2-26-2016 12:00 AM

Antenatal Depressive Symptoms and Antidepressant Use in Pregnancy

Jerry Yu-Hsiang Chen, *The Univeristy of Western Ontario*

Supervisor: Dr. M. Karen Campbell, *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics

Abstract

Review of the current literature reveals inconsistent findings on potential associations between antidepressant use during pregnancy and adverse fetal and child health and development. This study aims to examine the effect of antenatal SSRI exposure on several neonatal (preterm birth, small- and large-for-gestational age, Apgar score, and neonatal intensive care unit admission) and child developmental outcomes (measured by Ages and Stages Questionnaire) while controlling for confounding by indication. Data were obtained from the Prenatal Health Project, a longitudinal cohort study of 2,357 women in London, Ontario. Results from univariable analysis discovered that infants exposed to *in utero* SSRIs were more likely to be large-for-gestational age compared to infants of women exposed to antenatal depressive symptoms but not SSRIs and to infants of women unexposed to either antenatal depression or SSRIs. The small sample size of the antidepressant-exposed population limited our study and further research is warranted to verify the significance of our findings.

Keywords: antenatal depression; antidepressants; selective serotonin reuptake inhibitors; SSRIs; pregnancy; neonatal outcomes; child developmental outcomes

Acknowledgments

First, I would like to express my sincere gratitude to my supervisor, Dr. Karen Campbell, for her ongoing support, encouragement, guidance, and patience throughout my time in the program. I would also like to extend my gratitude for Dr. Kathy Speechley in her role as a member of the advisory committee and more importantly, her role as the graduate chair. As well, I'm grateful to Dr. Verinder Sharma for providing input and expertise on the thesis. The support, words of encouragement, and advice from every member of the committee were integral towards the completion of the thesis project.

Next, I would like to thank my family and friends who provided strong moral support throughout the process of graduate school. Especially my siblings, Jean and Jay, and my brother-in-law, Chris, whom all helped proofread this thesis. Also, I would like to dedicate a special thanks to my beloved dogs, Maya and Anca for always being there by my side. Lastly, my parents deserve all the thanks in the world for their unconditional love and encouragement every step of my academic journey.

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

SSRIs	Selective Serotonin Reuptake Inhibitors
SNRIs	Serotonin-Norepinephrine Reuptake Inhibitors
TCAs	Tricyclic Antidepressants
MDD	Major Depressive Disorder
CES-D	Center for Epidemiologic Studies Depression Scale
PHP	Prenatal Health Project
HPA-axis	Hypothalamic-Pituitary Adrenal Axis
SGA	Small-for-Gestational Age
IUGR	Intrauterine Growth Restriction
LGA	Large-for-Gestational Age
NICU	Neonatal Intensive Care Unit
TSC	Transferred to Specialized Care
ASQ	Ages and Stages Questionnaire
OR	Odds Ratio
MR	Morbidity Ratio
BCa	Bias Corrected and accelerated
CI	Confidence Interval

Chapter 1: Introduction, Rationale, and Objectives

The decision to take medication during pregnancy is a challenge faced by many pregnant women as all medications may potentially carry a risk of harming the developing fetus. This is certainly the case for depressed women determining whether or not to take antidepressant treatment during pregnancy. In order to assist women with evidence-based decisions, researchers and clinicians are faced with different challenges of assessing the risks and benefits of antidepressant treatment against the risks of untreated depression on the developing fetus. Even with the considerable amount of research, however, the risk of antidepressant treatment during pregnancy on the fetus and child development has been unclear [1, 2].

Due to ethical limitations in conducting randomized controlled trials (RCTs), all human studies to date that examined the safety and efficacy of antidepressant medication use during pregnancy on the subsequent neonatal and child development outcomes have been observational [3]. There are many challenges and limitations in designing an observational pharmacoepidemiological study in this field as well. The main challenge is in separating the effects of antidepressant use during pregnancy from the effects of underlying maternal antenatal depression on the outcomes of interest, since both have been individually found to be associated with adverse neonatal and long-term child developmental outcomes.

Therefore, the main goal for this thesis is to differentiate the effects between antenatal depression and *in utero* SSRI exposure on neonatal and child developmental outcomes. The majority of study designs in which outcomes of antidepressant exposure were investigated did not distinguish the effect of antenatal antidepressant use from any risk attached to the medical indications for antidepressant use, such as depression. Rather, studies have tended to compare an antidepressant exposure group to only the non-exposed group, which results in confounding by indication.

In this thesis, we will use a well-established prenatal cohort [4] in which data were collected prospectively. This allows us to design our study to reduce confounding by indication. In particular, we directly compare neonatal and child outcomes between those whose mothers had antenatal antidepressant use and antenatally depressed mothers

without antidepressant use, while using a group with neither exposure as the base comparison group. To our knowledge, only a small number of studies have this direct comparison for neonatal outcomes [5-8] and long-term developmental outcomes [9-13].

It is anticipated that this study will contribute to our understanding of the risks versus benefits of antidepressant use during pregnancy, in comparison to untreated antenatal depression. As this literature evolves, it will assist health care professionals in making evidence-based decisions.

1.1 Research Objectives

The primary goal of this project is to examine the neonatal and long-term developmental outcomes of antidepressant use, with special interest in SSRI use during pregnancy in women from London, Ontario, by using secondary data source from Prenatal Health Project (PHP). The specific objectives of this thesis project are as follows:

1. To describe the baseline characteristics of mothers who fit in the following study groups antenatally: 1) Antidepressant group: those who take antidepressants for any indication (indication unknown); 2) SSRI subgroup: those who take SSRIs; 3) Depressive Symptoms group: those who have elevated depressive symptoms but do not take antidepressants and; 4) Reference group: those who do not have elevated depressive symptoms and do not take antidepressants.
2. To compare neonatal outcomes among the study groups. Specific neonatal outcomes of interest are: preterm delivery, small-for-gestational age (SGA), large-for-gestational age (LGA), Apgar scores at one (Apgar-1) and five (Apgar-5) minutes, and NICU admissions.
3. To compare long-term development of toddlers and preschoolers (measured by Ages and Stages Questionnaire) among the study groups.

Chapter 2: Literature Review

2.1 Overview

The structure of this chapter outlines the characteristics and consequences of antenatal depression and antidepressant use during pregnancy, as well as the individual effect of both on neonatal and child development outcomes. It should be noted that this literature review will mainly focus on selective serotonin reuptake inhibitors (SSRIs) as they are the most studied, prescribed, and used antidepressant in our focused population.

2.2 Depression during Pregnancy: Characteristics and Consequences

2.2.1 Depression during Pregnancy: Prevalence

Pregnancy was generally believed to be protective against depressive disorders and thought to be associated with the state of emotional well-being [14]. However, evidence for this claim is sparse and many women have increased risk of developing and/or sustaining depressive disorders during pregnancy [14]. In fact, the first onset peak of depression for women is during the childbearing years [15]. According to the a meta-analysis conducted by Agency for Healthcare Research and Quality (AHRQ) [16], the point prevalence for combined major and minor depression during pregnancy was estimated to be 8.5 to 11.0 percent (3.1 to 4.9 percent for major depression alone) while the period prevalence of depressive disorder estimated from conception to birth was 14 to 23 percent. Bennett *et al.* [17] reported that the prevalence of depression increases from 7.4% in the first trimester to 12.8% in the second and 12.0% in the third trimester. Additionally, depression is a highly recurrent disorder and the risk of depressive relapse during pregnancy for women with a history of depression is approximately 43% [14]. Therefore depression is a prevalent condition affecting many women during pregnancy, notably more prevalent in disadvantaged groups such as young, single women with limited socioeconomical support [18].

2.2.2 Symptoms and Consequences of Antenatal Depression

Many pregnant women suffering from depression are often not recognized, or diagnosed, and subsequently not treated due to the similar features of depression and normal physiological and hormonal changes that occur during pregnancy such as changes

in mood, appetite, and sleep pattern [19]. The symptoms of antenatal depression are persistent low mood, loss of interest in daily activities, dramatic change in appetite, emotional disconnects with the unborn, negative thoughts, lack of self-care, and serious thoughts of suicide in severe cases [20, 21]. The consequences of these symptoms may lead to non-adherence to antenatal care, tobacco, alcohol, and drug use, poor weight gain or loss, poor nutrition, anxiety (strongly comorbid with depression), psychotic symptoms, preeclampsia, and post-partum depression [21, 22]. Despite the consequences and high prevalence of antenatal depression, many depressed pregnant women are under-treated or not treated at all [18, 23]. In a national survey, Dietrich *et al.* [24] found that fewer than half of obstetricians stated that residence training equipped them with the knowledge and training to recognize and treat depression. Additionally, the risk factors are not readily recognized [24].

2.2.3 Antenatal Depression Screening Tools

Early detection of antenatal depression improves the chances of effective treatment of depression and may prevent major depressive disorder (MDD) [25]. Therefore, the American College of Obstetricians and Gynecologists (ACOG) endorses screening for depressive symptoms at least once during pregnancy using a validated tool [26]. One of the most widely used and validated depression screening tools in antenatal research is the Center for Epidemiologic Studies Depression Scale (CES-D) [25, 27]. As well, it is recommended as part of the initial assessment for antenatal depression [25]. The CES-D measures the depressive symptoms (cognitive, somatic, affective, and behavioural) experienced by the participant in the past week [27]. The scale has 20 items and the score ranges from 0 to 60. A cut-off point of $\geq$16 is typically used to indicate clinical depression with a sensitivity and specificity of 60% and 92%, respectively [27].

Other tools such as the Edinburgh Postnatal Depression Scale (EPDS), Beck Depression Inventory (BDI), the BDI-II, the Patient Health Questionnaire-2 (PHQ-2), and the Pregnancy Depression Scale (PDS) are also implemented in antenatal health studies [25]. It is important to note that these tools do not serve as diagnostic tests for depression but rather indicate depressive symptoms and the possible risks of developing depressive disorder. To be clinically diagnosed with MDD by a physician, the patient

must fit the diagnostic criteria as described in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), which includes depressed mood or loss of pleasure in all or most of one's usual activities for more than 2 weeks and have experienced at least 5 out of 9 specific clinical features (depressed mood, significant weight change, insomnia or hypersomnia, suicidality, etc.) for nearly every day [28].

2.2.4 Antenatal Depression Risk Factors

Antenatal depression is associated with many factors including sociodemographic status, psychiatric comorbidities, life stresses, relationship quality, social support, substance abuse, and obstetric history [29]. A systematic review performed by Lancaster *et al.* [29] set out to identify the risk factors for antenatal depression that can be assessed in routine obstetric care. From 57 studies, they found that life stress, lack of social support, and domestic violence to be the strongest correlates with antenatal depression in their multivariable analyses. On the other hand, maternal anxiety, history of depression, unintended pregnancy, lower income, lower education, smoking, single status, and poor relationship quality were strongly associated with antenatal depression in their bi-variable analyses. Pregnant women with these risk factors are considered at high risk of developing antenatal depression and should be screened for depressive symptoms.

2.2.5 Antenatal Depression: Adverse Neonatal Outcomes

Depression during pregnancy has negative health consequences for both the mother and child. Antenatal depression has been found to be associated with increased risk of adverse neonatal events such as preterm delivery [30, 31], low birth weight [30, 31], intrauterine growth restriction (IUGR) [32, 33], and admissions to Neonatal Intensive Care Unit (NICU) [33]. The postulated mechanism is the dysregulation of the hypothalamic-pituitary adrenal axis (HPA-axis), sympathetic nervous system, and inflammatory system [34]. The increased secretion of maternal stress hormones such as corticotrophin releasing hormone, cortisol, and catecholoamines may directly or indirectly impact fetal development and epigenetically program the HPA-axis of the fetus via DNA methylation, which could potentially have long-term developmental consequences as well [35, 36]. In addition to the biological mechanisms, pregnant women

with depressive symptoms are also less likely to take care of themselves or to attend to antenatal care, and more likely engage in unhealthy lifestyle behaviours such as smoking and alcohol consumption that exacerbate the risk of adverse pregnancy outcomes [1, 35].

Numerous studies have examined the relationship between antenatal depression and adverse neonatal outcomes; however, many of these studies have methodological limitations due to lack of proper controls for confounders and size sample issues. In addition, the heterogeneity of study design further complicates the comparability of results [35]. The confounders that are inadequately controlled in most studies are the severity of depression, demographic factors, substance abuse, and comorbid psychosocial factors such as anxiety and self-reported stress [30, 35, 37]. Therefore, the findings for adverse neonatal outcomes such as preterm delivery, low birth weight, small-for-gestational age (SGA), low Apgar score, and admission to NICU are inconsistent.

Szegda *et al.* [35] critically reviewed studies that investigated antenatal depression and adverse neonatal outcomes including preterm birth, low birth weight, and SGA. Out of 27 studies, 12 found that antenatal depression, particularly early to mid-pregnancy, increased the risk of preterm birth with an odds ratio (OR) range of 1.3 to 4.9. The association between antenatal depression and low birth weight was less consistent as only 6 out of 20 studies discovered an increased risk with OR range of 1.4 to 2.2. An increased risk of SGA in infants exposed to antenatal depression, particularly during early to mid-pregnancy, was found in 5 out of 10 studies. A meta-analysis conducted by Grote *et al.* [30] gathered 29 prospective observational studies (n=48,004) and calculated the pooled relative risk. They found that antenatal depression was significantly associated with preterm birth (pooled RR: 1.13; 95% Confidence Interval (Cl): 1.06-1.21) and low birth weight (pooled RR: 1.18; 95% Cl: 1.07-1.30). Antenatal depression was not significantly associated with IUGR since only 2 out of 12 studies found this association. Conversely, another meta-analysis performed by Grigoriadis *et al.* [37] assessed the association between antenatal depression and adverse neonatal outcomes including premature delivery, gestational age, birth weight, NICU admission, and Apgar scores at 1 and 5 minutes. They examined 30 prospective observational studies and found an increased risk of premature delivery (OR: 1.37; 95% CI: 1.04-1.81) for depressed mothers during pregnancy. Other adverse neonatal outcomes were not found to be

significant. The postulated reasons for these discrepancies in results include the heterogeneity of study design, specifically the different tools used to measure depression, difference in the timing and severity of exposure, different confounding variables controlled, and different sample populations and sizes.

2.2.6 Antenatal Depression: Child Developmental Outcomes

Antenatal depression has been found to be associated with poorer child development including higher risk of cognitive delay [38-41], behavioural/social problems [38, 42, 43], reduced emotional ability [41], and attention problems [44] even after considering the confounding effects of other antenatal and postnatal risk factors. For instance, a prospective cohort study (n=10,125) examined the association between maternal depressive symptoms during pregnancy and child development at 18 months of age found that persistent depression (EPDS $\geq$ 10 at 18 and 32 weeks of gestation) was associated with developmental delay (OR: 1.34; 95% Cl: 1.11-16.2) for 18 month olds when adjusted for smoking, maternal age, and life events [38]. The association remained significant after adjustment for postnatal depression, although the effect was slightly attenuated.

Furthermore, the effects of antenatal depression have been illustrated be a predictor of violence [42] and depression [45] in adolescents. Pawlby *et al.* [45] conducted a prospective longitudinal community-based study and followed 84% (n=127) of the mother-child dyads from pregnancy to 16 years later. Psychological problems were assessed for adolescents at 16-years-old using the Child and Adolescent Psychiatric Assessment, in which 14% (18/127) were diagnosed with depressive disorder. The adolescents exposed to antenatal depression (11/17) had a 4.7 times greater odds (95% Cl: 1.60-13.86) of suffering from depression compared to youths not exposed. However, this effect was mediated by cumulative exposure to maternal depression during the lifetime of the child.

To add to this, antenatal depression is a strong predictor of postpartum depression [21]. It is well-documented in the literature that postpartum depression has a negative effect on mother-infant bonding and subsequent child development [46]. Hence, there are difficulties in examining the individual effect of antenatal depression on long-term child

development and adjusting for postnatal depression given that postnatal depression may be an intermediate in the causal pathway or a standalone factor influencing child development [38]. With that said, the effect of antenatal depression on child development is substantial and estimated to explain 10-15% of the poor emotional and behavioural outcomes in children [47].

2.3 Use of Selective Serotonin Reuptake Inhibitors (SSRIs) during Pregnancy: Characteristics and Consequences

2.3.1 Treatments of Antenatal Depression

Given the potential negative consequences of antenatal depression on the well-being of the mother-child dyad, it is important that women with depressive symptoms during pregnancy seek treatment. Antenatal depression can be treated or managed with two main modalities: depression-specific psychotherapy and pharmacotherapy. For pregnant women who are not suicidal and drug naïve (new to treatment for the illness) with mild to moderate symptoms of depression, interpersonal psychotherapy is recommended as initial treatment [48, 49]. For pregnant women who are suicidal or with moderate to severe depression and have past history of good response to medication, pharmacotherapy is recommended, specifically SSRIs, as the first line treatment, and is often supplemented with psychotherapy [49].

Other classes of antidepressant prescribed during pregnancy are: serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), serotonin antagonist and reuptake inhibitors (SARIs), and tricyclic antidepressants (TCAs). In a large Québec study of 97,680 database subjects, Ramos *et al.* [50] found that SSRIs (64.4%), SNRIs (12.3%), and TCAs (12.1%) were the three most commonly used classes of antidepressants during pregnancy.

2.3.2 SSRIs

Currently the most prescribed class of antidepressants during pregnancy is SSRIs, second-generation antidepressants [48, 50]. Although the first-generation antidepressants such as TCAs are as effective in managing depressive symptoms as SSRIs, first-generation antidepressants have a high adverse effect profile and narrower therapeutic-

toxicity window with common side effects of hypotension, sedation, and other anticholinergic effects [51]. Additionally, unlike TCAs, SSRI overdose does not cause cardiotoxicity and overdose-related death is rare [51]. However, there remain side effects that accompany SSRI use, such are nausea, headache, sexual dysfunction, weight gain, serotonin syndrome (headache, sweating, tremor), and increased risk of suicide in some (within the first to second month of treatment, especially noted in youth and young adults) [52]. There are currently six SSRIs available on the market in Canada: citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft) [51], all of which are approved for MDD treatment, except for fluvoxamine, which is only approved for obsessive compulsive disorder [53]. Clinicians also prescribe SSRIs for other approved or unlabeled therapeutic uses other than MDD, including anxiety disorder, obsessive-compulsive disorder, panic disorder, social phobia, post-traumatic stress disorder, premenstrual dysphoric disorder, and eating disorder [54].

Although as a class, various SSRIs share the basic mechanism of action, the chemical structures of different types of SSRIs are considerably distinct. Consequently, the pharmacokinetics properties, including absorption, distribution, metabolism, and elimination of the medications are quite dissimilar [55]. Hence, the dosages administrated and half-lives, which range from days to hours, are distinctive. For example, the half-life of norfluoxetine, active metabolite of fluoxetine, is 7 days, so patients who abruptly discontinue fluoxetine are less likely to suffer from discontinuation syndrome [55]. In addition, specific SSRIs are metabolized by different hepatic cytochrome P450 enzymes (CYPs) therefore blood concentration of metabolites highly depends on interindividual variability [55].

The main mechanism of action of SSRIs is via inhibition of the neuronal 5-hydroxytryptamine (5-HT) reuptake pump at the serotonergic synapse without affecting other neuroreceptors [55, 56]. SSRIs decrease the efficiency of the serotonin reuptake pump by 60% to 80%, thereby increasing the concentration of serotonin (5-hydroxtryptamine, 5-HT) at the synaptic gap, and further enhancing serotongeric neurotransmission [56]. Serotonin is known as the neurotransmitter associated with complex emotions, such as affection and happiness [57]. However, the serotonin-

deficiency syndrome offers a simplistic explanation for the complex pathology of depression. The alternative theory explains the root cause of depression as due to the deficiency of synaptogenesis and neurogenesis. An indirect effect of SSRIs activate the signal transduction pathway on serotonergic neurons, which causes an increase expression of regulatory factors such as Brain Derived Neurotropic Factor (BDNF) [58]. The functions of BDNF are to promote 5-HT neuron and synapse growth, differentiation, and survival [58]. Overall, a concrete theory on the pathology of depression has yet to be settled and the exact mechanisms of action of SSRIs are still under investigation.

2.3.3 Characteristics of SSRI Use during Pregnancy

It is estimated that 7% to 13% of pregnant women in the United States (US) use SSRIs [59] and approximately 2.3% of 4 million infants born in the US each year are exposed to *in utero* SSRIs according to the data from National Birth Defects Prevention Registry [60]. Also, the rate of SSRIs use during pregnancy has increased over past decade in North America [61] For example, in British Columbia, Canada, SSRI use during pregnancy doubled from 2.3% to 5% between 1998 and 2001 [6].

Ramos *et al.* [50] discovered that the prevalence rate of antidepressant use decreased significantly from 6.6% during the 12 months before the first day of gestation to 3.7% in the first trimester. This decreasing trend continues to the second (1.6%) and third trimester (1.1%) then significantly increases again to 7% during the 12 months after the end of pregnancy. Their results suggest that pregnant women are hesitant to continue treatment during pregnancy or healthcare providers are cautious about prescribing antidepressants during pregnancy. Pregnant women who discontinue antidepressant treatment are at an increased risk of relapse and withdrawal symptoms [14], which as aforementioned has negative consequences for the mother and fetus.

Ramos *et al.* [50] also found several predictors of antidepressant use on the first day and the end of pregnancy, which were advanced maternal age, recipient of welfare, having a higher number of prescription medications, a higher number of prescribers, a higher number of visits to physicians before pregnancy, and a depression diagnosis before or during pregnancy. These predictors suggest that women who initiated or opted

to continue antidepressant treatment during pregnancy were likely to have more severe depressive symptoms compared to women who did not initiate or discontinued.

According to the Food and Drug Administration (FDA), all SSRIs, except paroxetine, are classified as Pregnancy Category C drugs, meaning the risk is not ruled out given the lack of sufficient and well-controlled human studies to support animal studies that have produced evidences of adverse effect on the fetus [1, 61]. Paroxetine is labeled as Pregnancy Category D drug, which means there is positive evidence of fetal risk from human studies, specifically cardiovascular malformations [1, 61]. However, the potential benefits of both Categories C and D drugs may permit their use during pregnancy even with their potential risks [61].

