeking to promote positive mental health.

8.3 Conclusion

There are five take-home messages of the current research work in this thesis as follows:

1) Urban mothers were more likely to experience abuse and violence compared to rural mothers. Living in urban locales, being aboriginal, young, unmarried, a non-immigrant, economically disadvantaged, having more than four pregnancies and cigarette smoking, alcohol drinking and drug use before the pregnancy were all correlated with the abuse around the time of pregnancy. In both urban and rural areas, mothers who experienced abuse were more likely to have an increased risk of postnatal depression and stressful events. Additionally, abuse experience was only associated with an increased risk for preterm neonate among rural mothers but not among urban mothers.

2) There is a small but significant intergenerational transmission of maternal childhood maltreatment onto offspring's psychopathology. And both ethnicity and maternal depression moderated the relationship between maternal childhood maltreatment and offspring's psychopathology. The influence of paternal experience of childhood abuse is an under-researched topic.

3) Low birth-weight, premature birth, small gestational age, maternal education, socioeconomic status, having young parents (<20 years), having older parents (≥ 35 years), maternal smoking, paternal smoking, maternal stress, maternal anxiety, and maternal prenatal depression significantly increased the risk of depression among offspring. The qualitative analysis generally provides support for the meta-analysis findings and adds information on a range of additional risk factors influencing depression in offspring.

4) Childhood maltreatment was negatively associated with social support, positive coping skills and positive mental health but positively associated with psychological distress. Strong social support and positive coping skills, acting as personal resources, buffered the negative effects of childhood maltreatment on mental health outcomes among maltreated individuals.

5) There is a significant effect of income on self-perceived mental health at between-person (population) level, but not vice versa. However, no significant associations at within-person level were found. The effects of income on self-perceived mental health were stronger among males and older adults compared to their counterparts at only between-person level.

A dominant theme of this research is the role of early life stressful experiences on subsequent adolescent and adult mental health. Those early life experiences set a positive or negative

trajectory for future individual growth and development. Also evident is that the trajectory can be altered. There are personal and social resources that can positively influence that mental health trajectory. Those resources need to be nurtured and promoted.