2.3.4 Adverse Neonatal Outcomes of SSRI Use during Pregnancy

SSRIs are known to cross the human placenta so there are concerns over the impact of their use during pregnancy on fetal development and health [62]. In addition, the use of SSRIs during pregnancy remains controversial due to inconsistent results regarding the risks of their use on several adverse neonatal outcomes. For instance, SSRI usage late in pregnancy is known to be linked to a small increase in the risk of two adverse neonatal effects: neonatal abstinence syndrome (NAS) and persistent pulmonary hypertension (PPHN), although there are conflicting reports. Similarly, the finding for other adverse neonatal outcomes such as preterm birth, SGA, Apgar score at 1 and 5 minutes, and NICU admission have been inconsistent in the literature.

2.3.4.1 Neonatal Abstinence Syndrome (NAS)

NAS or poor neonatal adaptation syndrome (PNAS) has been linked to exposure to SSRIs in the late third trimester and is characterized by a list of signs and behaviours that include irritability, abnormal crying, tremour, respiratory distress, digestive disturbance, hypoglycemia, hypothermia, hyperreflexia, sleep disturbance, feeding issues, and seizures [63]. These signs and behaviours are usually self-limiting and abate within a few days to 2 weeks with strategies such as decreasing sensory stimulus and ensuring skin-to-skin contact between mother and infant [64]. Neonates with severe NAS require further monitoring and nursing in the NICU [65]. The pathophysiology of NAS is thought

be caused by the serotonergic withdrawal effect or overstimulation of serotonergic system from *in utero* SSRI exposure [63].

In a cohort study, Levinson-Castiel *et al.* [66] used the Finnegan score to assess NAS of 120 term infants. Of the 60 infants exposed to *in utero* SSRIs, 18 (30%) showed mild to severe symptoms of NAS whereas all non-exposed infants had normal Finnegan scores. In a review, Moses-Kolko *et al.* [64] calculated the risk ratio (RR) and 95% CI from the raw data of 5 cohort studies that examined the relationship between antenatal SSRI exposure and NAS and found that late SSRI exposure was associated with an increased risk (RR: 3.0; 95% CI: 2.0-4.4) of neonatal abstinence syndrome compared to early SSRI and no SSRI exposure. Consequently, these infants were admitted to special care nursery units (RR: 2.6; 95% CI: 1.4-4.7) and the hospital lengths of stay were longer. Furthermore, a meta-analysis [67] of 12 studies, which aggregated to 3780 infants exposed to antidepressants, found *in utero* antidepressants exposure was associated with NAS (OR: 5.07; 95% CI: 3.25-7.90), respiratory distress (OR: 2.20; 95% CI: 1.81-2.66), and tremours (OR: 7.89; 95% CI: 3.33-18.73)

Therefore the literature on the effect of late SSRI exposure on NAS has been quite consistent. The FDA has issued a warning for physicians and mothers to be aware the risk of NAS if taking antidepressants late in pregnancy, especially paroxetine due to its short half-life [65].

2.3.4.2 Persistent Pulmonary Hypertension (PPHN)

PPHN occurs when the pulmonary vascular resistance or blood pressure remains elevated after birth in newborns. This causes blood circulation to shunt from the right to the left side of the circulatory system (away from the lungs), resulting in hypoxemia [68]. PPHN is estimated to occur in 1 or 2 infants per 1000 live births and is associated with increased rate of mortality (10-20% even after treatment) and morbidity [68]. Due to compromised tissue oxygenation, survivors have increased risk of cognitive delay, hearing loss, and neurological abnormalities [69]. The findings on the relationship between SSRI exposure and PPHN have been inconsistent where some studies have found *in utero* SSRI exposure increases the risk of PPHN [68, 70-72], while others have not [73, 74].

A multinational population-based study [71] of over 1.6 million infants discovered that newborns whose mothers filled a prescription for SSRIs later than 20th week of gestation had a high risk of PPHN (adjusted OR: 2.1; 95% CI: 1.5-30). The absolute risk of PPHN was 2.9 per 1000 live births for SSRI-exposed infants versus 1.2 per 1000 live births for infants not exposed. A recent meta-analysis [72] of seven high quality studies showed that late pregnancy exposure to SSRIs was associated with PPHN (OR: 2.50; 95% CI: 1.32-4.73), but not early pregnancy exposure to SSRIs. Clinically speaking, the absolute risk of PPHN after late pregnancy SSRI exposure remained small at 2.9 to 3.5 per 1000 live births since it is a rare disease. In 2011, the FDA revised their warning and recommended that physicians continue their standard practice, as the findings are still inconclusive [65].

2.3.4.3 Preterm Birth

Preterm birth is defined as the birth of the neonate at less than 37 weeks of pregnancy [7] and continues to be one of the leading causes of neonatal and infant mortality and morbidity in developed nations [75]. Approximately 75% of perinatal mortality occurs in premature infants [75]. Additionally, premature infants are at higher risk of having neonatal complications and chronic health problems [75].

Findings on the relationship between *in utero* SSRI exposure and preterm birth have been inconsistent, as some studies have found evidence of a significant association between *in utero* SSRI exposure and preterm birth [5, 7, 8, 76-80] whereas others have not [63, 81, 82]. A retrospective cohort study of 33,791 mother-child pairs was conducted by Grzeskowiak *et al.* [7] to investigate the neonatal outcomes of infants exposed to *in utero* SSRIs during late gestation. They found that infants exposed to SSRIs during pregnancy had an increased risk of preterm delivery compared to infants whose mothers had psychiatric illness but no SSRI use (adjusted OR: 2.68; 95% CI: 1.83-3.93) and compared to infants whose mothers had no psychiatric illness at all (adjusted OR: 2.46; 95% CI: 1.75-3.50). A meta-analysis of 14 studies documented that antidepressant use during pregnancy was significantly associated with an increased risk of preterm birth (pooled OR: 1.55; 95% CI: 1.38-1.74) [80]. However, the clinical significance is questionable given the gestational age of neonates exposed to *in utero* SSRIs was three

days shorter than non-exposed neonates. A comparison of depressed women who took antidepressants during pregnancy versus depressed women who did not take antidepressants during pregnancy in five studies showed a marginal trend toward significance (pooled OR: 1.58; 95% CI: 0.97-2.56) suggesting that the effect of antidepressant use on preterm birth is perhaps independent of maternal depression [80]

Moreover, underlying maternal depression may be a significant confounding factor in the observed association between antenatal SSRI exposure and preterm birth. A prospective observational study (n=2,793) found an increased risk of preterm birth among women who took SSRIs during pregnancy with (OR: 2.1; 95% CI: 1-4.6) or without (OR: 1.6; 95% CI: 1.0-2.5) a major depressive episode. However, untreated women with a major depressive episode did not have increased risk of preterm birth [83]. After controlling for illness severity factors (age of illness onset, number of hospitalizations, number of depressive episodes, and suicidal ideation.), the effect of antenatal SSRI exposure on preterm birth was attenuated and no longer significant.

2.3.4.4 Apgar Score

Apgar score is a method used to assess the health of the newborn immediately after birth to determine whether the newborn requires immediate medical care [84]. It is based on five criteria: appearance/complexion (cyanosis, acrocyanosis, or no cyanosis), pulse rate (absent, <100 beats/minute, or >100 beats/minute), reflex irritability grimace (no response to stimulus, grimace on stimulus, or cry on stimulus), activity (no flexion, some flexion, or arms and legs resistance), and respiratory effort (no cry, weak gasping, or strong cry). The overall score is out of 10 with each criterion scored from 0 to 2 [84]. A score of 7 or higher is considered normal and 3 and below is critically low. The assessment is usually administrated at one and five minutes after birth and repeated if the score remains low. A low score at the one-minute test may indicate the newborn needs further medical attention but typically the score improves with subsequent Apgar calculations. If the score persists to be severely low at 10, 15, or 30 minutes, it is taken as an indication that the newborn may suffer from neurological problems in the long run [84].

Many studies have documented the relationship between *in utero* SSRI exposure and low Apgar scores [8, 76, 78, 85]. In a prospective cohort study, Lund *et al.* [8] compared neonatal outcomes among 329 pregnant mothers exposed to SSRI treatment, 4902 pregnant women who had a history of psychiatric illness but no SSRI exposure, and 51,770 pregnant women with no psychiatric history. Infants exposed to *in utero* SSRIs had an increased risk of scoring 7 or below for the 5-minute Apgar compared to infants whose mothers had a history of psychiatric illness (adjusted OR: 6.58; 95% CI: 3.39-12.74), and to infants whose mothers had no history of psychiatric illness (adjusted OR: 6.58; 95% CI: 3.39-12.74).

2.3.4.5 Neonatal Intensive Care Unit (NICU)

Several studies have documented that newborns exposed to *in utero* SSRIs are at an increased risk of admission to NICU [6-8, 63]. A potential explanation is that neonates exposed to *in utero* SSRIs have higher risk of developing NAS. Lund *et al.* [8] reported a higher rate of NICU admission among newborns exposed to SSRIs *in utero* compared to newborns whose mothers did not have a history of psychiatric illness (adjusted OR: 2.39; 95% CI: 1.69-3.39) and to newborns whose mothers did have a psychiatric history (adjusted OR: 2.04; 95% CI: 1.42-2.94). Comparable results with similar adjusted OR and 95% CI was reported by Grzeskowiak *et al.* [7]. Furthermore, a meta-analysis of 9 studies designed to investigate the relationship between late pregnancy SSRI exposure and NAS reported that late pregnancy exposure to SSRIs is associated with an increased risk of NICU admissions (OR: 3.3; 95% CI: 1.45-7.54) [63]. In contrast, Suri *et al.* [86] did not find an increase in NICU admission in infants exposed to *in utero* SSRIs.

2.3.4.6 Small-for-Gestational Age (SGA)

SGA is defined as birth weight less than the 10^{th} percentile for gestational age [7]. Of newborns who are defined as SGA, 70% are just constitutionally small and not at risk of neonatal complications [87]. SGA in newborns who are not constitutionally small are likely intrauterine growth restricted (IUGR) as a result of reduced oxygen and nutrient supply to the fetus due to genetic or environmental factors [7]. Consequently, the fetus is unable to reach its genetically programed potential growth. In addition, SGA in infants

with birth weight lower than the 3rd percentile for gestational age typically have severe IUGR, which can lead to neonatal complications including impaired thermoregulation, hypoglycemia, polycythemia, impaired immune system, and increased risk of mortality (4 to 8 times higher risk of mortality) [88]. Infants born SGA are also at increased risk of having health problems later in life such as psychiatric disorders [89], cardiovascular disease [90], and metabolic syndrome [90]. Thus far, the majority of studies have only examined birth weight without accounting for gestational age so infants categorized as low birth weight (<2500g) may include those of low gestation with appropriate birth weight for their gestational age. Risk factors associated with SGA and IUGR can be categorized into 3 classifications: maternal, fetal, and placental. Maternal factors include vasculopathy disorders (preeclampsia, nephropathy), virus infections, maternal substance abuse (smoking, alcohol use, illicit drug use), and other maternal demographic variables (race, age, and parity) [91]. Fetal factors involve genetic abnormalities and major congenital anomalies of the fetus. Lastly, placental factors include abnormal placental blood circulation and chronic placental inflammatory lesions [92].

Some studies have found an association between *in utero* SSRI exposure and SGA [6, 89] while others have not [7, 78, 85]. Oberlander *et al.* [6] used population health data to link records of neonatal birth outcomes with maternal health and antenatal SSRI prescription records and identified 1,451 depressed mothers treated with SSRIs, 14,234 depressed mothers without treatment, and 92,192 controls. They discovered that birth weight and gestational age were significantly lower for neonates exposed to SSRIs compared to neonates exposed to antenatal depression, but birth weight at less than 10th percentile for gestational age was not significant. When propensity score matching was used to control for severity of maternal illness, SSRI-exposed infants had a significantly increased incidence of birth weight below the 10th percentile.

2.3.4.7 Large-for-Gestational Age (LGA)

LGA is defined as birth weight greater than 90th percentile for the gestational age [93]. From the US birth registry, infants born at 40 weeks gestational age at 90th percentile and 97th percentile have birth weight greater than 4000 grams and greater than 4400 grams, respectively [94]. Infants weighing 4000 grams and beyond are diagnosed as

macrosomia and the morbidity, neonatal, and delivery (e.g. shoulder dystocia) complication rates increase at this threshold [93, 95]. Infants born LGA are also at risk for the development of Type II Diabetes Mellitus and metabolic syndrome later in life [95]. The incidence of macrosomia has increased in developed countries as maternal age, weight, and incidence of gestational diabetes at the time of pregnancy has increased and the prevalence of smoking decreased [95]. The maternal risk factors associated with excessive intrauterine growth are factors that cause excess delivery of nutrients to the fetus including maternal diabetes, maternal pre-pregnancy weight, and excess gestational weight gain [96]. Other risk factors are multiparity, advanced maternal age, post-term pregnancy, previous LGA birth, genetic syndromes, race and ethnicity [96].

SSRI use has been found to be associated with weight gain (via stimulation of appetite) [97], insulin resistance [98], diabetes [99], and obesity [100] therefore SSRI use during pregnancy may indirectly influence LGA. Kallen *et al.* [78] used the Swedish Medical Birth Registry to identify and prospectively collect a sample of over half a million infants. Infants exposed to *in utero* SSRIs had an increased risk of being LGA compared to total population group after adjusting for confounders, but which did not reach statistical significance. The same result was found 6 years later in their follow-up study [85].

2.3.5 Child Developmental Outcomes of SSRI Use during Pregnancy

Studies on the long-term development of children exposed to *in utero* SSRIs are relatively limited compared to studies that examined adverse neonatal effects of SSRI exposure. Our literature review identified 26 observational studies that investigated the long-term child development outcomes of children born to mothers who took SSRIs during pregnancy: 14 prospective [9-11, 101-111], 6 retrospective [12, 13, 112-115], and 6 case-control studies [116-121]. The age of the children involved in these studies ranges from infants (6-months-old) to adolescence (17-years-old in a case-control study on autism) with the majority of studies focused on children less than 6 years of age. Different studies implemented different developmental tests to measure a wide range of developmental outcomes. For example, for cognitive testing, the Bayley Scales of Infant Development, Wechsler Preschool and Primary Scale of Intelligence, or McCarthy Scales

were implemented by different studies. The sample size ranged from 22 children (prospective study) to 8,833 children (population-based register study) exposed to *in utero* SSRIs. The majority of the prospective studies had very small sample sizes. For instance, a sample cohort from British Columbia, Canada was followed longitudinally and examined in 3 different studies had an exposure group of ≤ 33 children [105-107]. The main developmental outcomes studied were organized into cognitive functioning, fine motor movement, gross motor movement, personal/social behavioural development, communication/language development, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD).

2.3.5.1 Role of Serotonin

As mentioned previously, SSRIs increase the serotonin availability in the neural network and are known to cross the placenta to the fetus [62]. In the early stages of embryogenesis, serotonin is one of the main signaling molecules vital for fetal neurodevelopment due to its importance in neuronal cell proliferation, migration, signaling, synaptogenesis, and ultimately development of the CNS [122]. Therefore, increased levels of serotonin during the crucial period of embryogenesis and fetal brain development may have adverse consequences. In animal models, the early administration of SSRIs in neonates and the subsequent increase in neural serotonin level have been found to influence fetal brain development, as seen in changes in neuronal structure of the somatosensory cortex and the related behavioural changes in adolescent rats [123] (See Appendix A for animal model literature review).

Changes in serum protein levels integral for fetal neurodevelopment, such as Activing A and Reelin gene expression, have been found linked to *in utero* SSRI exposure in human studies [124, 125]. Additionally, serotonin is responsible for various physiological pathways and has an extensive role in the CNS involving cognition, memory, learning, and muscle tone [126].

2.3.5.2 Cognition/Problem Solving

No studies to date have found an association between *in utero* SSRI exposure and adverse cognitive outcomes [9, 101-104, 121] in children. A prospective study conducted

by Nulman *et al.* [9] recruited participants through the Motherisk Program and selected four different study groups: depressed women on Venlafaxine (SNRI) during pregnancy (n=62), depressed women on SSRIs during pregnancy (n=62), depressed women who were untreated (n=54), and healthy women (n=62). They reported that the children (3 to 6-years-old) of healthy mothers had a significantly higher verbal and full scale IQ scores (measured by Wechsler Preschool and Primary Scale of Intelligence) than children whose mothers were on Venlafaxine and SSRIs while pregnant. However, by performing the regression analysis and accounting for confounders, maternal IQ was discovered to be a significant predictor for the child's IQ. The difference found in verbal and full scale IQ between the children exposed to *in utero* SSRIs and children of healthy mothers was accounted for by maternal IQ and child's gender and not by drug exposure.

2.3.5.3 Fine and Gross Motor Movements

Many studies have found an association between antenatal SSRI exposure and a deficiency in fine [103] and gross [12, 103, 104, 109] motor movement in children. Casper *et al.* [103] found that children (6 to 40-months-old) exposed to *in utero* SSRIs had significantly lower scores on the Bayley Psychomotor Developmental Index (scoring motor skills such as rolling, crawling, grasp, and use of utensils) and the Bayley Behavioural Rating Scales, specifically on fine motor movement and tremulousness sub-scores. However, the study was underpowered with 31 children exposed to *in utero* SSRIs and 13 children in the control group. In a similar study [104], children with longer *in utero* exposure to SSRIs had an increased risk of having lower scores on the Psychomotor Developmental Index compared to controls. However, results from subsequent neurological examination discovered that the motor functioning of children remained within the normal range.

A large population study [12] investigated the effect of antenatal SSRI exposure on normal milestone development at 6 and 19 months of age. Using the Danish National Birth Cohort database, a sample size of 81,946 was obtained and divided into 3 study groups: women on antidepressant during pregnancy (n=415), depressed women without antidepressant treatment (n=489), and non-depressed women (n=81,042). They found that at the sixth-month developmental milestone evaluation, children who were exposed

to SSRIs during the second and third trimesters had increased odds (adjusted OR: 2.1; 95% CI: 1.23-3.60) of abnormal gross motor development, specifically sitting without support, compared to children of untreated mothers. However, this developmental delay was within normal range of development and resolved by 19 months of age.

2.3.5.4 Communication/ Language Development

A Norwegian population-based prospective pregnancy cohort study [111] of 45,266 mothers with 51,748 children examined the language competency of 3-year-old children using the language grammar rating scale questionnaire. They reported that women with long-term SSRI use during pregnancy were more likely to have children with lower language competency compared to children whose mother did not take SSRIs during pregnancy. The underlying maternal anxiety and depression before and during pregnancy were independent of the observed moderate language delay. Whether the moderate language delay manifests later in the child's life is unclear.

Other than the above study by Skurtveit *et al.* [111], no other studies to date has found an association between *in utero* SSRI exposure and delayed communication/language development [101, 102, 109, 115].

2.3.5.5 Personal/Social Behavioural Development

Majority of studies did not indicate an association between antenatal SSRI exposure and personal/social behavioural problems in children [9, 10, 13, 101, 102, 106, 107]; however, a few did [12, 104, 108, 110]. Casper *et al.* [104] found that longer antenatal exposure to SSRIs (throughout pregnancy) significantly increased the risk of lower Behavioural Rating Scale scores in 12-to-40-month-old children, particularly on orientation/engagement and emotional regulation ($p=0.007$). However, based on a subsequent neurological examination, mental development of children was found to be normal. Pedersen *et al.* [12] reported that children exposed to SSRIs in the second or third trimester had attention problems, specifically an inability to occupy themselves for 15 minutes, at the 19th month milestone evaluation compared to children whose mother had untreated depression (OR: 2.1; 95% CI: 1.09-4.02) after adjusting for several covariates including postnatal depression. Another study longitudinally followed 30

children who developed SSRI-induced NAS and 52 children without NAS at the age of 2 to 6 years [108]. They discovered that children with NAS had normal cognitive ability and developmental scores but were at an increased risk for abnormal social-behavioral development (OR: 3.03; 95% CI: 1.07-8.60) compared to 52 children without NAS [108]. In another small sample study, Hanley *et al.* [110] found that children exposed to *in utero* SSRIs had higher levels of internalizing behaviour (withdrawal, anxiety, depression) at three and six years of age compared to non-exposed children independent of maternal status of mood disorders throughout pregnancy and childhood.

Misri *et al.* [107] and Oberlander *et al.* [106] assessed internalizing (emotional reactivity, withdrawal, irritability, depression, or anxiety) and externalizing (activity, attention, and impulsivity) behaviors, respectively, in four and five year olds who were and were not exposed to SSRIs antenatally. The level of internalizing behaviour was not different between the children in the exposed and non-exposed groups. Instead, maternal depression and anxiety were associated with an increase of internalizing behavior of their children [107]. Antenatal SSRI and depression exposure did not predict externalizing behaviours; on the other hand, current maternal mood and stress did [106]. In a follow-up study, Oberlander *et al.* [105] explored the effect of antenatal SSRI exposure on behavioural development of three-year-olds using Child Behavior Checklist. They found that antenatal exposure to SSRIs in combination with concurrent maternal anxiety were associated with an increased rate of internalizing behaviour. Externalizing behavior was associated with current maternal mood but not antenatal SSRI exposure.

2.3.5.6 Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD)

The evidence for an association between *in utero* SSRI exposure and ASD in children has been inconsistent where some studies supported a positive association [114, 116, 117, 127] and some did not [113, 118, 119]. All the studies used health care databases to select their sample, with sample sizes ranging from 812 to 654,288. A meta-analysis [128] of 4 case-control studies [116-119] supports the association between *in utero* SSRI exposure and ASD (adjusted OR: 1.81; 95% CI: 1.47-2.24). However, the

causality is unknown. Furthermore, the two population cohort studies [113, 114] from the same database produced contradictory results.

Figueroa *et al.* [112] found that *in utero* exposure to SSRIs was not associated with ADHD using claims-based data. However, a recent large database case-control study [120] supported an association between antenatal antidepressant exposure and ADHD after controlling for maternal depression (OR: 1.81; 95% CI: 1.22-2.70).

2.3.5.7 Covariates

Studies examined in this review of literature have controlled a variety of confounders, including maternal age [12, 13, 104, 108], maternal IQ [9, 101, 102], socioeconomic status [9, 101, 102], education [102, 103, 106], household income [9, 110], parity [7, 10], weight gain in pregnancy [101, 102], alcohol or tobacco use during pregnancy [101, 102], severity and duration of depressive [101, 106, 107] and anxiety symptoms [102, 105, 107], duration of treatment [106], presence of postpartum depression [12, 102, 105], Apgar score [105], perinatal complications [112], breastfeeding status [12], and other maternal medical factors (maternal diabetes, hypertension, asthma, and thyroid disorder) [7, 103, 104]. A conceptual model based on causality and temporality was constructed from the most commonly used confounders and is shown in Appendix B. The model framed the objectives for this study.

2.3.5.8 Summary of Long-Term Developmental Studies

Some studies indicated that antenatal SSRI use could lead to adverse developmental outcomes; however, the clinical relevance of such findings and their manifestation later in life remain unclear. In all, the results of numerous studies seem to suggest that antenatal SSRI usage does not have a serious detrimental impact on long-term development of children. However, due to the heterogeneity of study design, difference in sample population and size, variation in confounder adjustment, and different SSRI usage, it is very difficult to compare results and draw a definite conclusion.

To date only a few studies have compared long-term outcomes of children of depressed mothers, with or without SSRI usage during pregnancy, to non-depressed

mothers during pregnancy [9-13]. These studies, therefore, were able to compare the impact of maternal mood on child development and directly relate this to the effects of antenatal SSRI exposure. The remaining studies had women who were not depressed during pregnancy and were not using SSRIs as a control group, precluding the separation of depression and SSRIs in their outcomes. Therefore, more well-designed studies are needed to determine with certainty the long-term effects of antenatal SSRI exposure on offspring.

Chapter 3: Methods

3.1 Secondary Data Source: The Prenatal Health Project

This thesis project used data from a longitudinal cohort study, the Prenatal Health Project (PHP). The PHP was designed to understand how prenatal factors impact the health and wellbeing of mothers and children before and after pregnancy.

Pregnant women residing in the London-Middlesex, Canada region were recruited, via convenience sampling, in ultrasound clinics in London, Ontario, Canada between the periods of 2002 to 2005. Only women 16 years of age and older who carried singleton pregnancies between 10 to 22 weeks gestation, spoke English, and lived in London-Middlesex region were eligible. Exclusion criteria were high-risk pregnancy and known congenital abnormalities. Data were collected throughout the three project phases: prenatal, perinatal, and toddler/childhood phase, as described below.

PHP data collection was approved by the Ethics Review Broad for Health Science Research Involving Human Subjects at the University of Western Ontario. The review numbers of ethics approval are 08253E and 10787E.

3.1.1 Prenatal Phase

Women were initially informed about the PHP by ultrasound technicians at their scheduled ultrasound appointments. Informed written consent and contact information were gathered from women who were interested in participating after speaking with the PHP research assistant. Participants were then contacted on the day of the scheduled telephone interview to complete the prenatal survey (Appendix C). A trained interviewer collected information on socio-demographics factors, maternal lifestyle, dietary intake, and medical health. The variables of interest to this thesis are described in more detail in Section 3.4.

3.1.2 Perinatal Phase

Consent for review of perinatal hospital medical records, including delivery room charts and maternal and neonatal medical records, had been obtained at recruitment. Data on obstetrical risk factors, delivery process and complications, and neonatal health status and measurements were abstracted by a trained medical records technician using a Data

Abstraction Form. The perinatal variables of interest to this thesis are also discussed in detail in Sections 3.4.

3.1.3 Toddler/Childhood Phase

Women who were recruited at the start of the PHP were contacted again after their child was between two to five years of age. Data regarding the mother's and her child's psychosocial, developmental and nutritional health, and health system use were collected over a scripted telephone interview. After completing the postnatal survey, mothers were asked to participate in a short survey regarding the child's development. If mothers were interested in participating, the Ages and Stages Questionnaire (ASQ) was mailed to the participating mothers. Mothers had the options of submitting the ASQ via mail, online website, or over the telephone. Again, specific variables of interest will be discussed in Section 3.4.

3.2 Prenatal Health Project Cohort

The recruitment flow chart is summarized in Figure 3.1. Initially, 3656 women were asked to take part in the study and 2761 women agreed to participate. Of those women who agreed, 2421 completed the prenatal survey via telephone interview for a response rate of 66%. Women with a miscarriage, abortion, neonatal demise, or had missing perinatal data were eliminated from the study (n=23). Additionally, 15 women were lost to follow-up. Also, 26 women completed the survey twice for different pregnancies; therefore one of the duplicates were chosen at random and excluded from the sample. Overall, the PHP cohort consisted of 2357 women for whom both the prenatal survey data and perinatal chart data were complete.

At the toddler/childhood phase when the children were two to five-years-old, 1608 (68%) participants from the original sample participated in the follow-up survey. An aspect of the data collection at this phase included completion of a mailed Ages and Stages Questionnaire (ASQ). Of those women who participated in the follow-up survey, 980 (61%) returned the completed ASQ.

3.3 Study Groups

The study groups were identified based on the following prenatal variables: prescription medication questions; and the 20-item Centre for Epidemiological Studies Depression Scale (CES-D) score.

The Antidepressant group included mothers who were taking antidepressants during pregnancy. Antidepressant use during pregnancy was collected during the prenatal telephone survey by asking women to list the prescription medications they took regularly at the time. Information on the amount (number of pills and dosage) and the frequency of antidepressant use was also available. All antidepressants (SSRIs, SNRIs, NDRIs, SARIs, and TCAs) reported were of interest for this thesis due to their shared mechanism of action in inhibiting neurotransmitter (serotonin, norephinephrine, and dopamine) reuptake at the synapse cleft to prolongs the neurotransmission [51]. The selective serotonin reuptake inhibitors (SSRIs) class of antidepressants was especially of interest since it is currently the most commonly prescribed and used class of antidepressants during pregnancy [59] therefore it was further classified as its own subgroup. In brief, women who reported taking antidepressants during pregnancy belonged in the Antidepressant group with a subset in the SSRI subgroup.

The Depressive Symptoms group included mothers with depressive symptoms but not taking antidepressants. Maternal depressive symptoms were assessed using the 20-item CES-D score from the prenatal survey. The CES-D is a commonly used screening instrument for depressive symptomology associated with major clinical depression in the general population [27] and its use is recommended for the initial evaluation of antenatal depressive symptoms [25]. The 20 items inquire how often (<1 day, 1-2 days, 3-4 days, or 5-7 days) the participant felt a certain way (feeling of guilt, worthlessness, loss of appetite) in the past week with each answer scored on a 4-point Likert scale ranging from 0 to 3. CES-D scores range from zero to sixty and the higher scores indicate greater depressive mood. The cutoff point for possible clinical depression is ≥16 [27]. Therefore, women who scored 16 or higher on the CES-D but did not take antidepressants belonged in the Depressive Symptoms group.

Lastly, the Reference group consisted of women who did not take antidepressants during pregnancy and scored lower than 16 on the CES-D.

During the postnatal period, specifically when the toddler was >24 months, mothers were asked “have you ever been diagnosed as having depression or a mood disorder?” Previously diagnosed depression or mood disorder was dichotomized to yes or no. To confirm the study group classifications, a cross tabulation was performed between this variable and the study groups to compare the frequency distribution.

3.4 Variables of Interest

The following section of the thesis lists and describes in detail the applicable PHP variables established *a priori* based on literature. Table 3.1 describes the variables on maternal characteristics, details on coding, the original questions asked in the survey, and when the variables were collected. Additionally, neonatal outcome variables gathered during the perinatal phase are described in detail in Section 3.4.4 and Table 3.2. Furthermore, Section 3.4.5 describes the developmental outcome measure, specifically, Ages and Stages Questionnaire

3.4.1 Baseline Maternal Variables

Maternal Age

Participants self-reported their date of birth during the prenatal telephone survey. Maternal age at the time of delivery was calculated by subtraction from delivery date. The maternal age variable was kept continuous.

Parity

Parity was measured by asking women the year of each previous pregnancy and whether it was a livebirth, stillbirth, or miscarriage/abortion. Parity was defined as the number of times a woman has given live birth excluding stillbirth, miscarriages, and fetal demises and dichotomized as 0 (nulliparous) or ≥1 (primiparous/multiparous) at the time of the current pregnancy.

Education

Women reported their highest level of education as: elementary school, some high school, completed high school, some college or university, college diplomas, university

degree, trade school, or other (specified). Education was dichotomized to less than/completed high school or greater than high school education. Less than high school and completed high school were grouped together due to small cell sizes.

Income

Income was ascertained by asking women their best estimate of total gross income (monetary value in CAN$) from all members of the household before taxes and deductions in the past year. Women had the initial option of selecting <$30K or ≥$30K then subsequent selection further divides into eight other total gross income amount options ranging from <$10,000 to >$80,000. No income, don't know, refuse to answer were also available options and were coded as missing.

Income was then categorized as <30K (low-income), 30K-80K (middle-income), and >80K (upper-middle-income). This categorization is based on a Statistics Canada report on low-income-cut-off for urban community size of 100,000 to 499,999 in 2005, which was $27,386 and $33,251 before taxes for family household of three and four persons, respectively [129]. Conveniently, the cutoff given in the questionnaire was consistent with the Statistics Canada cutoff for low-income families.

Marital Status

Women reported their current marital status as: married, common law (or living as married), single/never married, separated/divorced, and widowed. Marital Status was then categorized as married, common law, and other (single/never married/separated/divorced) in the study. There were no widows in the cohort.

Pre-Pregnancy Body Mass Index

Body mass index (BMI) was calculated from the participant's self-reported height and weight and was calculated in kg/m^2. Women were asked how tall they were without shoes and how much they weighed before pregnancy. The standardized cutoff points were categorized based on the current WHO categories: <18.5 (underweight); 18.5 to <25 (normal); 25 to <30 (overweight); and ≥30 (obese) [130]. Underweight and normal

weight were grouped together due to the small cell size of underweight category in the Antidepressant group.

3.4.2 Prenatal Maternal Variables

Alcohol use

Alcohol use during pregnancy was recorded by asking women the number of drinks (i.e. glass of wine, beer, or mixed drink) they consumed typically per week at the time. The detrimental effects of alcohol consumption during pregnancy are well documented and there are no known safe level and time of alcohol consumption during pregnancy. Therefore, alcohol usage during pregnancy was dichotomized as yes or no.

Smoking status

Women were asked “how many cigarettes do you typically smoke each day now?” Like alcohol use, there are no safe levels and time of smoking during pregnancy so smoking status during pregnancy was categorized as smoker during pregnancy and non-smoker during pregnancy.

State Anxiety

State anxiety quantifies how anxious a person is feeling at a particular moment and is measured using the 12-item shortened state version of the State-Trait Anxiety Inventory (STAI) [131]. The STAI is one of the most widely researched and administered tests for general anxiety. Women were asked how they were feeling in the past week regarding their state of anxiety with questions such as “I am calm” and “I am jittery”. Responses were recorded using the 4-point Likert scale ranging from 1 to 4: not at all, somewhat, moderately so, and very much so. The STAI is a validated and reliable screening tool for state anxiety and the higher score indicates higher level of state anxiety [131]. Since there are no known cutoffs for STAI scores, the scores were kept continuous and converted to standardized score for analysis.

Medical Conditions

Women were asked whether or not they currently have or had any of the following health conditions: heart disease/cardiovascular disease, high blood pressure before pregnancy, high blood pressure during pregnancy, diabetes before pregnancy, diabetes during pregnancy, asthma, and/or thyroid conditions. Medical conditions of interest for this thesis were hypertension before and during pregnancy, diabetes before and during pregnancy, asthma, and thyroid conditions. Each medical conditions of interest was dichotomized as yes or no.

Weight Gain during Pregnancy

Weight gain during pregnancy was collected during the perinatal phase from the Data Abstraction Forms under summary information on the additional maternal risk factors during pregnancy. The underlying data source, the perinatal chart, only classifies weight gain as: low ($\leq$20lbs), appropriate (21lbs to 39lbs), and high weight gain ($\geq$40lbs).

3.4.4 Neonatal Outcome Variables

Preterm birth

Gestational age was obtained and calculated from the following data sources: participant's self-reported last menstrual period during the prenatal survey and newborn's date of birth; participant's self-reported gestational period during the ultrasound clinic visit and newborn's date of birth; and infant's delivery chart (gestational age recorded at the time of delivery by medical experts). Gestational age from infant's hospital chart was deemed as the final and correct estimation if the gestational ages from the three data sources were within seven days of each other. However, when an estimate from a data source was discordant from the other estimates by more than seven days, then all available hospital records were reviewed by a medical records technician to investigate the possibilities of transcription error. In the case that the estimates were truly different by more than 7 days, an OB/GYN reviewed all the hospital charts of the participant and determined the best and final gestational age estimate. Gestational age was rounded to the

following week if the days were ≥5. Preterm birth is defined as the birth of the baby at less than 37 week; therefore it was dichotomized as <37 weeks and ≥37 weeks [7].

Size for Gestational Age

Size for gestational age was categorized as small-for-gestational age (birth weight ≤10^{th} percentile for gestational age), average for gestational age (birth weight >10^{th} to 90^{th} percentile for gestational age) and large-for-gestational age (birth weight >90^{th} percentile for gestational age). The variables required to calculate size for gestational age were newborn birth weight, gender, and gestational age. The method for this calculation is based on Canadian population standards from Kramer *et al.* [132].

Apgar Score

Apgar scores taken at one (Apgar-1) and five (Apgar-5) minutes after birth were abstracted from the infant's hospital chart by trained technicians onto the Data Abstraction Form during the perinatal stage. Apgar score assesses the following criteria of the newborn: appearance/complexion, pulse rate, reflex irritability/grimace, activity, and respiratory effort. Each criterion is scored from 0 to 2, with the overall score ranging from 0 to 10. A score of 7 or higher is considered normal therefore Apgar score was dichotomized as <7 and ≥7 [84].

Transferred to Specialized Care (TSC)

Infants transferred to specialized care (TSC) involved those admitted to Pediatric critical care unit (PCCU) and neonatal intensive care unit (NICU) after birth. TSC was dichotomized to whether newborns were transferred to PCCU/NICU or not.

3.4.5 Developmental Outcome Variables

Toddler/child development was examined using the age specific ASQ administrated by the parents. ASQ is a developmental screening tool that evaluates five domains: communication, gross motor, fine motor, problem solving, and personal social skills [133]. Each domain has six items pertaining various domain-specific tasks such as sentence formation, running, and drawing. The responses for each item are categorized as

yes, sometimes, or not yet, each worth ten, five, and zero points, respectively. The maximum score for each domain is sixty.

Conventionally, the score from each domain is compared to an age specific cut-off point. According to the ASQ manual, a child is considered a "fail" on the ASQ if the child scored below but near the cutoff point for just one domain [133]. However, for the purpose of this thesis project, the scores from each domain were kept continuous and analyzed separately.

Missing items were handled according to the ASQ manual where missing items were imputated with the average score for the specific domain [133]. Parents who completed fewer than three items for each domain were removed from the sample. Out of the 980 women who returned the ASQ, three ASQs were removed because one ASQ could not be linked to the mother's Study ID, one did not answer any questions, and another only answered one question per domain. In addition, 67 toddlers/children were preterm infants and were excluded, resulting in 910 toddlers/children analyzed for this thesis.

3.6 Statistical Analysis

3.6.1 Preliminary Inspection and Handling of Dataset

Preliminary inspection of the dataset was executed using exploratory univariate analysis to inspect the variables' distribution, missing variables, and to ensure all relevant variables were cleaned and made sense. Categories of variables with low observed frequencies were collapsed together. After the subsequent data cleaning, variables were recoded to the desired and intended use described in previous sections.

3.6.2 Descriptive Analysis: Objective 1

To describe the baseline characteristics of mothers who belonged in the Antidepressant, SSRI, Depressive Symptoms, and Reference group for Objective 1, cross tabulation analysis was used for categorical variables to report the frequency distribution of maternal characteristics described in Section 3.4.1 and 3.4.2. Continuous variables were compared among the study groups using descriptive analysis.

3.6.3 Descriptive Analysis: Objective 2

To compare neonatal outcomes among the study groups for Objective 2, bi-variable cross tabulation analysis was used again to examine the frequency distribution of preterm delivery, small-for-gestational age (SGA), large-for-gestational age (LGA), Apgar score, and TSC. Due to the imbalanced dataset of the study groups and the small sample size of the Antidepressants group and SSRI subgroup, the Morbidity Ratio (MR) methodology of Liddell [134] was used to obtain a 95% confidence interval of the rate ratio for a Poisson estimate. The MR was the ratio of morbidity (preterm and LGA) observed to those expected morbidity rate. The expected morbidity rate was based on some reference population, in this case, the Reference group and the Depressive Symptoms group.

The analysis of Apgar scores and TSC were restricted to only infants born at term to eliminate the potential of confounding by preterm birth. To calculate the expected morbidity rate of the remaining neonatal outcomes (Apgar-1, Apgar-5, and TSC) for the MR, the reference population was based only on the Depressive Symptoms group due to the low frequency count of adverse events and the similar rates of neonatal outcomes among the Reference group and Depressive Symptoms group.

The two assumptions made were the Observed Counts (O) follows a Poisson distribution (random variable with a Poisson distribution) and Expected Counts (E) were error-free because it is based on a sufficiently large sample [134]. The linked relationship between the Poisson and Chi-square distribution allowed us to use the Chi-square distribution to get the critical value to calculate the confidence limits. The following equations were used to calculate the lower and upper limits of the 95% confidence interval [134].

$$\text{Lower limit: find } \chi^2_L \text{ for which } Q(\chi^2_L|2O) = 1 - \frac{1}{2}\alpha;$$

$$\text{then } E_L = \frac{1}{2}\chi^2_L \text{ and } MR_L = \frac{1}{2}\chi^2_L/E;$$

$$\text{Upper limit: find } \chi^2_U \text{ for which } Q(\chi^2_U|2O+2) = \frac{1}{2}\alpha;$$

$$\text{then } E_U = \frac{1}{2}\chi^2_U \text{ and } MR_U = \frac{1}{2}\chi^2_U/E$$

3.6.4 Descriptive Analyses: Objective 3

The ASQ score for each domain was negatively skewed with a ceiling effect due to the normal development of the vast majority of toddlers and children. Therefore to compare the long-term child development outcomes (communication, fine motor movement, gross motor movement, problem solving, and social/personal skills) of toddlers, preschool age children among the study groups for Objective 3, bootstrapping method was used where observations from the original datasets were resampled 2000 times with replacement for each study group's domains to construct a normal distribution. The 95% confidence interval for each study group of each domain was calculated from the mean values of the bootstrapped samples using the Bias Corrected and accelerated (BCa) method. The BCa method adjusts for the bias in the bootstrap estimates using the bias correction and acceleration coefficients hence it is considered the improved bootstrap confidence interval [135]. The SAS macro *Jackboo*t was downloaded from the SAS website in order to run the bootstrap [136].

3.6.5 Secondary Analyses

The small sample size of the Antidepressant group prevented an adequate multivariable analysis for the investigation of the increased frequency of LGA observed in the Antidepressant group. To investigate whether this increased frequency was related to antidepressant use or the maternal characteristics of those taking antidepressants, a multivariable analysis of the Reference group was performed. The Reference group was chosen as a proxy population for the Antidepressant group due to the substantially larger sample size and the similar maternal baseline characteristics between the two groups. Missing cases for LGA were deleted and missing variables were handled using listwise deletion.

Univariable analysis, specifically Pearson chi-square or Fishers exact test was performed to examine the relationship between the individual categorical covariates and LGA. The crude relationships between the individual covariates and LGA were examined using simple logistic regression. Variables with significance level of $p \leq 0.2$ were fitted in the multivariable logistic regression model. The backward elimination procedure was used with the pre-set significant level of $p < 0.05$. The model included maternal education,

income, pre-pregnancy BMI, parity, smoking status during pregnancy, diabetes before and during pregnancy, and weight gained during pregnancy. Alcohol use during pregnancy was not included in the model due to low cell count. Statistical analyses were performed using SAS 9.4.

Figure 3.1. Prenatal Health Project Recruitment Flow Chart

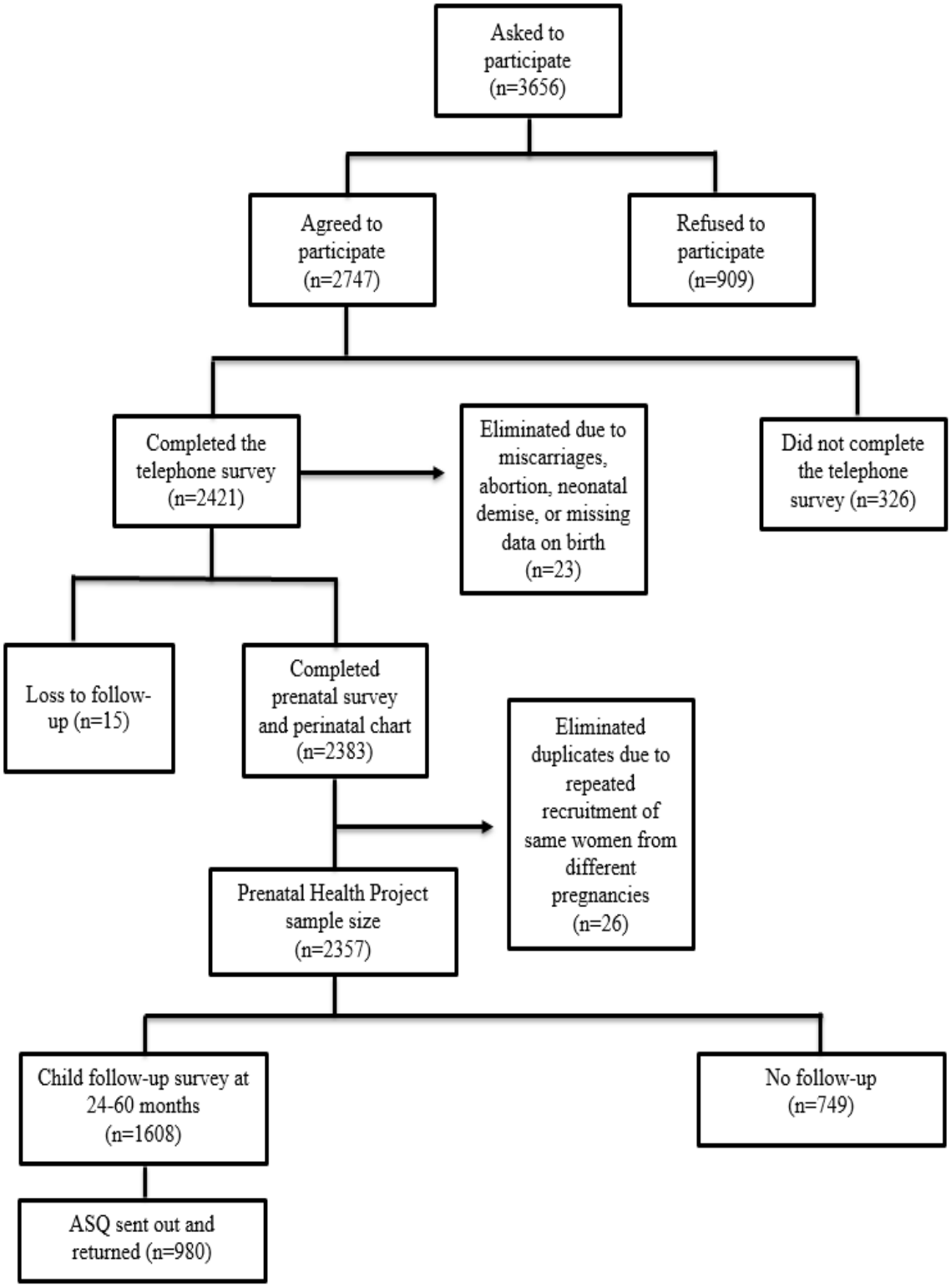


Table 3.1. Variable definitions of maternal characteristics

Maternal Characteristics Variables	**Original Question Asked in PHP Questionnaire**	**Original Format of Variable**	**Variable Codes**	**When the Variable was Acquired (Phase)**
Smoking Status	How many cigarettes do you typically smoke each day now?	Numeric Value	0 = Non-smoking during pregnancy (0) 1 = Smoked during pregnancy (≥ 1)	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)
Alcohol Use	How many drinks do you typically have per week now? By drink I mean a glass of wine, beer, or a mixed drink	Numeric Value	0 = Non-consumer during pregnancy (0) 1= Consumer during pregnancy (≥ 1)	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)
Parity – Previous live births (excluding stillbirths, miscarriages, and fetal demises)	Please tell me the year that each of your previous pregnancies ended, and if it was a livebirth, stillbirth, miscarriage, or abortion.	Numeric Value (1 to 8)	0 = 0 live births 1 ≥ 1 live births	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)
Education – Highest education level	What is your highest level of formal education you have completed?	1=Elementary School 2=Some high school 3=Completed high school 4= Some college or university 5=College diploma 6=University degree 7=Trade school 8=Other	0 = Did not complete high school or Completed high school 1 = More than high school	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)

Income – Total household income	Best estimate of total gross income from all member of the household before taxes and deductions in the past year What is your best estimate of the total income of all members of your household from all sources before taxes and deductions for the past year? By total income I mean total gross income from paid employment, government assistance, student loans, or inheritance.	1 = less than 30K 2 = greater than or equal to 30K 3 = less than 15K 4 = greater than or equal to 15K 5 = less than 60K 6 = greater than equal to 60K 7 = less than 10K 8 = 10K to $14,900 9 = 15K to 19,999 10 = 20K to 29,999 11 = 30K to 39,999 12 = 40K to 59,999 13 = 60K to 79,999 14 = 80K or more 15 = no income 16 = don't know 17 = refused to answer	1 = less than 30k 2 = 30k-80k 3 = more than 80K Refused to answer/unclear coded as missing	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)
Marital Status	What is your current marital status?	1=Married 2=Common Law 3=Single/Never married 4=Separated/divorced 5=Widowed	1 = Married 2 = Common Law 3 = Single/Never married, Separated/divorced	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)
Maternal Age	What is your date of birth?	Women's' date of birth	Continuous	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)

Maternal pre-pregnancy BMI	How tall are you without shoes? How much did you weigh prior to this pregnancy	Numeric Variable then calculated to BMI (kg/m^2)	1 = <18.5 (underweight), 18.5-<25 (normal) 2 = 25-<30 (overweight) 3 = ≥30 (obese)	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)
Weight gain during pregnancy	Other risk factors during pregnancy: Other	0=20lbs or less 1=appropriate 2=40lbs or more Comes from Pregnancy risk factors in perinatal data set (s3_orisk1_details and s3_orisk2_details)	0 = 20lbs or less 1 = appropriate 2 = 40lbs or more	After birth; Data extracted from the hospital medical records (Perinatal Phase)
Antidepressant Use	Please tell me any OTC and prescription medications you take regularly now, the number of pills or dosage if you know it, and how many times you take them per day	List of medications	0 = none 1 = Antidepressants	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)
Depressive Symptoms	20-items CES-D questionnaire	Numeric Variable	0 = less than 16 1= equal or greater than 16	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)
Anxiety Measure	12 items shorten state version of the State-Trait Anxiety Inventory (STAI)	Numeric Variable	Continuous	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)

Diagnosed with Depression or Mood Disorder in the Past	Have you ever been diagnosed as having depression or a mood disorder?	Yes or No	Dichotomized	≥24 months old follow up questionnaire (Postnatal Phase)
Medical Conditions	Pre-existing/Existing Health Conditions I am going to read a list of health conditions. For each, please say yes if you currently have conditions or have had the condition in the past. If you do not have, or have never had the condition please respond with no. Do you have or have you ever had.	Yes or No: High blood pressure before pregnancy Diabetes before pregnancy Asthma Thyroid condition	Dichotomized	Telephone interview after first visit to ultrasound clinic (Prenatal Phase)

Table 3.2. Variable definitions of neonatal outcomes

Neonatal outcomes	**Available in Dataset**	**Original Format of Variable**	**Variable Codes**	**When the Variable was Acquired (Phase)**
Preterm	Gestational Age: 1. Patient's self-reported LMP and baby's date of birth 2. Gestational age at reported at delivery (expert's medical opinion) 3. Patient's self-reported gestational at recruitment and baby's date of birth Preterm Labour: <37 weeks	Dichotomous	0 = term birth 1 = preterm birth	After birth; Data extracted from the hospital medical records (Perinatal Phase)
Size for Gestational Age	Gestational Age: 1. Patient's self-reported LMP and baby's date of birth 2. Gestational age at reported at delivery (expert's medical opinion) 3. Patient's self-reported gestational at recruitment and baby's date of birth Infant Birth weight: Grams, Lbs, Oz Infant Gender: Male or Female	Numeric	0 = 3rd percentile (severe SGA)/3rd to 10th percentile (moderate SGA) 1 = 10th to 50th percentile (AGA)/50th-90th percentile (AGA) 2 = >90th percentile (LGA)	After birth; Data extracted from the hospital medical records (Perinatal Phase)

Apgar-1	Apgar Score Total	Numeric	1 = less than 7 2 = equal to or greater than 7	After birth; Data extracted from the hospital medical records (Perinatal Phase)
Apgar-5	Apgar Score Total	Numeric	1 = less than 7 2 = equal to or greater than 7	After birth; Data extracted from the hospital medical records (Perinatal Phase)
Transferred to Specialized Care (TSC)	Transferred to home, triage/7east, with mother/well nursery, PCCU, NICU triage, or NICU admission	Dichotomous	0 = not admitted to NICU and PCCU 1 = admission to NICU and PCCU	After birth; Data extracted from the hospital medical records (Perinatal Phase)

Chapter 4: Results

4.1 Study Sample

As presented in Section 3.2, the initial PHP cohort consisted of 2357 women who completed the cross sectional survey and consented to the release of perinatal birthing information. Only women who completed the CES-D question and prescription drugs questions were included for the study. Of the initial cohort, 16 women did not complete CES-D Score, one woman did not complete the prescription drugs question, and another woman did not complete either; therefore, 18 women were excluded, leaving the sample size of 2339 women with both prenatal and perinatal information. Figure 4.1 shows the sample size flow of the study groups in the Prenatal, Perinatal, and Postnatal Stages. The sample size for each study group at the outset (prenatal) was as followed:

- 44 women (1.88%) reported antidepressant use during the pregnancy (Antidepressant group);
- 32 women (1.37%) were on SSRIs (SSRI subgroup);
- 421 women (18.00%) reported clinically significant depressive symptoms without antidepressant intervention (Depressive Symptoms groups);
- 1874 women (80.12%) did not have clinically significant depressive symptoms nor report antidepressant use (Reference group).

4.2. Antidepressant Use

The specific antidepressants used during pregnancy are presented in Table 4.1. Of the 44 women who reported antidepressant use during pregnancy, 32 (72.7%) were SSRIs, five (11.4%) were SNRIs, four (9.1%) were on TCAs, two (4.6%) on NDRIs and one (2.3%) on SARI. Further data on the amount and frequency of use is presented in Table 4.2. The dose for all women was within the recommended range and two women were on the maximum recommended dose: sertraline (SSRI) – 200mg/day and nefazondone (SARI) – 600mg/day. All women reported having taken antidepressants daily except for three women: one took venlafaxine (SNRI) every 2-3 days, one took sertraline daily if she could afford it, and one took fluoxetine (SSRI) every other day.

4.3 Characteristics of the Study Groups

Maternal characteristics are presented in Table 4.3, stratified by study group membership. Given the imbalanced sample size distribution of the study groups and the small sample size of the Antidepressants group and SSRI subgroup, we were left to describe the maternal characteristics of the study groups by comparing frequency distribution and means.

To begin, women in the Antidepressant group and SSRI subgroup were more likely to be overweight or obese, where the Antidepressant group had the largest percentage (30.2%) of overweight (BMI 25 - <30kg/m^2) women before pregnancy and the SSRI subgroup had the largest percentage (25%) of obese (BMI ≥30kg/m^2) women before pregnancy. The Antidepressant group and SSRI subgroup were also more likely to be primiparous/multiparous (61.4% and 56.3%, respectively), whereas the percentages of nulliparous and primiparous/multiparous for both Reference group and Depressive Symptoms groups are close to equal at 50%.

Furthermore, women in the Antidepressant group and SSRI subgroup were older, more likely to be married, more likely to have higher than a high school education, and more affluent relative to women in the Depressive Symptoms group. Specifically, the mean maternal age of women in the Antidepressant group and Depressive Symptoms group were about 31 (standard deviation [SD] of 4.4) and 28 (standard deviation [SD] of 5.5), respectively. The rates of women who had an education higher than high school in the Antidepressant group and SSRI subgroup were 86.4% and 84.4%, respectively, compared to 67.7% of women in the Depressive Symptoms group.

The majority (75%) of women in the Antidepressant group and SSRI subgroup were married compared to 56.4% in the Depressive Symptoms group. Women in the Depressive Symptoms group were more likely to be single/never married, or separated/divorced (20%) compared to other study groups (3.1% - 6.8%).

Women in the Antidepressant group and SSRI subgroup were also more affluent such that 36.4% and 37.5% had an annual household income greater than $80,000 compared to 24.8% of women in the Depressive Symptoms group. Furthermore, women in the Depressive Symptoms group were more likely to report an annual household

income of less than $30,000 (25.6%) compared to the Antidepressant group (18.2%) and SSRI subgroup (15.6%).

The demographic characteristics (maternal age, income, marital status, and education) of women in the Antidepressant group and SSRI subgroup were comparable to women in the Reference group. Women in the Reference group were the most affluent and only 8.5% of women reported an annual household income of less than $30,000.

Notably, the women in the Depressive Symptoms group were more likely to display high-risk behaviours during pregnancy. Women in the Depressive Symptoms group had higher rate of smoking (22.5%) and alcohol consumption (4.5%) during pregnancy compared to the other groups (smokers: 7.8%-11.4%; alcohol use: 1.8%-3.1%). Furthermore, women in the Depressive Symptoms group were the most likely to gain 40 pounds or more during pregnancy (15.7%) and the SSRI subgroup had the fewest women gaining 40 pounds or more during (9.4%). Other than that, weight gain during pregnancy was relatively comparable in all groups.

Very few women in the study gained 40lbs or more during pregnancy, had hypertension, diabetes, and thyroid condition before and/or during pregnancy with cell counts at $\leq$5 in the Antidepressant group and SSRI subgroup. Women in all study groups had similar rates of hypertension before and/or pregnancy (9.3%-11.4%). Both the Antidepressant group and SSRI subgroup were more likely to have a thyroid condition (6.8% and 9.4%) and diabetes (4.5% and 6.3%); however, the cell sizes were too small to make further inferences. The occurrence of asthma was more likely for women in the Antidepressant group (25%) compared to other study groups. The mean (SD) state anxiety STAI raw scores for the Antidepressant, SSRI, Depressive Symptoms, and Reference group were 23.3 (7.2), 23.2 (7.0), 27.5 (5.5), and 19.4 (4.4), respectively.

For the confirmation of the classification of study groups, it was found that high percentages (87.5% and 94.1%) of women in the Antidepressant group and SSRI subgroup were diagnosed with depression or mood disorder in the past. Whereas 31.9% and 11.7% of women in the Depressive Symptoms group and Reference group were diagnosed with depression or mood disorder in the past.

4.4 Study Groups and Outcomes

4.4.1 Neonatal Outcomes

The frequency distributions for preterm birth, SGA, and LGA are shown in Table 4.4a. The rate of preterm birth and LGA was higher in the Antidepressant group (preterm: 13.6%; LGA: 32.6%) and the SSRI subgroup (preterm: 18.8%; LGA: 32.3%) than the Depressive Symptoms (preterm: 7.6%; LGA: 12.0%) and Reference group (preterm: 5.3%; LGA: 12.6%). SGA infants were not observed in the Antidepressant group and SSRI subgroup.

Table 4.4b presents the expected count of preterm birth, SGA, and LGA (based on the rate of the Reference group), the MR of observed/expected, and the 95% Poisson confidence interval of the rate ratio. There was a significantly higher count of preterm births in the SSRI subgroup when the expected rate was based on the rate of the Reference group (MR=3.4, 95% CI: 1.3-7.7). The count of LGA was also significantly higher in the Antidepressant group (MR=2.6, 95% CI: 1.4-4.4) and SSRI subgroup (MR=2.6, 95% CI: 1.2-4.7). When using the rate based on the Depressive Symptoms group, the number of LGA was significantly higher in both the Antidepressant (MR=2.6, 95% CI: 1.4-4.4) group and SSRI (MR=2.7, 95% CI: 1.3-5.0) subgroup as presented in Table 4.4c.

The frequency distributions for Apgar-1, Apgar-5, and TSC of infants born at term are shown in Table 4.5. Preterm newborns (n=138) were excluded; therefore, the sample sizes of the study groups of infants born at term were reduced to: 38 in the Antidepressant group, 26 in the SSRI subgroup, 389 in the Depressive Symptoms group, and 1774 in the Reference group. The number of newborns in the Antidepressant group and SSRI subgroup who were transferred to specialized care units and scored lower than seven on the Apgar at one and five minutes were very diminutive at less than five observations. However, infants in the Antidepressant group and SSRI subgroup were more likely to score less than seven on the Apgar at one and five minutes relative to the Depressive Symptoms and Reference group. The small cell sizes make it difficult to show significant increased risks when the expected rate was based on Depressive Symptoms group. The rates of TSC were comparatively similar for all the study groups.

4.4.2 Developmental Outcomes

Table 4.6 presents the bootstrapped mean and the 95% Bootstrap Bias Corrected and accelerated (BCa) Confidence Interval of the ASQ score for each domain. Due to loss to follow up (n=749), unwillingness to participate in the ASQ survey (n=628), removal of the returned incomplete ASQ survey (n=3), and the elimination of toddler/children who were born preterm (n=67), the sample sizes of the study groups were reduced to 15 in the Antidepressant group, 9 in the SSRI subgroup, 120 in the Depressive Symptoms group, and 775 in the Reference group.

Toddlers/children of the Reference group and the Depressive Symptoms groups had very similar bootstrapped mean scores and overlapping confidence intervals across all domains.

The Antidepressant group had a lower bootstrapped mean score for the communication (54.8; 95% CI: 49.2-58.6), gross motor (53.7; 95% CI: 45.2-58.9), fine motor (49.9; 95% CI: 40.7-55.2), and personal/social skills (54.3; 95% CI: 49.3-58.3) domain compared to the Depressive Symptoms and Reference groups. The SSRI subgroup had the lowest bootstrapped mean score for the communication (52.4; 95% CI: 45.8-58.1), gross motor (49.4; 95% CI: 36.5-57.1), fine motor (44.4; 95% CI: 32.2-56.0), and personal/social skills (52.2; 95% CI: 45.3-58.2) domains compared to all the groups. Due to the small sample size of the Antidepressant group and SSRI subgroup, the 95% Bootstrap Bias Corrected and accelerated (BCa) Confidence Intervals were very wide and overlapped in all the study groups for all development domains and further analysis and inference was not possible.

4.5 Secondary Analysis on the Reference Group

Given an increased frequency of LGA in the Antidepressant group, it was of interest to investigate whether this increased frequency was due to the Antidepressant, *per se*, or the maternal characteristics of those taking antidepressants. The small sample sizes precluded a full multivariable analysis of this question. However, the role of various covariates in the risk of LGA in the Reference group was investigated to explore inferences related to maternal characteristics.

Table 4.7 presents the frequency distribution and the univariable association between maternal characteristics and LGA using Pearson chi-square test and Fisher exact test. The sample size used for this analysis was 1854 after removing 20 missing cases from the size of gestational age variable. The results of the univariable and multivariable logistic regression analysis are shown in Table 4.8. The variables that had $p \leq 0.2$ in univariable analysis, thus included in the multivariable logistic regression model, were: education level, annual income, pre-pregnancy BMI, parity, smoking status during pregnancy, diabetes before and/or during pregnancy, and weight gain during pregnancy. Although alcohol use during pregnancy had a p-value of 0.1227, it was not included in the model due to small cell size.

The final sample size of the multivariable logistic regression model was 1684. The variables that stayed significantly associated ($p<0.05$) to LGA in the model were pre-pregnancy BMI, parity, smoking during pregnancy, diabetes before and/or during pregnancy, and weight gained during pregnancy.

Compared to women whose pre-pregnancy BMI was <25 (normal or underweight), women whose pre-pregnancy BMI was ≥30 (obese) had increased odds of having infants born LGA (OR=2.05, 95% CI: 1.36-3.08). Women who had a pre-pregnancy BMI of 25 to <30 also had increased odds of having infants born LGA (OR=1.58, 95% CI: 1.12-2.24) compared to the infants of women whose pre-pregnancy BMI was <25 (normal or underweight).

Women who were primiparous or multiparous were more likely to have LGA infants compared to women who were nulliparous (OR=1.51, 95% CI: 1.12-2.04). Women who smoked during pregnancy were less likely to have LGA infants compared to women who did not smoke during pregnancy (OR=0.47, 95% CI: 0.23-0.96). Furthermore, women who had diabetes before and/or during pregnancy had an increased risk of having LGA infants compared to women who did not have diabetes before and/or during pregnancy (OR=2.79, 95% CI: 1.43-5.46).

Lastly, compared to women who had appropriate weight gain during pregnancy (>20 to <40lbs), women who gained 40lbs or more had an increased risk of delivering LGA infants (OR=2.23, 95% CI: 1.51-3.30).

In the model diagnostic, the Hosmer and Lemeshow goodness-of-fit test showed that the multivariable logistic regression model was a good fit (chisq: 3.15, df: 6, p=0.7901). The pseudo R-square and max-rescaled pseudo R-square for the model were 0.0290 and 0.0544, respectively. The diagnostic test for multicollinearity indicated that it was not a concern since all the predictor variables had variance inflation factor of lower than two.

4.6 Summary of Findings

In regards to Objective 1, our findings suggested that women on antidepressants were more likely to be overweight and obese before pregnancy, primiparous or multiparous, and asthmatic in comparison to the other study groups. Furthermore, women displaying depressive symptoms were younger, less likely to have more than high school education, less likely to be married, less financially well-off, more likely to display harmful behaviours during pregnancy, and had the highest STAI raw scores compared to the other study groups.

In regards to Objective 2, the results from the univariable analysis suggested that infants exposed to antidepressants and SSRIs *in utero* were more likely to be LGA compared to the infants whose mothers belonged to the Depressive Symptoms or Reference groups. Based on the multivariable logistic regression of the Reference group, women who were primiparous/multiparous, overweight and obese before pregnancy, diabetic before and/or during pregnancy, and had weight gain of 40lbs or more during pregnancy had an increased odd of having LGA infants.

In regards to Objective 3, toddlers/preschoolers of women who were on SSRIs had lowest mean score in the communication, fine and gross motor movement, and personal/social skills domain of the ASQ compared to the other groups.

Figure 4.1. Sample flow for the Prenatal, Perinatal, and Postnatal Phases: the Flow Pertains to the Analyses for this Thesis Project.

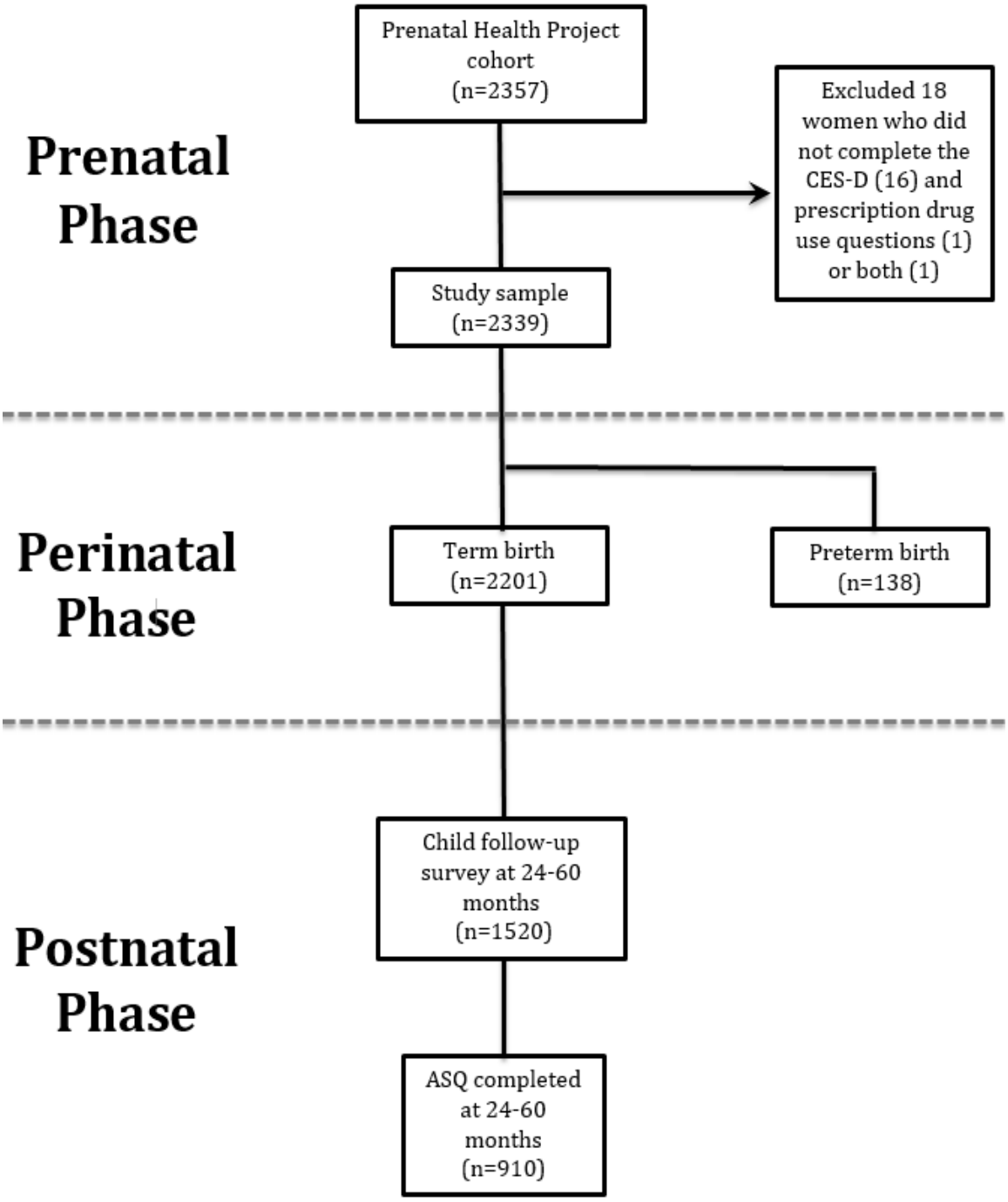


Table 4.1. Antenatal antidepressant use

Antidepressants (n=44)	**Frequency (%)**
SSRIs (n=32)	
Citalopram (Celexa)	5 (11.4%)
Fluvoxamine (Luvox)	1 (2.3%)
Paroxetine (Paxil)	9 (20.4%)
Sertraline (Zoloft)	9 (20.4%)
Fluoxetine (Prozac)	7 (15.9%)
Unknown	1 (2.3%)
SNRIs (n=5)	
Venlafaxine (Effexor)	5 (11.4%)
NDRIs (n=2)	
Bupropion (Wellbutrin)	1 (2.3%)
Bupropion (Zyban)	1 (2.3%)
SARIs (n=1)	
Nefazodone (Serzone)	1 (2.3%)
TCAs (n=4)	
Amitriptyline	4 (9.1%)

Table 4.2. Amount and frequency of antenatal antidepressant use

Antidepressants	**Count – Amount/day**
SSRIs	
Citalopram (Celexa)	5 – 20mg/day
Fluvoxamine (Luvox)	1 – 50mg/day
Paroxetine (Paxil)	1 – 10mg/day 6 – 20mg/day 1 – 30mg/day 1 – 40mg/day
Sertraline (Zoloft)	1 – 25mg/day 1 – 50mg/day 5 – 100mg/day 2 – 200mg/day[1]
Fluoxetine (Prozac)	1 – 10mg every other day 2 – 20mg/day 3 – 40mg/day 1 – 60mg/day
Unknown	1 – 75mg/day
SNRIs	
Venlafaxine (Effexor)	1 – 20mg every 2-3 days 2 – 75mg/day 1 – 150mg/day 1 – 250mg /day
NDRIs	
Bupropion (Wellbutrin)	1 – 150mg/day
Bupropion (Zyban)	1 – 2 tablets/day
SARIs	
Nefazodone (Serzone)	1 – 600mg/day[1]
TCAs	
Amitriptyline	1 – 20mg/day 2 – 25mg/day 1 – 60mg/day

[1]Maximum recommended dose

Table 4.3 Maternal characteristics in the four study groups: exposed to any antidepressant, exposed to SSRIs, exposed to maternal depressive symptoms without antidepressant use, and unexposed to either depressive symptoms or antidepressants (Total N=2339)

Maternal Characteristics	Antidepressant Use (n=44)	SSRI Use (n=32)	Depressive Symptoms, no Antidepressant Use (n=421)	Neither Depressive Symptoms nor Antidepressant Use (n=1874)
Baseline Maternal Variables	**Frequency (%)**			
Parity (n=2339)				
0	17 (38.6%)	14 (43.8%)	214 (50.8%)	927 (49.5%)
≥ 1	27 (61.4%)	18 (56.2%)	207 (49.2%)	947 (50.5%)
Education Level (n=2339)				
≤High School	6 (13.6%)	5 (15.6%)	136 (32.3%)	268 (14.3%)
>High School	38 (86.4%)	27 (84.4%)	285 (67.7%)	1606 (85.7%)
Annual Income* (n=2189)				
<30K	8 (18.2%)	5 (15.6%)	95 (25.6%)	150 (8.5%)
30K-80K	20 (45.4%)	15 (46.9%)	184 (49.6%)	893 (50.3%)
>80K	16 (36.4%)	12 (37.50%)	92 (24.8%)	731 (41.2%)
			50 missing	100 missing
Marital Status* (n=2338)				
Married	33 (75.0%)	24 (75.0%)	237 (56.4%)	1518 (81.0%)
Common-law	8 (18.2%)	7 (21.9%)	99 (23.6%)	259 (13.8%)
Other	3 (6.8%)	1 (3.1%)	84 (20.0%)	97 (5.2%)
			1 missing	
Pre-Pregnancy BMI* (n=2251)				
Underweight (<18.5) and Normal (18.5 - <25)	21 (48.8%)	17 (53.1%)	247 (62.5%)	1197 (66.0%)
Overweight (25 - <30)	13 (30.2%)	7 (21.9%)	82 (20.8%)	394 (21.7%)
Obese (≥30)	9 (20.9%)	8 (25.0%)	66 (16.7%)	222 (12.3%)
	1 missing		26 missing	61 missing
	Mean (SD)			
Maternal Age (n=2339)	31.0 (4.4)	30.8 (4.3)	28.3 (5.5)	30.3 (4.8)
Prenatal Maternal Variables	**Frequency (%)**			
Smoked During Pregnancy* (n=2317)	5 (11.4%)	3 (9.4%)	94 (22.5%)	145 (7.8%)
			3 missing	19 missing
Alcohol Use During Pregnancy* (n=2316)	1 (2.3%)	1 (3.1%)	19 (4.5%)	34 (1.8%)
			3 missing	20 missing
Hypertension Before and/or During Pregnancy (n=2339)	5 (11.4%)	3 (9.4%)	44 (10.4%)	174 (9.3%)
Diabetes Before and/or During Pregnancy (n=2339)	2 (4.5%)	2 (6.3%)	18 (4.3%)	55 (2.9%)
Asthma (n=2330)*	11 (25.0%)	5 (15.6%)	78 (18.6%)	263 (14.1%)
			2 missing	7 missing
Thyroid Condition (n=2339)	3 (6.8%)	3 (9.4%)	15 (3.6%)	86 (4.6%)

Diagnosed with Depression or Mood Disorder in the Past (n=1345)**				
Yes	21 (87.5%)	16 (94.1%)	66 (31.9%)	130 (11.7%)
No	3 (12.5%)	1 (5.9%)	141 (68.1%)	984 (88.3%)
Weight Gain during Pregnancy (n=2339)				
20lbs or less	0	0	22 (5.22%)	68 (3.6%)
Appropriate	39 (88.6%)	29 (90.62%)	333 (79.10%)	1592 (85.0%)
40lbs or more	5 (11.4%)	3 (9.38%)	66 (15.68%)	214 (11.4%)
	Mean (SD)			
State Anxiety (STAI Raw Score) (2337)	23.3 (7.2)	23.2 (7.0)	27.5 (5.5) 1 missing	19.4 (4.4) 1 missing

*Calculated percentage does not include missing observations

** Percentage based on postnatal data

Table 4.4a Neonatal outcomes in the four study groups: exposed to any antidepressant, exposed to SSRIs, exposed to maternal depressive symptoms without antidepressant use, and unexposed to either depressive symptoms or antidepressants (Total N=2339)

	Antidepressant Use (n = 44)	**SSRI Use (n = 32)**	**Depressive Symptoms, no Antidepressant Use (n = 421)**	**Neither Depressive Symptoms nor Antidepressant Use (n = 1874)**
	Frequency (%)			
Gestational Age				
Preterm	6 (13.6%)	6 (18.8%)	32 (7.6%)	100 (5.3%)
Size for Gestational Age*				
SGA	0 (0)	0 (0)	30 (7.2%)	126 (6.8%)
LGA	14 (32.6%)	10 (32.3%)	50 (12.0%)	234 (12.6%)
	1 missing	1 missing	6 missing	20 missing

*Calculated percentage does not include missing observations

Table 4.4b The expected count in each study group (reference = unexposed to either depressive symptoms or antidepressants), the ratio of observed/expected and the 95% Poisson confidence interval of the rate ratio of observed/expected

		Antidepressant Use	**SSRI Use**	**Depressive Symptoms, no Antidepressant Use**
Preterm	expected number	2.3	1.7	22.5
	observed/expected (CI)	2.6 (1.0, 5.7)	3.5 (1.3, 7.7)*	1.42 (1.0, 2.0)
LGA	expected number	5.4	3.9	52.4
	observed/expected (CI)	2.6 (1.4, 4.4)*	2.56 (1.2, 4.7)*	1.0 (0.7, 1.3)

Note: expected is based on the rate in the No Depressive Symptoms/No Antidepressant group
*statistically significant

Table 4.4c The expected count in each study group (reference = exposed to depressive symptoms and unexposed to antidepressants), the ratio of observed/expected and the 95% Poisson confidence interval of rate ratio of observed/expected

		Antidepressant Use	**SSRI Use**
Preterm	expected number	3.3	2.4
	observed/expected (CI)	1.8 (0.7, 4.0)	2.5 (0.9, 5.4)
LGA	expected number	5.3	3.7
	observed/expected (CI)	2.6 (1.4, 4.4)*	2.7 (1.3, 5.0)*

Note: expected is based on the rate in the Depressive Symptoms/No Antidepressant group
*statistically significant

Table 4.5a Neonatal outcomes of term infants in the four study groups: exposed to any antidepressant, exposed to SSRIs, exposed to maternal depressive symptoms without antidepressant use, and unexposed to either depressive symptoms or antidepressants (Total N=2201)

	Antidepressants Use (n = 38)	**SSRI Use (n = 26)**	**Depressive Symptoms, no Antidepressant Use (n = 389)**	**Neither Depressive Symptoms nor Antidepressant Use (n = 1774)**
	Frequency (%)			
Apgar-1* (n=2132)				
<7	4 (11.4%)	4 (17.4)	24 (6.5)	143 (8.3)
≥7	31 (88.6%)	19 (82.6)	346 (93.5)	1584 (91.7)
	3 missing	3 missing	19 missing	47 missing
Apgar-5* (n=2132)				
<7	1 (2.9)	1 (4.4)	1 (0.3)	8 (0.5)
≥7	34 (97.1)	22 (95.6)	370 (99.7)	1718 (99.5)
	3 missing	3 missing	18 missing	48 missing
TSC* (n=2198)				
Yes	2 (5.3)	1 (3.8)	13 (3.3)	42 (2.4)
No	36 (94.7)	25 (96.2)	376 (96.7)	1729 (97.6)
				3 missing

*Calculated percentage does not include missing observations

Table 4.5b The expected count in each exposure group (reference = exposed to depressive symptoms and unexposed to antidepressants), the ratio of observed/expected, and the 95% Poisson confidence interval of rate ratio of observed/expected

		Antidepressant Use	**SSRI Use**
Apgar-1 <7	expected number	2.4	1.5
	observed/expected (CI)	1.7 (0.5, 4.2)	2.7 (0.7, 6.9)
Apgar-5 <7	expected number	0.1	0.1
	observed/expected (CI)	10.6 (0.3, 59.0)	16.1 (0.4, 89.7)
TSC	expected number	1.3	0.9
	observed/expected (CI)	1.6 (0.2, 5.7)	1.15 (0.03, 6.4)

Note: expected is based on the rate in the Depressive Symptoms/No Antidepressant group

Table 4.6 Mean and the 95% Bootstrap Bias Corrected and accelerated (BCa) Confidence Interval of ASQ Scores from five domains of term toddlers in the four study groups: exposed to any antidepressant, exposed to SSRIs, exposed to maternal depressive symptoms without antidepressant use, and unexposed to either depressive symptoms or antidepressants (Total N=910)

ASQ Domains	**Antidepressants (n = 15)**	**SSRIs (n = 9)**	**Depressive Symptoms/No Treatment Exposure (n = 120)**	**No Depressive Symptoms (n = 775)**
	Bootstrap Mean (95% Bootstrap BCa Confidence Interval)			
Communication (n=909)	54.8 (49.2, 58.6)	52.4 (45.8, 58.1)	55.3 (53.6, 56.9)	56.0 (55.4, 56.5) 1 missing
Gross Motor (n=909)	53.7 (45.2, 58.9)	49.4 (36.5, 57.1)	55.2 (52.5, 56.9)	56.4 (55.8, 56.8) 1 missing
Fine Motor (n=906)	49.9 (40.7, 55.2)	44.4 (32.2, 56.0)	50.6 (47.8, 53.0) 1 missing	51.4 (50.6, 52.3) 3 missing
Problem Solving (n=908)	57.3 (47.0, 60.0)	56.7 (44.7, 60.0)	55.2 (53.0, 57.0)	55.0 (54.4, 55.5) 2 missing
Personal/Social (n=908)	54.3 (49.3, 58.3)	52.2 (45.3, 58.2)	55.5 (52.9, 57.0)	55.1 (54.5, 55.6) 2 missing

Table 4.7 LGA frequency by maternal characteristics (n=1854)

Categorical Maternal Characteristics	LGA Frequency (%)	P-value
Education Level (n=1854)		
≤High School	27/265 (10.2%)	0.1977[a]
>High School	207/1589 (13.0%)	
Annual Income (n=1755)		
<30K	15/148 (10.1%)	
30K-80K	124/886 (14.0%)	0.1854[a]
>80K	82/721 (11.4%)	
Marital Status (n=1854)		
Married	195/1502 (13.0%)	0.6235[a]
Common-law	28/255 (11.0%)	
Other	11/97 (11.3%)	
Pre-Pregnancy BMI (n=1793)		
Underweight (<18.5) and		
Normal (18.5 - <25)	123/1184 (10.4%)	0.0003[a]
Overweight (25 - <30)	63/388 (16.2%)	
Obese (≥30)	40/221 (18.1%)	
Parity (n=1854)		
0	97/915 (10.6%)	0.0097[a]
≥ 1	137/939 (14.6%)	
Smoked During Pregnancy (n=1835)		
Yes	9/143 (6.3%)	0.0173[a]
No	223/1692 (13.2%)	
Alcohol Use During Pregnancy (n=1834)		
Yes	1/34 (2.9%)	0.1138[b]
No	229/1800 (12.7%)	
Hypertension Before and/or During Pregnancy (n=1848)		
Yes	23/171 (13.4%)	0.7277[a]
No	210/1677 (12.5%)	
Diabetes Before and/or During Pregnancy (n=1854)		
Yes	16/53 (30.2%)	<.0001[a]
No	218/1801 (12.1%)	
Asthma (n=1847)		
Yes	35/261 (13.4%)	
No	197/1586 (12.4%)	0.6551[a]
Thyroid Condition (n=1854)		
Yes	8/84 (9.5%)	0.3816[a]
No	226/1770 (12.8%)	

Weight Gain during Pregnancy (n=1854) 20lbs or less Appropriate 40lbs or more	 6/66 (9.1%) 185/1575 (11.8%) 43/213 (20.2%)	 0.0016[a]
Numeric Maternal Characteristics	**LGA Frequency (%) Mean (SD)**	**Non LGA Freq (%) Mean (SD)**
State Anxiety (Standardized) (1853)	234 (12.6%) 0 (1)	1619 (87.4%) 0 (1)
Maternal Age (n=1854)	234 (12.6%) 30.6 (4.7)	1620 (87.4%) 30.3 (4.9)

[a]Pearson chi-square test
[b]Fisher exact test
Note: significant level ≤ 0.2

Table 4.8 Univariable and multivariable logistic regression of maternal characteristics and LGA

Categorical Maternal Characteristics	OR (95% Wald CI) [p-value]	
	Univariable	**Multivariable (n=1684)**
Education Level		entered
≤High School	0.76 (0.50, 1.16) [0.1992]	
>High School	[reference]	
Annual Income		
<30K	0.88 (0.49, 1.57) [0.6637]	entered
30K-80K	1.27 (0.94, 1.71) [0.1184]	
>80K	[reference]	
Marital Status		
Married	[reference]	not entered
Common-law	0.83 (0.54, 1.26) [0.3752]	
Other	0.86 (0.45, 1.64) [0.6401]	
Pre-Pregnancy BMI		
Underweight (<18.5) and Normal (18.5 - <25)	[reference]	[reference]
Overweight (25 - <30)	1.67 (1.20, 2.32) [0.0021]	1.58 (1.12, 2.24) [0.0093]*
Obese (≥30)	1.91 (1.29, 2.82) [0.0012]	2.05 (1.36, 3.08) [0.0006]*
Parity		
0	[reference]	[reference]
≥ 1	1.44 (1.09, 1.90) [0.0100]	1.51 (1.12, 2.04) [0.0072]*
Smoked During Pregnancy		
Yes	0.44 (0.22, 0.88) [0.0205]	0.47 (0.23, 0.96) [0.0376]*
No	[reference]	[reference]
Alcohol Use During Pregnancy		
Yes	0.21 (0.03, 1.53) [0.1227]	not entered
No	[reference]	
Hypertension Before and/or During Pregnancy		not entered
Yes	1.09 (0.68, 1.72) [0.7277]	
No	[reference]	
Diabetes Before and/or During Pregnancy		
Yes	3.14 (1.72, 5.74) [0.0002]	2.79 (1.43, 5.46) [0.0028]*
No	[reference]	[reference]
Asthma		
Yes	1.09 (0.74, 1.61) [0.6552]	not entered
No	[reference]	
Thyroid Condition		
Yes	0.72 (0.34, 1.51) [0.3843]	not entered
No	[reference]	
Weight Gain during Pregnancy		
20lbs or less	0.75 (0.32, 1.76) [0.5113]	0.68 (0.28, 1.65) [0.3973]
Appropriate	[reference]	[reference]
40lbs or more	1.90 (1.32, 2.76) [0.0006]	2.23 (1.51, 3.30) [<.0001]*

State Anxiety (Standardized)	1.00 (0.87, 1.15) [0.9743]	not entered
Maternal Age	1.02 (0.99, 1.05) [0.2534]	not entered

*statistically significant level <0.05

Note: Alcohol use during pregnancy not entered into model due to small cell

Chapter 5: Discussion

The purpose of this thesis study is to investigate the effects of maternal antidepressant use, with special focus on SSRI use during pregnancy on neonatal and long-term child developmental outcomes. Specifically, the first objective is to describe the baseline characteristics of pregnant women who belonged in the following study groups: those who took antidepressants during pregnancy (Antidepressant group); those who took SSRIs during pregnancy (SSRIs subgroup); those who have elevated depressive symptoms during pregnancy but not taking antidepressants (Depressive Symptoms group); and those who do not have elevated depressive symptoms and do not take antidepressants during pregnancy (Reference group). The second objective is to compare the neonatal outcomes, specifically, preterm delivery, small-for-gestational age (SGA), large-for-gestational age (LGA), Apgar scores at one and five minutes, and NICU admission among newborns whose mothers belonged to the study groups. The third objective is to compare the long-term development of toddlers and preschoolers whose mothers belonged to the study groups. Due to the low prevalence of antidepressant use during pregnancy, the issues of small cell sizes precluded the control for potential confounding variables. This needs to be recognized beforehand, as it might have impacted the findings. Nonetheless, this study had findings consistent with the current literature concerning the use of antidepressants during pregnancy.

5.1 Discussion Pertaining to Objective 1: Study Group Baseline Characteristics

In regards to Objective 1, our findings from the descriptive analysis suggested women in the Antidepressant group were more likely to have BMI greater than or equal to 25 (overweight and obese) before pregnancy, were of higher parity, and more likely to be asthmatic compared to women in the Depressive Symptoms and Reference group.

These findings support those of prior large Canadian population-based studies that investigated the relationship between antidepressant use, depression, and obesity [137-139]. Specifically in a 10-year longitudinal cohort study, Patten et al. [137] found an association between obesity (BMI $\geq$30) and antidepressant use, particularly SSRIs and Venlafaxine (SNRI), but not major depressive episodes after adjusting for covariates. Their follow up study found that major depressive episodes and antidepressant use were

both associated with significant but modest increase in BMI over time [138]. In contrast, another Canadian cross sectional study reported a lack of association between depression and overweight/obesity status however an elevated risk of obesity (BMI ≥ 30) was observed among depressed women taking antidepressants, specifically TCAs [139].

Generally, there is a large body of literature supporting the association between depression and obesity [140, 141]. Various comorbid conditions of depression, especially atypical depression and obesity, have been suggested to operate bi-directionally through interlinked psychological, behavioural, and biological (HPA-axis disruption) factors and share common pathological pathways involving the inflammatory, metabolic, and endocrine systems [140, 141]. Grundy et al. [139] suggest that, for those on antidepressants, antidepressant use might have played a role as an intermediate between the depression and obesity.

A plausible explanation for the observed association is the side effect of weight gain related with antidepressant treatment. Evidence from the current literature and a meta-analysis indicate that the antidepressants, amitriptyline (TCA) and paroxetine (SSRI) are most consistently associated with clinically significant weight gain that could lead to overweightness or obesity [97, 100, 142, 143]. Citalopram (SSRI) has been reported on a fairly consistent basis to increase the risk of moderate weight gain over long term use [100]. Other types of SSRIs (Fluvoxamine, Sertraline, and Fluoxetine) and classes of antidepressants including bupropion (NDRI), venlafaxine (SNRI), and nefazodone (SARI) used by the women in the Antidepressant group have generally been found to be weight neutral and even weight loss promoting [100]. However, long term use of the "weight neutral" SSRIs have been reported to be associated with slight weight gain as well [143].

The proposed mechanisms underlying antidepressant induced weight gain are the alternation of a highly complex and overlapping network of signaling molecules including hormones (cortisol via HPA-axis), cytokines (leptin, tumor necrosis factor, etc), and neurotransmitters (serotonin, norepinephrine, etc) involved in hunger, satiety, insulin resistance, and overall metabolic homeostasis [97]. This manifests in an increase of caloric intake due to food craving, reduction resting metabolic rate, and ultimately, the promotion of the metabolic syndrome including obesity [97, 100]. Therefore the evidence

provides a strong indication that the use of antidepressants in our population may have played a role in the increased rate of high BMI (≥25) observed in the Antidepressant group and SSRI subgroup.

During the postnatal (follow-up) survey, 87.5% and 94.1% of women in the Antidepressant group and SSRI subgroup, respectively reported past diagnosis of depression or mood disorder. Hence the underlying psychiatric illness may have been a contributing risk factor for high BMI (overweightness and obesity) in the Antidepressant group and SSRI subgroup. Confounding by prescriber expectancy might also partially explain this result such that physicians prescribed SSRIs to women more susceptible to weight gain [137].

Overall, given evidence provided in the literature and our results, we hypothesize that the combined factors of antidepressant use and underlying psychiatric illness could have affected the risk of overweight and obesity in our sample population and those variables are all involved in a mutual causal pathway. However, it is worth mentioning that we did not model the determinants of overweight and obesity in our data because it is beyond the scope of this thesis.

Moreover, the association between overweightness/obesity and asthma might explain the increased cases of asthma observed in women taking antidepressants. The increased secretion of cytokine, specifically leptin from fat tissue commonly observed in obesity is suggested to contribute in the pathology of asthma, a chronic inflammatory disorder of the airways [144].

Women in the Antidepressant group and Reference group were similar in regards to a number of characteristics including older age, married status, higher income and education. This is partially consistent with the literature that report pregnant women on antidepressants are more likely to be older [50, 145], have higher education (>12 years of education) [145], be recipients of welfare [50], and more likely to consume alcohol and smoke [145]. These high-risk behaviours during pregnancy were observed in women of the Depressive Symptoms group, which could be related to their demographics of lower education level, lower income, younger age, non-married status, and poorer mental health compared to other groups. All those characteristics relating to disadvantages are associated with higher risk of adverse lifestyle practices (concurrent alcohol and tobacco

use) during pregnancy [146] and are common risk factors of antenatal depression [29]. Furthermore, women in the Antidepressant group exhibited lower mean state anxiety STAI raw score than women in the Depressive Symptoms group. This result was expected given that depression and anxiety are frequent co-morbid conditions with overlapping symptoms and antidepressants have an anti-anxiety effect, which reduces the level of anxiety symptoms and elevates mood [146].

The findings that women with elevated depressive symptoms during pregnancy were more likely to display harmful behaviours, have poorer mental health, and be disadvantaged are consistent with the current literature [22, 23]. This result suggests that women with these risk factors need to be readily recognized and require special attention in primary obstetric care settings in order to target screening and treatment efforts. However, many pregnant women with depressive symptoms are undertreated or not treated during this vulnerable time [18, 23], which could be the case for the women in the Depressive Symptoms group. Importantly, untreated depression during pregnancy can persist into postpartum period [147].

5.2 Discussion Pertaining to Objective 2: Neonatal Outcomes

In regards to Objective 2, our univariable results indicated that infants exposed to *in utero* antidepressants (Antidepressant group) were at significantly higher risk to be LGA compared to the infants whose mothers belonged to the Depressive Symptoms and Reference groups. Exposure to SSRIs *in utero* was also found to increase the risk of LGA compared the Depressive Symptoms and Reference group. A previous observational study reported an increased risk of LGA in women exposed to antidepressants during pregnancy compared to the total population after adjusting for potential confounders (year of birth, maternal age, parity, and smoking during pregnancy), although the difference was not statistically significant [78]. The same result was found in their follow-up study [85].

Given the small sample size of the Antidepressant group, an analysis at the multivariable level was precluded, thus potential confounders were not accounted for. Instead, the Reference group was analyzed to investigate the maternal characteristics in relation to LGA. Our results from the multivariable logistic regression of the Reference

group found that women who were primiparous/multiparous, overweight and obese before pregnancy, diabetic before and/or during pregnancy, or had weight gain of 40lbs or more were associated with an increased odds of having LGA infants, whereas smoking during pregnancy was associated with decreased likelihood of having LGA infants. This is consistent with previous literature [96, 148] and other analyses in this dataset citing these maternal factors as strong predictors of delivering LGA infants [149]. Thus it is possible that these maternal characteristics known to affect insulin resistance may offer an explanation for the increased frequency of LGA in the Antidepressant group.

Although antidepressant use is not a known risk factor for delivering LGA infants, observational studies have produced sufficient data indicating the association between antidepressant use, particularly TCAs and SSRIs, and the risk factors pertaining to LGA including insulin resistance [98], dyslipidemia [98, 150], diabetes [99, 151], and as discussed above (Section 5.1), obesity [100]. Specifically, in a Norwegian general community cross sectional study, overall SSRI use was found to be associated with abdominal and general obesity, hypercholesterolemia, and an observed trend toward diabetes [98]. A meta-analysis of 12 high quality observational studies concluded that there was a significantly increased risk of type 2 diabetes mellitus among long-term users of SSRIs and TCAs after adjusting for body weight, depression severity, and physical activity [152]. Additionally, consistent data from the literature review suggested the use of paroxetine increases the risk of dyslipidemia and glucose intolerance [100]. The increased risk of diabetes among women in the Antidepressant group and SSRI subgroup was not observed. As a result, it is assumed that their glucose tolerance, albeit not considered in our study, might have been compromised to a certain degree given Grave *et al.* [149] found abnormal glucose tolerance as a significant risk factor of LGA in this dataset.

Generally, it is suspected that antidepressants increase serum cortisol level and insulin resistance by altering the HPA axis [153]. Specifically, TCAs inhibit noradrenaline reuptake transporters at the synapses increasing noradrenaline, which then leads to a hyperglycemic effect [99]. Furthermore, some SSRIs have been found to activate insulin receptor 1 kinases resulting in inhibition of insulin signaling and induction of cellular insulin resistance [154]. Therefore we hypothesized that the

antidepressant-induced hyperglycemic effect during pregnancy increases glucose availability and delivery to the fetus resulting in fetal hyperinsulinemia and increases the risk of LGA. Dyslipidemia in pregnant women has also been found to have a positive influence on fetal growth due to increased serum lipid availability [155]. In addition, the relationship between the risk of LGA and pre-pregnancy BMI is directly proportional and independent of gestational diabetes in women with adequate gestational weight gain [96]. So in connection to Discussion section 5.1, the increased rate of high BMI (≥25) in the Antidepressant group may be a main factor explaining the increased frequency of LGA infants in this group. Overall, the mechanism of antidepressants induces unwanted side effects that fit under the umbrella of metabolic syndrome and could have potentially contributed to LGA in the Antidepressant group.

On the other hand, because antidepressant use occurs in the context of underlying depression, the comorbid conditions of depression and obesity are worthy of discussion since they share common pathological pathways such as increased level of pro-inflammatory cytokines, insulin resistance, and altered plasma glucose levels [156], which could contribute to LGA as well.

Furthermore, infants exposed to antenatal SSRIs had an increased risk of being preterm compared to infants of the Reference group. Results regarding the relationship between antenatal SSRI exposure and premature birth have been inconsistent in the literature [21, 79]. Evidence indicates that longer duration [76] and late trimester (2^{nd} and 3^{rd}) [157, 158] exposure of antenatal SSRIs is associated with preterm birth and other adverse birth outcomes. We had limited information on the timing and duration of antidepressant use in our database. Research has demonstrated that antidepressant use decreases significantly once pregnancy is identified from the rate of 6.6% (12 months before gestation) to 3.7% (first trimester) and continues to decrease to 1.6% (second trimester) and 1.1% (third trimester) [50]. Most women in the Antidepressant group and SSRI subgroup were in the second trimester (38 out of 44 and 29 out of 32) and the rest in the first trimester at the time of the prenatal survey. Coupled with the fact that most pregnant women take antidepressant for a prolonged period as maintenance therapy to prevent recurrences of psychiatrics episodes [145], it is likely that majority of women were adherent to the treatment throughout pregnancy and the difference in the timing and

duration of exposure did not greatly affect our results. Furthermore, it is possible that the increased risk of preterm birth observed in the SSRI subgroup may be confounded by the underlying maternal depression.

Additionally, non-significant increases in the risk of low Apgar-1, Apgar-5, and TSC were observed in infants exposed to *in utero* antidepressants. However, due to both the exclusion of preterm infants and the sample size limitation, these adverse outcomes were rare events with low frequency count for the Antidepressant group and SSRI subgroup. Therefore we had low statistical power to detect significant differences.

5.3 Discussion Pertaining to Objective 3: Toddler/Child Development

In regards to Objective 3, our descriptive analysis found lower mean scores in the communication, fine and gross motor movement, and personal/social skill domains of the ASQ among toddlers and children whose mothers that belonged in the SSRI subgroup during pregnancy in comparison to the other groups. The largest deficit was observed in the fine and gross motor domains by a maximum difference margin of approximately 7 points between the SSRI subgroup versus both the Depressive Symptoms and Reference group. Furthermore, consistent with all previous studies that investigated cognitive development [9, 12, 101-104, 121], we did not observe a deficit in the mean score for the problem-solving domain among toddlers and children in the SSRI subgroup. The interpretation of our results warrants caution since the sample size was small and we were unable to control for confounders. As a result, the clinical significance is not known.

Nonetheless, our preliminary findings are supported by several observational studies that found a deficit in motor development among children exposed to antenatal SSRIs. Specifically, a few small sized studies (31 to 51 exposed participants) reported an association between SSRI use during pregnancy and significantly lower scores on the Bayley Psychomotor Developmental Index particularly in the gross motor development in two studies [104, 109] and in the fine motor and tremulousness sub-scores of the Bayley Behavioural Rating Scales in another study [103]. However, Casper *et al.* [104] reported normal range of motor development after the neurological exam. Additionally, a large cohort-based Danish population study [12] found that 6 month old children who were exposed to SSRIs during second and third trimester had increased odds of delayed

gross motor development, specifically sitting without support compared to children of untreated mothers even after adjusting for covariates including postnatal symptoms of depression. Again, the motor development milestones were within the normal expected range and the gross motor delays were resolved at the age of 19 months. Other studies have also reported a transient motor delay in the infancy and early toddlerhood (1-1.5 years) stages that later resolves past approximately 1.5 years of age [11, 121]. The authors of these studies suggested *in utero* SSRI exposure may impact early fetal motor development that is self-limiting later in infancy and young toddlerhood due possibly to a washout effect, however our study and other studies [103, 104] indicate that motor impairment might persist to the ages of two to five years. Therefore further follow-up studies are needed to clarify the persistence of fetal SSRI exposure on motor development in children. This finding was not completely unanticipated since the role of serotonin is essential in the maturation of the sensorimotor areas during development, including the cerebellum, basal ganglia and those areas innervated by and under the control of serotonergic fibers [159].

We observed a difference margin of approximately 3 points in the communication and personal/social domains between the SSRI subgroup versus both the Depressive Symptoms and Reference group. Again, whether this 3-point difference is statistically or clinically significant is inconclusive, however these potential developmental deficits are supported by previous observational and animal model studies. A recent large Norwegian population-based cohort study reported that prolonged *in utero* SSRI exposure was associated with moderate language delays in 3 year olds independent of the underlying maternal depression before, during, and after pregnancy [111]. However the authors suggested moderate language delay may later resolve since severe language delay or clinical delay was not included as part of the outcome. No other studies to date have found an association between communication or language delay and antenatal SSRI exposure [101, 102, 109, 115]. Therefore even if our result was statistically significant, the clinical importance for communication deficit is unlikely based on evidence from the literature.

In addition, the majority of studies suggested that antenatal SSRI exposure was not associated with an increased risk of personal/social behavioural problems in children

[9, 10, 13, 101, 102, 106, 107], although, a few observational [12, 104, 108, 110] and animal studies [160, 161] did find such an association. For example, previous observational research has illustrated that antenatal exposure to SSRIs was associated with increased risk of lower Behavior Rating Score (orientation/engagement, emotional regulation, and motor quality) in a small sample of 12 to 40 month olds [104], inability to occupy themselves alone for 15 minutes (attention) in 19 month olds after controlling for postnatal depressive symptoms [12], and higher levels of internalizing behaviour (withdrawal, anxiety, depression) in 3 and 6 year olds after controlling maternal mood during antenatal, postnatal, and childhood period [110]. In animal models, the early administration of SSRIs in neonates and the subsequent increase in serotonin level have been shown to cause permanent impairment in the neural connection of the somatosensory cortex, as well as impairment in social behaviours such as reduced exploratory behaviour and depressive and anxiety-related behaviour in adulthood [160, 161]. Recently, *in utero* SSRI exposure was found to be associated with a change in serum concentration of proteins such as reelin and activin A that are imperative in early neurodevelopment during gestation in humans [124, 125].

Since our analysis was descriptive, there remains a significant possibility for confounding variables such as the severity of underlying antenatal and postnatal maternal psychiatric illnesses and its related behaviours to affect our findings in the long-term development of children. For instance, Nulman *et al.* [9] reported that children exposed to SSRIs had a lower IQ compared to children not exposed to SSRIs. However, regression analysis discovered that the severity of maternal depression during and after pregnancy and maternal IQ predicted problematic behaviour and cognitive outcomes, respectively, while duration and dose of antidepressant exposure during pregnancy did not predict developmental outcomes. Similarly, Misri *et al.* [107] discovered that current maternal depression and anxiety were associated with increased internalizing behaviour and not SSRI use. On the other hand, Oberlander *et al.* [105] found that antenatal exposure to SSRIs in combination with current maternal anxiety were associated with an increased rate of internalizing behavior at 3 years of age. This suggests that there may be a complex association between underlying maternal mental disorders, medication use, and the long-term developmental outcome.

At this point, the significance of our results on long-term development remains uncertain and whether these "deficits" manifest in clinically relevant issues later in life is even more unclear and doubtful. Based on the literature, this area of research is still in the beginning stages without a definitive conclusion regarding the clinical relevance due to the challenges in designing observational studies with adequate sample size that accounts for residual confounding variables. However, the use of SSRIs during pregnancy could increase the risk of some development delays involving psychomotor and personal/social behavioural development with unknown clinical implications. The future direction for this research area is discussed in section 5.5.

5.4 Strengths and Limitations

One of the main strengths of this study was the inclusion of women with depressive symptoms but not taking antidepressants, which to some degree allowed us to directly examine the effect of antidepressant exposure on neonatal and long-term outcomes independent from potential underlying maternal illness and account for any unmeasured or unidentified variables associated with having depressive symptoms. In addition, women who participated in the PHP were unaware of the aim of this study when filling out the ASQ, therefore participant bias was unlikely present. Another strength of this study was the benefit of utilizing the well-designed PHP dataset, which prospectively collected a plethora of information on relevant pregnancy exposures and neonatal and child development outcomes. For instance, although clinical diagnosis of psychiatric illnesses and its severity were unknown, the PHP utilized widely validated psychological screening tests including the CES-D and STAI to identify individuals at risk for clinical depression and to detect the incidence and severity of state anxiety symptoms, respectively [162, 163]. Additionally, the CES-D is widely used in antenatal research and recommended as an initial assessment for depressive symptoms during pregnancy [25]. Furthermore, we were able to use the Canadian population reference to account for gestational age when examining birth weight where many previous studies had not done so [21]. From the postnatal survey, 87.5% and 94.1% of women in the Antidepressant group and SSRI subgroup, respectively reported past diagnosis of depression or mood

disorder so it is likely that the indication of antidepressant use was for what it was intended.

Given the PHP was not designed to investigate this specific thesis topic, we acknowledge a number of limitations. As previously mentioned, we were unable to produce precise risk estimates and control for confounding variables because of the small number of women taking antidepressant in our study sample. This relatively low prevalence of antidepressant use is comparable to many observational studies being one of the common challenges in this research area. To compensate for the lack of robust statistical analysis, this thesis provided a concise descriptive analysis and thorough literature review on the neonatal and long-term outcomes of antidepressant use during pregnancy. Furthermore, our method of controlling for confounding by indication for the treatment may have introduced selection bias since women who opt for treatment during pregnancy may be inherently different from women who do not receive treatment during pregnancy. For instance, it is probable that women with more severe psychiatric illness were required to continue their treatment during pregnancy, which may have overestimated the impact of antidepressant use on neonatal and long-term developmental outcomes. Ramos *et al.* [50] support this notion by reporting that pregnant women who initiate or continue antidepressant treatment were more likely to have a higher number of prescribers, a higher number of visits to the doctors before pregnancy, and a depression diagnosis before or during pregnancy.

The potential for misclassification of variables due to self-reporting and recall bias needs to be recognized. Specifically, self-reported height and weight used for the calculation of pre-pregnancy BMI might be underestimated from the overestimation of height and underestimation of weight. Misclassification of weight gained during pregnancy also needs to be addressed because it was captured as a categorical variable without accounting for the recommended weight gain based on the maternal BMI. For instance, the recommended range of total weight gain during pregnancy for an overweight woman is 15-25lbs and using our categorization would misclassify their weight gain as appropriate (21lbs-39lbs) [149]. Antidepressant medication use was also self-reported by participants, however they were asked to list all the medication used

currently at the time of the survey as well as the amount and frequency of use thereby reducing the likelihood of recall bias.

The ASQ is a validated developmental screening tool compared to other professionally administered assessments such as the Bayley Scale of Infant Development [164]. However, the reliance on the ASQ to assess child developmental is another limitation worth mentioning since we did not utilize the ASQ as it was intended as a dichotomized outcome (pass or fail) test. Nonetheless, the intention was not to investigate the individual pass or fail but to utilize the continuous ASQ scores for its ability to compare scores among different groups. The ASQ may also underestimate developmental delays and generally identify development as normal given the evidence of the negative skew distribution and ceiling effect in our sample population. The benefit, however, of utilizing the ASQ is that it can be self-administered quickly and easily at home by parents [164].

In addition, self-reported evaluation of child development using the ASQ might have been influenced by maternal mood because psychologically distressed mothers have the propensity to over-report or underreport their child development resulting in inaccurate assessment [165, 166]. Furthermore, developmental assessment was reported at a single time point, which might have restricted our result, as child development is likely to change over time. On a related note, whether depressive symptoms persists throughout pregnancy or discontinues is unknown given CES-D was utilized at a single time frame. However, depressive symptoms have been found to persist and remain uniform through pregnancy [167]. Lastly, this is an observational study, therefore the direction of effect or causality between exposure and outcome cannot be confirmed.

5.5 Conclusion and Future Directions

The main goal of this thesis was to differentiate the effect of antenatal antidepressant exposure from that of antenatal maternal depressive symptoms on neonatal health and subsequent long-term development. By doing so, our univariable results suggests that newborns exposed to antidepressants and SSRIs *in utero* had an increased risk of being LGA compared to infants born to untreated women with depressive symptoms and healthy women. However, this could be explained by third-variable

factors including high pre-pregnancy BMI possibly induced by the combination of antidepressant use and underlying depression. Additionally, newborns exposed to SSRIs *in utero* had an increased risk of being preterm compared to infants born to healthy women. We also observed lower mean ASQ scores in the fine motor, gross motor, communication, and personal/social domains among children exposed to *in utero* SSRIs in our descriptive analysis. Our findings contribute to the growing literature on antenatal antidepressant use and its potential risks, yet it is important to acknowledge that these findings are still tentative and further studies with larger sample size are needed.

In this area of research, it is challenging to design observational pharmacoepidemiological studies without encountering some level of confounding by indication, residual confounding, and small sample size of exposure group. In addition, the heterogeneity of study design across the literature makes it extremely difficult to formulate any conclusions on the risk or benefits of antidepressant use during pregnancy for clinical recommendations. For instance, currently there is not a single meta-analysis on antidepressant exposure during pregnancy and its effect on child development due to the diverse methodologies and outcome measures in the literature.

Thus, in order for advancement in this field of research, new strategies are needed, especially for the investigation of long-term developmental outcomes. Recently, sibling discordance designs have been implemented that allowed for the control of familial and genetic factors, however this design is limited by sample size and potential bias by other discordance factors [168]. Another approach is to include participants receiving different antidepressant medication for the same underling disease, however cross interaction of neurotransmitters limits this method. Perhaps, then, well-designed randomized controlled trials (RCTs) are the future direction for this area of research as recommended by El Marroun *et al.* [145], since RCTs are immune from confounding by indication. They advise recruiting women who are planning for pregnancy and considering the cessation of their maintenance pharmacotherapy in order to address the ethical dilemma. Moreover, future studies, albeit extremely difficult, need to include the importance and complexity of genetic polymorphism of cytochrome P450 enzymes (CYPs) as different CYPs metabolize certain antidepressants more effectively which could provide an explanation for the difference in study outcomes [169].

Overall the results from this thesis do not warrant any changes in the current clinical practices nor diminish the importance of antidepressant treatment in cases of recurrent and severe depression; however, our results will bring awareness of the possible risks of antidepressant use and contribute to the developing literature. There are indeed complex challenges in treating depression and other psychiatric illness during pregnancy due to the potential unwanted drug effects and unwanted effect of untreated depression on the offspring. Ultimately, it is crucial for clinicians to thoroughly discuss the risk and benefits of the specific antidepressant treatment during pregnancy to patients on a case-by-case basis for patients to make well-informed decisions for the well-being of both the mothers and their children.

References

1. Muzik, M. and S. Borovska, *Perinatal depression: implications for child mental health.* Ment Health Fam Med, 2010. **7**(4): p. 239-47.
2. Cohen, L.S., et al., *Treatment of mood disorders during pregnancy and postpartum.* Psychiatr Clin North Am, 2010. **33**(2): p. 273-93.
3. Howland, R.H., *Antidepressant medication and pregnancy: time for randomized controlled trials.* J Psychosoc Nurs Ment Health Serv, 2013. **51**(2): p. 11-4.
4. Sontrop, J.M., et al., *Fish consumption among pregnant women in London, Ontario: associations with socio-demographic and health and lifestyle factors.* Can J Public Health, 2007. **98**(5): p. 389-94.
5. El Marroun, H., et al., *Maternal use of selective serotonin reuptake inhibitors, fetal growth, and risk of adverse birth outcomes.* Arch Gen Psychiatry, 2012. **69**(7): p. 706-14.
6. Oberlander, T.F., et al., *Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data.* Arch Gen Psychiatry, 2006. **63**(8): p. 898-906.
7. Grzeskowiak, L.E., A.L. Gilbert, and J.L. Morrison, *Neonatal outcomes after late-gestation exposure to selective serotonin reuptake inhibitors.* J Clin Psychopharmacol, 2012. **32**(5): p. 615-21.
8. Lund, N., L.H. Pedersen, and T.B. Henriksen, *Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes.* Arch Pediatr Adolesc Med, 2009. **163**(10): p. 949-54.
9. Nulman, I., et al., *Neurodevelopment of children following prenatal exposure to venlafaxine, selective serotonin reuptake inhibitors, or untreated maternal depression.* Am J Psychiatry, 2012. **169**(11): p. 1165-74.
10. Grzeskowiak, L.E., et al., *Prenatal antidepressant exposure and child behavioural outcomes at 7 years of age: a study within the Danish National Birth Cohort.* Bjog, 2015.
11. Santucci, A.K., et al., *Impact of prenatal exposure to serotonin reuptake inhibitors or maternal major depressive disorder on infant developmental outcomes.* J Clin Psychiatry, 2014. **75**(10): p. 1088-95.
12. Pedersen, L.H., T.B. Henriksen, and J. Olsen, *Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age.* Pediatrics, 2010. **125**(3): p. e600-8.
13. Pedersen, L.H., et al., *Prenatal antidepressant exposure and behavioral problems in early childhood--a cohort study.* Acta Psychiatr Scand, 2013. **127**(2): p. 126-35.
14. Cohen, L.S., et al., *Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment.* Jama, 2006. **295**(5): p. 499-507.
15. Weissman, M.M. and M. Olfson, *Depression in women: implications for health care research.* Science, 1995. **269**(5225): p. 799-801.

16. Gaynes, B.N., et al., *Perinatal depression: prevalence, screening accuracy, and screening outcomes.* Evid Rep Technol Assess (Summ), 2005(119): p. 1-8.
17. Bennett, H.A., et al., *Prevalence of depression during pregnancy: systematic review.* Obstet Gynecol, 2004. **103**(4): p. 698-709.
18. Vesga-Lopez, O., et al., *Psychiatric disorders in pregnant and postpartum women in the United States.* Arch Gen Psychiatry, 2008. **65**(7): p. 805-15.
19. Altshuler, L.L., V. Hendrick, and L.S. Cohen, *Course of mood and anxiety disorders during pregnancy and the postpartum period.* J Clin Psychiatry, 1998. **59 Suppl 2**: p. 29-33.
20. Leigh, B. and J. Milgrom, *Risk factors for antenatal depression, postnatal depression and parenting stress.* BMC Psychiatry, 2008. **8**: p. 24.
21. Grzeskowiak, L.E., A.L. Gilbert, and J.L. Morrison, *Investigating outcomes following the use of selective serotonin reuptake inhibitors for treating depression in pregnancy: a focus on methodological issues.* Drug Saf, 2011. **34**(11): p. 1027-48.
22. Zuckerman, B., et al., *Depressive symptoms during pregnancy: relationship to poor health behaviors.* Am J Obstet Gynecol, 1989. **160**(5 Pt 1): p. 1107-11.
23. Marcus, S.M., et al., *Depressive symptoms among pregnant women screened in obstetrics settings.* J Womens Health (Larchmt), 2003. **12**(4): p. 373-80.
24. Dietrich, A.J., et al., *Depression care attitudes and practices of newer obstetrician-gynecologists: a national survey.* Am J Obstet Gynecol, 2003. **189**(1): p. 267-73.
25. Breedlove, G. and D. Fryzelka, *Depression screening during pregnancy.* J Midwifery Womens Health, 2011. **56**(1): p. 18-25.
26. *The American College of Obstetricians and Gynecologists Committee Opinion no. 630. Screening for perinatal depression.* Obstet Gynecol, 2015. **125**(5): p. 1268-71.
27. Radloff, L., *The CES-D Scale: A Self-Report Depression Scale for Research in the General Population.* Appl Psych Meas, 1977. **1**(3): p. 385-401.
28. American Psychiatic Association, *Diagnostic and statistical manual of mental disorder (5th ed.)* 2013, Arlington, VA: American Psychiatric Publishing.
29. Lancaster, C.A., et al., *Risk factors for depressive symptoms during pregnancy: a systematic review.* Am J Obstet Gynecol, 2010. **202**(1): p. 5-14.
30. Grote, N.K., et al., *A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction.* Arch Gen Psychiatry, 2010. **67**(10): p. 1012-24.
31. Field, T., M. Diego, and M. Hernandez-Reif, *Prenatal depression effects on the fetus and newborn: a review.* Infant Behav Dev, 2006. **29**(3): p. 445-55.
32. Hoffman, S. and M.C. Hatch, *Depressive symptomatology during pregnancy: evidence for an association with decreased fetal growth in pregnancies of lower social class women.* Health Psychol, 2000. **19**(6): p. 535-43.
33. Chung, T.K., et al., *Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes.* Psychosom Med, 2001. **63**(5): p. 830-4.

34. Dunkel Schetter, C., *Psychological science on pregnancy: stress processes, biopsychosocial models, and emerging research issues.* Annu Rev Psychol, 2011. **62**: p. 531-58.
35. Szegda, K., et al., *Depression during pregnancy: a risk factor for adverse neonatal outcomes? A critical review of the literature.* J Matern Fetal Neonatal Med, 2014. **27**(9): p. 960-7.
36. Oberlander, T.F., et al., *Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses.* Epigenetics, 2008. **3**(2): p. 97-106.
37. Grigoriadis, S., et al., *The impact of maternal depression during pregnancy on perinatal outcomes: a systematic review and meta-analysis.* J Clin Psychiatry, 2013. **74**(4): p. e321-41.
38. Deave, T., et al., *The impact of maternal depression in pregnancy on early child development.* Bjog, 2008. **115**(8): p. 1043-51.
39. Barker, E.D., et al., *The contribution of prenatal and postnatal maternal anxiety and depression to child maladjustment.* Depress Anxiety, 2011. **28**(8): p. 696-702.
40. Evans, J., et al., *The timing of maternal depressive symptoms and child cognitive development: a longitudinal study.* J Child Psychol Psychiatry, 2012. **53**(6): p. 632-40.
41. Hay, D.F., et al., *Antepartum and postpartum exposure to maternal depression: different effects on different adolescent outcomes.* J Child Psychol Psychiatry, 2008. **49**(10): p. 1079-88.
42. Hay, D.F., et al., *Mothers' antenatal depression and their children's antisocial outcomes.* Child Dev, 2010. **81**(1): p. 149-65.
43. Hay, D.F., et al., *Known risk factors for violence predict 12-month-old infants' aggressiveness with peers.* Psychol Sci, 2011. **22**(9): p. 1205-11.
44. Van Batenburg-Eddes, T., et al., *Parental depressive and anxiety symptoms during pregnancy and attention problems in children: a cross-cohort consistency study.* J Child Psychol Psychiatry, 2013. **54**(5): p. 591-600.
45. Pawlby, S., et al., *Antenatal depression predicts depression in adolescent offspring: Prospective longitudinal community-based study.* Journal of Affective Disorders, 2009. **113**(3): p. 236-243.
46. Pearlstein, T., et al., *Postpartum depression.* Am J Obstet Gynecol, 2009. **200**(4): p. 357-64.
47. Glover, V., *Maternal depression, anxiety and stress during pregnancy and child outcome; what needs to be done.* Best Pract Res Clin Obstet Gynaecol, 2014. **28**(1): p. 25-35.
48. Yonkers, K.A., et al., *The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists.* Gen Hosp Psychiatry, 2009. **31**(5): p. 403-13.
49. Yonkers, K.A., S. Vigod, and L.E. Ross, *Diagnosis, pathophysiology, and management of mood disorders in pregnant and postpartum women.* Obstet Gynecol, 2011. **117**(4): p. 961-77.
50. Ramos, E., et al., *Prevalence and predictors of antidepressant use in a cohort of pregnant women.* Bjog, 2007. **114**(9): p. 1055-64.

51. Nierenberg, A.A., et al., *A brief review of antidepressant efficacy, effectiveness, indications, and usage for major depressive disorder.* J Occup Environ Med, 2008. **50**(4): p. 428-36.
52. Hu, X.H., et al., *Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate.* J Clin Psychiatry, 2004. **65**(7): p. 959-65.
53. Figgitt, D.P. and K.J. McClellan, *Fluvoxamine. An updated review of its use in the management of adults with anxiety disorders.* Drugs, 2000. **60**(4): p. 925-54.
54. Gartlehner, G., et al., *AHRQ Comparative Effectiveness Reviews*, in *Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review*. 2011, Agency for Healthcare Research and Quality (US): Rockville (MD).
55. Hiemke, C. and S. Hartter, *Pharmacokinetics of selective serotonin reuptake inhibitors.* Pharmacol Ther, 2000. **85**(1): p. 11-28.
56. Preskorn, S.H., *Clinically relevant pharmacology of selective serotonin reuptake inhibitors. An overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism.* Clin Pharmacokinet, 1997. **32 Suppl 1**: p. 1-21.
57. Sangkuhl, K., T.E. Klein, and R.B. Altman, *Selective serotonin reuptake inhibitors pathway.* Pharmacogenet Genomics, 2009. **19**(11): p. 907-9.
58. Martinowich, K. and B. Lu, *Interaction between BDNF and serotonin: role in mood disorders.* Neuropsychopharmacology, 2008. **33**(1): p. 73-83.
59. Andrade, S.E., et al., *Use of antidepressant medications during pregnancy: a multisite study.* Am J Obstet Gynecol, 2008. **198**(2): p. 194.e1-5.
60. Reefhuis, J., S.A. Rasmussen, and J.M. Friedman, *Selective serotonin-reuptake inhibitors and persistent pulmonary hypertension of the newborn.* N Engl J Med, 2006. **354**(20): p. 2188-90; author reply 2188-90.
61. Payne, J.L. and S. Meltzer-Brody, *Antidepressant use during pregnancy: current controversies and treatment strategies.* Clin Obstet Gynecol, 2009. **52**(3): p. 469-82.
62. Hendrick, V., et al., *Placental passage of antidepressant medications.* Am J Psychiatry, 2003. **160**(5): p. 993-6.
63. Lattimore, K.A., et al., *Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and effects on the fetus and newborn: a meta-analysis.* J Perinatol, 2005. **25**(9): p. 595-604.
64. Moses-Kolko, E.L., et al., *Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications.* Jama, 2005. **293**(19): p. 2372-83.
65. Epstein, R.A., K.M. Moore, and W.V. Bobo, *Treatment of nonpsychotic major depression during pregnancy: patient safety and challenges.* Drug Healthc Patient Saf, 2014. **6**: p. 109-29.
66. Levinson-Castiel, R., et al., *Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants.* Arch Pediatr Adolesc Med, 2006. **160**(2): p. 173-6.

67. Grigoriadis, S., et al., *The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis.* J Clin Psychiatry, 2013. **74**(4): p. e309-20.
68. Chambers, C.D., et al., *Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn.* N Engl J Med, 2006. **354**(6): p. 579-87.
69. Rohana, J., et al., *Neurodevelopmental outcome of newborns with persistent pulmonary hypertension.* Malays J Med Sci, 2011. **18**(4): p. 58-62.
70. Kallen, B. and P.O. Olausson, *Maternal use of selective serotonin re-uptake inhibitors and persistent pulmonary hypertension of the newborn.* Pharmacoepidemiol Drug Saf, 2008. **17**(8): p. 801-6.
71. Kieler, H., et al., *Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries.* Bmj, 2012. **344**: p. d8012.
72. Grigoriadis, S., et al., *Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis.* Bmj, 2014. **348**: p. f6932.
73. Andrade, S.E., et al., *Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn.* Pharmacoepidemiol Drug Saf, 2009. **18**(3): p. 246-52.
74. Wilson, K.L., et al., *Persistent pulmonary hypertension of the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors.* Am J Perinatol, 2011. **28**(1): p. 19-24.
75. Slattery, M.M. and J.J. Morrison, *Preterm delivery.* Lancet, 2002. **360**(9344): p. 1489-97.
76. Wisner, K.L., et al., *Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes.* Am J Psychiatry, 2009. **166**(5): p. 557-66.
77. Wen, S.W., et al., *Selective serotonin reuptake inhibitors and adverse pregnancy outcomes.* Am J Obstet Gynecol, 2006. **194**(4): p. 961-6.
78. Kallen, B., *Neonate characteristics after maternal use of antidepressants in late pregnancy.* Arch Pediatr Adolesc Med, 2004. **158**(4): p. 312-6.
79. Huang, H., et al., *A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight.* Gen Hosp Psychiatry, 2014. **36**(1): p. 13-8.
80. Ross, L.E., et al., *Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis.* JAMA Psychiatry, 2013. **70**(4): p. 436-43.
81. Diav-Citrin, O., et al., *Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study.* Br J Clin Pharmacol, 2008. **66**(5): p. 695-705.
82. Ferreira, E., et al., *Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates.* Pediatrics, 2007. **119**(1): p. 52-9.
83. Yonkers, K.A., et al., *Depression and serotonin reuptake inhibitor treatment as risk factors for preterm birth.* Epidemiology, 2012. **23**(5): p. 677-85.

84. Finster, M. and M. Wood, *The Apgar score has survived the test of time.* Anesthesiology, 2005. **102**(4): p. 855-7.
85. Reis, M. and B. Kallen, *Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data.* Psychol Med, 2010. **40**(10): p. 1723-33.
86. Suri, R., et al., *The impact of depression and fluoxetine treatment on obstetrical outcome.* Arch Womens Ment Health, 2004. **7**(3): p. 193-200.
87. Battaglia, F.C. and L.O. Lubchenco, *A practical classification of newborn infants by weight and gestational age.* J Pediatr, 1967. **71**(2): p. 159-63.
88. Zamudio, S., et al., *Hypoglycemia and the origin of hypoxia-induced reduction in human fetal growth.* PLoS One, 2010. **5**(1): p. e8551.
89. Jensen, H.M., et al., *The effects of maternal depression and use of antidepressants during pregnancy on risk of a child small for gestational age.* Psychopharmacology (Berl), 2013. **228**(2): p. 199-205.
90. Barker, D.J., et al., *Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth.* Diabetologia, 1993. **36**(1): p. 62-7.
91. Gaudineau, A., *[Prevalence, risk factors, maternal and fetal morbidity and mortality of intrauterine growth restriction and small-for-gestational age].* J Gynecol Obstet Biol Reprod (Paris), 2013. **42**(8): p. 895-910.
92. Albu, A.R., et al., *Predictive factors for intrauterine growth restriction.* J Med Life, 2014. **7**(2): p. 165-71.
93. Xu, H., F. Simonet, and Z.C. Luo, *Optimal birth weight percentile cut-offs in defining small- or large-for-gestational-age.* Acta Paediatr, 2010. **99**(4): p. 550-5.
94. Alexander, G.R., et al., *A United States national reference for fetal growth.* Obstet Gynecol, 1996. **87**(2): p. 163-8.
95. Gyselaers, W. and G. Martens, *Increasing prevalence of macrosomia in Flanders, Belgium: an indicator of population health and a burden for the future.* Facts Views Vis Obgyn, 2012. **4**(2): p. 141-3.
96. Kim, S.Y., et al., *Association of maternal body mass index, excessive weight gain, and gestational diabetes mellitus with large-for-gestational-age births.* Obstet Gynecol, 2014. **123**(4): p. 737-44.
97. Zimmermann, U., et al., *Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients.* J Psychiatr Res, 2003. **37**(3): p. 193-220.
98. Raeder, M.B., et al., *Obesity, dyslipidemia, and diabetes with selective serotonin reuptake inhibitors: the Hordaland Health Study.* J Clin Psychiatry, 2006. **67**(12): p. 1974-82.
99. Andersohn, F., et al., *Long-term use of antidepressants for depressive disorders and the risk of diabetes mellitus.* Am J Psychiatry, 2009. **166**(5): p. 591-8.
100. McIntyre, R.S., et al., *The association between conventional antidepressants and the metabolic syndrome: a review of the evidence and clinical implications.* CNS Drugs, 2010. **24**(9): p. 741-53.
101. Nulman, I., et al., *Neurodevelopment of children exposed in utero to antidepressant drugs.* N Engl J Med, 1997. **336**(4): p. 258-62.

102. Nulman, I., et al., *Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study.* Am J Psychiatry, 2002. **159**(11): p. 1889-95.
103. Casper, R.C., et al., *Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy.* J Pediatr, 2003. **142**(4): p. 402-8.
104. Casper, R.C., et al., *Length of prenatal exposure to selective serotonin reuptake inhibitor (SSRI) antidepressants: effects on neonatal adaptation and psychomotor development.* Psychopharmacology (Berl), 2011. **217**(2): p. 211-9.
105. Oberlander, T.F., et al., *Prenatal effects of selective serotonin reuptake inhibitor antidepressants, serotonin transporter promoter genotype (SLC6A4), and maternal mood on child behavior at 3 years of age.* Arch Pediatr Adolesc Med, 2010. **164**(5): p. 444-51.
106. Oberlander, T.F., et al., *Externalizing and attentional behaviors in children of depressed mothers treated with a selective serotonin reuptake inhibitor antidepressant during pregnancy.* Arch Pediatr Adolesc Med, 2007. **161**(1): p. 22-9.
107. Misri, S., et al., *Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications.* Am J Psychiatry, 2006. **163**(6): p. 1026-32.
108. Klinger, G., et al., *Long-term outcome following selective serotonin reuptake inhibitor induced neonatal abstinence syndrome.* J Perinatol, 2011. **31**(9): p. 615-20.
109. Hanley, G.E., U. Brain, and T.F. Oberlander, *Infant developmental outcomes following prenatal exposure to antidepressants, and maternal depressed mood and positive affect.* Early Hum Dev, 2013. **89**(8): p. 519-24.
110. Hanley, G.E., U. Brain, and T.F. Oberlander, *Prenatal exposure to serotonin reuptake inhibitor antidepressants and childhood behavior.* Pediatr Res, 2015. **78**(2): p. 174-80.
111. Skurtveit, S., et al., *Prenatal exposure to antidepressants and language competence at age three: results from a large population-based pregnancy cohort in Norway.* Bjog, 2014. **121**(13): p. 1621-31.
112. Figueroa, R., *Use of antidepressants during pregnancy and risk of attention-deficit/hyperactivity disorder in the offspring.* J Dev Behav Pediatr, 2010. **31**(8): p. 641-8.
113. Hviid, A., M. Melbye, and B. Pasternak, *Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism.* N Engl J Med, 2013. **369**(25): p. 2406-15.
114. Sorensen, M.J., et al., *Antidepressant exposure in pregnancy and risk of autism spectrum disorders.* Clin Epidemiol, 2013. **5**: p. 449-59.
115. Simon, G.E., M.L. Cunningham, and R.L. Davis, *Outcomes of prenatal antidepressant exposure.* Am J Psychiatry, 2002. **159**(12): p. 2055-61.
116. Croen, L.A., et al., *Antidepressant use during pregnancy and childhood autism spectrum disorders.* Arch Gen Psychiatry, 2011. **68**(11): p. 1104-12.

117. Gidaya, N.B., et al., *In utero exposure to selective serotonin reuptake inhibitors and risk for autism spectrum disorder.* J Autism Dev Disord, 2014. **44**(10): p. 2558-67.
118. Harrington, R.A., et al., *Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay.* Pediatrics, 2014. **133**(5): p. e1241-8.
119. Rai, D., et al., *Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study.* Bmj, 2013. **346**: p. f2059.
120. Clements, C.C., et al., *Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system.* Mol Psychiatry, 2015. **20**(6): p. 727-34.
121. Galbally, M., A.J. Lewis, and A. Buist, *Child developmental outcomes in preschool children following antidepressant exposure in pregnancy.* Aust N Z J Psychiatry, 2015. **49**(7): p. 642-50.
122. Velasquez, J.C., N. Goeden, and A. Bonnin, *Placental serotonin: implications for the developmental effects of SSRIs and maternal depression.* Front Cell Neurosci, 2013. **7**: p. 47.
123. Lee, L.J., *Neonatal fluoxetine exposure affects the neuronal structure in the somatosensory cortex and somatosensory-related behaviors in adolescent rats.* Neurotox Res, 2009. **15**(3): p. 212-23.
124. Brummelte, S., et al., *Antidepressant use during pregnancy and serotonin transporter genotype (SLC6A4) affect newborn serum reelin levels.* Dev Psychobiol, 2013. **55**(5): p. 518-29.
125. Bellissima, V., et al., *Antenatal maternal antidepressants drugs affect Activin A concentrations in maternal blood, in amniotic fluid and in fetal cord blood.* J Matern Fetal Neonatal Med, 2011. **24 Suppl 2**: p. 31-4.
126. Zafeiriou, D.I., A. Ververi, and E. Vargiami, *The serotonergic system: its role in pathogenesis and early developmental treatment of autism.* Curr Neuropharmacol, 2009. **7**(2): p. 150-7.
127. Eriksson, M.A., et al., *First-degree relatives of young children with autism spectrum disorders: some gender aspects.* Res Dev Disabil, 2012. **33**(5): p. 1642-8.
128. Man, K.K., et al., *Exposure to selective serotonin reuptake inhibitors during pregnancy and risk of autism spectrum disorder in children: a systematic review and meta-analysis of observational studies.* Neurosci Biobehav Rev, 2015. **49**: p. 82-9.
129. Poverty Lines. *Before-Tax, 2005; c2006* 2006 [cited 2015 May 14]; Available from: http://www.ccsd.ca/factsheets/fs_lico05_bt.htm.
130. BMI Classification. *Global Database on Body Mass Index. World Health Organization*. 2015; Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.
131. Spielberger CD, G.R., Lushene RE, *Test manual for the State Trait Anxiety Inventory*. 1970, Palo Alto, California: Consulting Psychologists Press.
132. Kramer, M.S., et al., *A new and improved population-based Canadian reference for birth weight for gestational age.* Pediatrics, 2001. **108**(2): p. E35.

133. Squire J, P.L., Bricker D, *The ASQ User's Guide (2nd ed)*. 1999, Baltimore, MD: Brooks Publishing Co.
134. Liddell, F.D., *Simple exact analysis of the standardised mortality ratio.* J Epidemiol Community Health, 1984. **38**(1): p. 85-8.
135. Haukoos, J.S. and R.J. Lewis, *Advanced statistics: bootstrapping confidence intervals for statistics with "difficult" distributions.* Acad Emerg Med, 2005. **12**(4): p. 360-5.
136. SAS. *Jackknife and Bootstrap Analyses*. 2015; Available from: http://support.sas.com/kb/24/982.html.
137. Patten, S.B., et al., *Major depression, antidepressant medication and the risk of obesity.* Psychother Psychosom, 2009. **78**(3): p. 182-6.
138. Patten, S.B., et al., *Weight gain in relation to major depression and antidepressant medication use.* J Affect Disord, 2011. **134**(1-3): p. 288-93.
139. Grundy, A., et al., *Associations between anxiety, depression, antidepressant medication, obesity and weight gain among Canadian women.* PLoS One, 2014. **9**(6): p. e99780.
140. Luppino, F.S., et al., *Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies.* Arch Gen Psychiatry, 2010. **67**(3): p. 220-9.
141. de Wit, L., et al., *Depression and obesity: a meta-analysis of community-based studies.* Psychiatry Res, 2010. **178**(2): p. 230-5.
142. Serretti, A. and L. Mandelli, *Antidepressants and body weight: a comprehensive review and meta-analysis.* J Clin Psychiatry, 2010. **71**(10): p. 1259-72.
143. Schwartz, T.L., et al., *Psychiatric medication-induced obesity: a review.* Obes Rev, 2004. **5**(2): p. 115-21.
144. Poulain, M., et al., *The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies.* Cmaj, 2006. **174**(9): p. 1293-9.
145. El Marroun, H., et al., *Maternal use of antidepressant or anxiolytic medication during pregnancy and childhood neurodevelopmental outcomes: a systematic review.* Eur Child Adolesc Psychiatry, 2014. **23**(10): p. 973-92.
146. Powers, J.R., et al., *A prospective study of prevalence and predictors of concurrent alcohol and tobacco use during pregnancy.* Matern Child Health J, 2013. **17**(1): p. 76-84.
147. Ryan, D., L. Milis, and N. Misri, *Depression during pregnancy.* Can Fam Physician, 2005. **51**: p. 1087-93.
148. Frick, A.P., et al., *Prediction of large for gestational age neonates: Screening by maternal factors and biomarkers in the three trimesters of pregnancy.* Ultrasound Obstet Gynecol, 2015.
149. Graves, E., et al., *The impact of abnormal glucose tolerance and obesity on fetal growth.* J Diabetes Res, 2015. **2015**: p. 847674.
150. Beyazyuz, M., et al., *Relationship between SSRIs and Metabolic Syndrome Abnormalities in Patients with Generalized Anxiety Disorder: A Prospective Study.* Psychiatry Investig, 2013. **10**(2): p. 148-54.
151. Pan, A., et al., *Use of antidepressant medication and risk of type 2 diabetes: results from three cohorts of US adults.* Diabetologia, 2012. **55**(1): p. 63-72.

152. Yoon, J.M., et al., *Antidepressant use and diabetes mellitus risk: a meta-analysis.* Korean J Fam Med, 2013. **34**(4): p. 228-40.
153. Carvalho, F., et al., *Hyperglycemia induced by acute central fluoxetine administration: role of the central CRH system and 5-HT3 receptors.* Neuropeptides, 2004. **38**(2-3): p. 98-105.
154. Levkovitz, Y., et al., *Antidepressants induce cellular insulin resistance by activation of IRS-1 kinases.* Mol Cell Neurosci, 2007. **36**(3): p. 305-12.
155. Kulkarni, S.R., et al., *Maternal lipids are as important as glucose for fetal growth: findings from the Pune Maternal Nutrition Study.* Diabetes Care, 2013. **36**(9): p. 2706-13.
156. Shelton, R.C. and A.H. Miller, *Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression.* Prog Neurobiol, 2010. **91**(4): p. 275-99.
157. Chambers, C.D., et al., *Birth outcomes in pregnant women taking fluoxetine.* N Engl J Med, 1996. **335**(14): p. 1010-5.
158. Costei, A.M., et al., *Perinatal outcome following third trimester exposure to paroxetine.* Arch Pediatr Adolesc Med, 2002. **156**(11): p. 1129-32.
159. Nichols, R.A., *Serotonin, presynaptic 5-HT(3) receptors and synaptic plasticity in the developing cerebellum.* J Physiol, 2011. **589**(Pt 21): p. 5019-20.
160. Ansorge, M.S., E. Morelli, and J.A. Gingrich, *Inhibition of serotonin but not norepinephrine transport during development produces delayed, persistent perturbations of emotional behaviors in mice.* J Neurosci, 2008. **28**(1): p. 199-207.
161. Ansorge, M.S., et al., *Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice.* Science, 2004. **306**(5697): p. 879-81.
162. Boyd, R.C., H.N. Le, and R. Somberg, *Review of screening instruments for postpartum depression.* Arch Womens Ment Health, 2005. **8**(3): p. 141-53.
163. Julian, L.J., *Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A).* Arthritis Care Res (Hoboken), 2011. **63 Suppl 11**: p. S467-72.
164. Gollenberg, A.L., et al., *Concurrent validity of the parent-completed Ages and Stages Questionnaires, 2nd Ed. with the Bayley Scales of Infant Development II in a low-risk sample.* Child Care Health Dev, 2010. **36**(4): p. 485-90.
165. Gartstein, M.A., et al., *Depressed Mood and Maternal Report of Child Behavior Problems: Another Look at the Depression-Distortion Hypothesis.* J Appl Dev Psychol, 2009. **30**(2): p. 149-160.
166. Benzies, K., R. Mychasiuk, and S. Tough, *What patterns of postpartum psychological distress are associated with maternal concerns about their children's emotional and behavioural problems at the age of three years?* Early Child Dev Care, 2015. **185**(1): p. 1-16.
167. Evans, J., et al., *Cohort study of depressed mood during pregnancy and after childbirth.* Bmj, 2001. **323**(7307): p. 257-60.
168. Furu, K., et al., *Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design.* Bmj, 2015. **350**: p. h1798.

169. van der Weide, J. and J.W. Hinrichs, *The influence of cytochrome P450 pharmacogenetics on disposition of common antidepressant and antipsychotic medications.* Clin Biochem Rev, 2006. **27**(1): p. 17-25.

Appendices

Appendix A: Animal model literature review

In rodent studies, the phenomenon of paradoxical behaviour outcomes has been noted, meaning that SSRIs administered during early neurodevelopmental period (antenatal, neonatal, and adolescent) causes anxiety- and depression-like behaviours in adulthood, whereas SSRI exposure during adulthood has the opposite behavioural effects [1]. This observed paradox is likely explained by SSRI-induced changes in neural serotonin levels during critical neurodevelopment periods [2].

A study conducted by Hansen *et al.* [3] was the first to find an adverse long-term neurobehavioural effect of SSRI exposure. SSRIs were administered during 8^{th} to 21^{st} postnatal days, which corresponded to the events of brain maturation that began during the third trimester of pregnancy and early childhood in humans. At the age of fourth months, both saline- and SSRI-treated groups were assessed in open field, forced swim, and social interaction tests. A significant difference was only found in the forced swim test where the SSRI-treated group had a prolonged immobility time, which was purported to represent behavioural despair and negative mood. This result indicates that the central serotonergic system play a role in the pathology of depression.

An innovative study performed by Ansorge *et al.* [4] administered fluoxetine or saline postnatally from day 4 to 21 for mice of different serotonin transport (5-HTT) genotypes. Tests were conducted 9 weeks after the last injection of fluoxetine or saline. Decreased exploratory behaviours, longer latencies to begin feeding, and longer average latency to escape foot shock were observed in wildtype (5-HTT+/+) and heterozygous (5-HTT+/-) mice treated with fluoxetine compared to those treated with saline. Similar behaviours were detected in mutated (5-HTT-/-) mice that were treated with either fluoxetine or saline. These results suggest that alteration of neural serotonin level either by permanent genetic modification of 5-HTT or transient SSRI treatments during critical neurodevelopment periods changes the neural connections in the central nervous system (CNS) that regulate depression- and anxiety-related behaviours in adulthood.

Increased neural serotonin concentration during the neurodevelopmental stages may also affect aggression in adulthood. Manhães de Castro *et al.* [5] investigated the

degree of aggression in adult mice (90-120 days old) exposed to citalopram from 1st to 19th postnatal days. The duration of aggressive behaviour in the mice treated with citalopram decreased by 41.4% compared to the control group. Additionally, Maciag *et al.* [6] found decreased expression of tryptophan hydroxylase (rate-limiting serotonin synthetic enzyme) and 5-HTT in the CNS of adult mice exposed to citalopram postnatally (8-21 days). Motor movement activity and sexual behavior were increased and decreased, respectively [6]. Another study found anatomical changes in the fine neural wiring of the somatosensory cortex in adult rats exposed to fluoxetine postnatally (0-6 days) [7]. Consequently, behavioural deficits related to somatosensory, such as tactile impairment, thermal perceptions delay, and locomotion activity reduction (exploratory behavioural reduction), were observed [7].

Popa *et al.* [8] also discovered depression-like behaviours such as an increase in rapid eye movement (REM) sleep and anhedonia in mice exposed to escitalopram during early postnatal life. The depressive symptoms, however, improved after long-term escitalopram treatment. Similar to the findings of Ansorge *et al.* [4], mice with genetically deficient expression of 5-HTT had comparable depression-like symptoms as the mice that were treated transiently with escitalopram during postpartum periods.

Bairy *et al.* [9] also reported transient motor development delay in rats exposed to antenatal fluoxetine (6th to 20th day of pregnancy), but other behavioural outcomes were not negatively affected. Interestingly, rats exposed to higher doses of fluoxetine performed well in the water maze test, which suggested an improvement in cognitive abilities, particularly in learning and memory. In a similar study, pups exposed to antenatal SSRIs had anxiety-like behaviours accompanied with decrease in social behaviours during adulthood, but behavioural despair, anhedonia, and abnormal sexual behaviour were not detected [10]. Lastly, mice pups exposed to fluoxetine during pregnancy and lactation had decreased ambulation, impulsivity (as demonstrated via the intruder-resident test), and increased immobility time (forced swim test) [11].

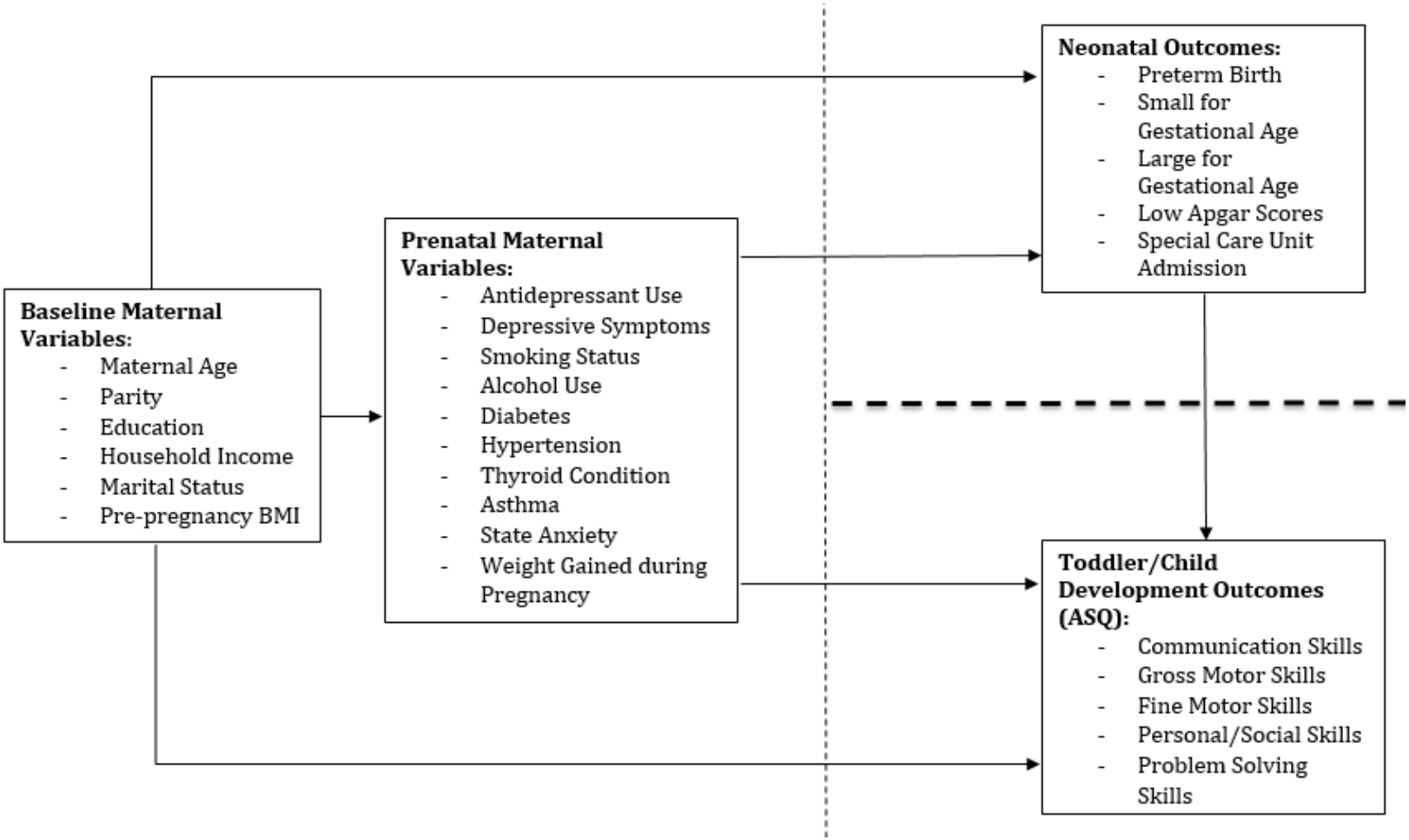
In conclusion, the above-mentioned studies were suggestive of adverse behavioural changes, specifically depression- and anxiety-like symptoms, which developed in adult rodents exposed to SSRIs during crucial neurodevelopment phases.

References

1. Homberg, J.R., D. Schubert, and P. Gaspar, *New perspectives on the neurodevelopmental effects of SSRIs.* Trends Pharmacol Sci, 2010. **31**(2): p. 60-5.
2. Olivier, J.D., et al., *The age-dependent effects of selective serotonin reuptake inhibitors in humans and rodents: A review.* Prog Neuropsychopharmacol Biol Psychiatry, 2011. **35**(6): p. 1400-8.
3. Hansen, H.H., C. Sanchez, and E. Meier, *Neonatal administration of the selective serotonin reuptake inhibitor Lu 10-134-C increases forced swimming-induced immobility in adult rats: a putative animal model of depression?* J Pharmacol Exp Ther, 1997. **283**(3): p. 1333-41.
4. Ansorge, M.S., et al., *Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice.* Science, 2004. **306**(5697): p. 879-81.
5. Manhaes de Castro, R., et al., *Reduction of intraspecific aggression in adult rats by neonatal treatment with a selective serotonin reuptake inhibitor.* Braz J Med Biol Res, 2001. **34**(1): p. 121-4.
6. Maciag, D., et al., *Neonatal antidepressant exposure has lasting effects on behavior and serotonin circuitry.* Neuropsychopharmacology, 2006. **31**(1): p. 47-57.
7. Lee, L.J., *Neonatal fluoxetine exposure affects the neuronal structure in the somatosensory cortex and somatosensory-related behaviors in adolescent rats.* Neurotox Res, 2009. **15**(3): p. 212-23.
8. Popa, D., et al., *Lasting syndrome of depression produced by reduction in serotonin uptake during postnatal development: evidence from sleep, stress, and behavior.* J Neurosci, 2008. **28**(14): p. 3546-54.
9. Bairy, K.L., et al., *Developmental and behavioral consequences of prenatal fluoxetine.* Pharmacology, 2007. **79**(1): p. 1-11.
10. Olivier, J.D., et al., *Fluoxetine administration to pregnant rats increases anxiety-related behavior in the offspring.* Psychopharmacology (Berl), 2011. **217**(3): p. 419-32.
11. Lisboa, S.F., et al., *Behavioral evaluation of male and female mice pups exposed to fluoxetine during pregnancy and lactation.* Pharmacology, 2007. **80**(1): p. 49-56.

Appendix B: Conceptual model

Figure B1: Conceptual model based on literature review: neonatal and developmental outcomes of antenatal depressive symptoms and antidepressant exposure



Appendix C: Relevant Sections from the Prenatal Health Project Questionnaire.

1. What is your date of birth?
Year Month Day

5. How tall are you without shoes? _____ cm OR ____ ft ____ inches ◯ Don't Know

6. How much did you weigh prior to this pregnancy? _____ kg OR ____ lbs ◯ Don't Know

10. I am going to read a list of health conditions. For each, please say 'yes' if you currently have the condition or have had the condition in the past. If you do not have, or have never had the condition please respond with 'no.'

Do you have, or have you ever had:

Yes	No	
◯	◯	heart disease or cardiovascular disease
◯	◯	high blood pressure before pregnancy
◯	◯	high blood pressure during pregnancy
◯	◯	diabetes before pregnancy
◯	◯	diabetes during pregnancy
◯	◯	asthma
◯	◯	other medical conditions _____

please specify

12a. Please tell me the year that each of your previous pregnancies ended, and if it was a livebirth, stillbirth, miscarriage or abortion.

YOU MAY NEED TO PROMPT THE RESPONDENT BY ASKING ABOUT THE MOST RECENT PREGNANCY THEY HAD, AND THEN SAYING, AND BEFORE THAT ETC.

Please record on Relationship Sheet if participant has children.

Please code abortion as miscarriage.

Year of Pregnancy	Live birth / Stillbirth / Miscarriage	Gestational Age Weeks	Birth Weight grams	lbs	oz

23b. How many cigarettes do you typically smoke each day now?..... each

27. Please tell me any over-the-counter and prescription medications you take regularly now, the number of pills or dosage if you know it, and how many times you take them per day:

◯ I don't take any over-the-counter or prescription medications

Name	Amount	Frequency

24. How many drinks do you typically have per week now? By drink I mean a glass of wine, beer, or a mixed drink. each

29. What is your best estimate of the total income of all members of your household from all sources before taxes and deductions for the past year. By total income I mean total gross income from paid employment, government assistance, student loans or inheritance. Was the total household income:

- Less than $30,000
  - Less than $15,000
    - Less than $10,000
    - $10,000 to $14,999
  - Greater than or equal to $15,000
    - $15,000 to $19,999
    - $20,000 to $29,999
- Greater than or equal to $30,000
  - Less than $60,000
    - $30,000 to $39,999
    - $40,000 to $59,999
  - Greater than or equal to $60,000
    - $60,000 to $79,999
    - $80,000 or more

- *NO INCOME*
- *DON'T KNOW*
- *REFUSE TO ANSWER*

32. What is your current marital status?

- Married
- Common law (or living as married)
- Single / never married
- Separated/divorced
- Widowed

40. How have you been feeling over this past week ?

	Not at all	Somewhat	Moderately so	Very much so
I feel calm	1	2	3	4
I feel secure	1	2	3	4
I am regretful	1	2	3	4
I am presently worrying over possible misfortunes	1	2	3	4
I am anxious	1	2	3	4
I feel self-confident	1	2	3	4
I am jittery	1	2	3	4
I feel "high strung"	1	2	3	4
I am relaxed	1	2	3	4
I feel over-excited and "rattled"	1	2	3	4
I feel joyful	1	2	3	4
I feel pleasant	1	2	3	4

11 People will feel different ways in different situations. The following are some sentences that say something about how people sometimes feel. Please listen to each sentence and tell me how often you have felt this way in the past 7 days.
(Please refer to column G in your response option table.)

41. During the past seven days, have you felt this way: Rarely or none of the time (less than one day), Some or a little of the time (1 to 2 days), Occasionally or a moderate amount of time (3 to 4 days), Most or all of the time (5 to 7 days)

I was bothered by things that usually don't bother me.	1	2	3	4
I did not feel like eating; my appetite was poor.	1	2	3	4
I felt that I could not shake off the blues even with help from my family or friends.	1	2	3	4
I felt that I was just as good as other people.	1	2	3	4
I had trouble keeping my mind on what I was doing.	1	2	3	4
I felt depressed.	1	2	3	4
I felt that everything I did was an effort.	1	2	3	4
I felt hopeful about the future.	1	2	3	4
I thought my life had been a failure.	1	2	3	4
I felt fearful.	1	2	3	4
My sleep was restless.	1	2	3	4
I was happy.	1	2	3	4
I talked less than usual.	1	2	3	4
I felt lonely.	1	2	3	4
People were unfriendly.	1	2	3	4
I enjoyed life.	1	2	3	4
I had crying spells.	1	2	3	4
I felt sad.	1	2	3	4
I felt that people disliked me.	1	2	3	4
I could not get "going".	1	2	3	4

54. What is the highest level of formal education you have completed?

- ○ elementary school
- ○ some high school
- ○ completed high school
- ○ some college or university
- ○ college diploma
- ○ university degree
- ○ trade school
- ○ other _____ please specify

Curriculum Vitae

Name:	Jerry Yu-Hsiang Chen
Post-secondary Education and Degrees:	The University of Western Ontario London, Ontario, Canada 2007-2011 BM.Sc., Honours Specialization in Medical Science The University of Western Ontario London, Ontario, Canada 2011-2016 M.Sc., Epidemiology and Biostatistics
Honours and Awards:	Schulich Graduate Scholarship The University of Western Ontario 2011-2013 Ontario Graduate Scholarship 2011-2012 Children Health Research Institute Research Graduate Fellowship 2012-2013
Related Work Experience	Research Assistant The University of Western Ontario 2011-2013