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Neonatal and childhood neurodevelopmental, health and educational outcomes of children exposed to antidepressants and maternal depression during pregnancy: protocol for a retrospective population-based cohort study using linked administrative data

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ABSTRACT

Introduction: Antidepressants are commonly prescribed during pregnancy; however, there are inconsistent data on the safety of these medications during the prenatal period. To address this gap, this study will investigate short-term and long-term neurodevelopmental, physical and mental health, and educational outcomes of children who have been exposed to selective serotonin reuptake inhibitors (SSRIs) or selective serotonin norepinephrine reuptake inhibitors (SNRIs) and/or maternal depression during pregnancy.

Methods and analysis: Administrative data will be linked to generate 4 population-based exposed groups from all children born in Manitoba between 1996 and 2014 whose mother had at least 2 prescriptions for either an SSRI or SNRI: (1) throughout the prenatal period (beginning of pregnancy until birth); (2) in the first trimester (≤14 weeks gestation); (3) in the second trimester (15–26 weeks gestation); (4) in the third trimester (≥27 weeks gestation) and 1 population-based unexposed group consisting of children whose mothers had a diagnosis of mood or anxiety disorder during pregnancy but did not use antidepressants. Propensity scores and inverse probability treatment weights will be used to adjust for confounding. Multivariate regression modelling will determine whether, compared with untreated mood/anxiety disorder, prenatal exposure to antidepressant medications is associated with: (1) adverse birth and neonatal outcomes, including: preterm birth, low birth weight, low Apgar scores, respiratory distress, congenital malformations and persistent pulmonary hypertension; (2) adverse early childhood outcomes, including: early childhood education challenges, diagnosis of neurodevelopmental disorders and diagnosis of mental disorders. We will determine if exposure effects differ between SSRIs and SRNIs, and determine if exposure effects differ between gestation timing of exposure to antidepressants.

Strengths and limitations of this study

- Through the use of linked clinical and administrative data, the Manitoba Centre for Health Research Repository allows the generation of a large population-based sample of children exposed to prenatal mood/anxiety disorders, with or without exposure to prenatal antidepressants, which allows us to control for underlying maternal mood/anxiety disorders.
- This study uses a provincially regulated prescription database that eliminates recall bias and enhances data regarding the dose, exposure and type of medications.
- The Manitoba Centre for Health Policy data facilitate sensitivity analysis between selective serotonin reuptake inhibitors and selective serotonin norepinephrine reuptake inhibitors, producing results that could inform prescribing practices.
- Through linking health, education and social data, we can examine broader and longer term outcomes in later childhood that have not been examined at a population level including: the onset of neurodevelopmental disorders (autism spectrum disorder), attention deficit hyperactivity disorder, mental disorders and learning disabilities.
- The study is subject to the limitations of administrative data and is reliant on the accuracy of data submitted by the organisations that deliver services.

Ethics and dissemination: Ethical approval was obtained from the University of Manitoba Health Research Ethics Board. Dissemination of results will include engagement of stakeholders and patients, writing of reports for policymakers and patients, and publication of scientific papers.

INTRODUCTION

The incidence of depression in women of childbearing age is rising, resulting in an increased used of antidepressants during pregnancy.[1–5] Approximately 15–20% of women experience depression during pregnancy, and about 5–13% of pregnant women are treated with antidepressant medications.[6 7] Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed medications during this period.[3 6–9] Despite the high utilisation of antidepressants during pregnancy, their safety during the prenatal period remains controversial as there are conflicting data regarding the risks,[10–14] making the clinical management of depression a significant clinical challenge.

Several studies have investigated the effect of in utero antidepressants on neonatal outcomes and have yielded conflicting results: studies in the early 2000s demonstrated increased risk of congenital malformations,[15–21] and persistent pulmonary hypertension in infants;[22–24] however, more recent studies state there is no increased risk of these outcomes.[18 25–31] Studies have also demonstrated an association with low birth weight and preterm birth; however, meta-analysis found that the strength of the effect of the medications was small.[32] Antidepressant use during late pregnancy has also been associated with neonatal adaptation syndrome.[33]

Key factors contributing to the conflicting data regarding antidepressant use during pregnancy are the methodological challenges to conducting research in this area and the lack of evidence of the effects of untreated maternal depression and antidepressant withdrawal.[10 11 34 35] Owing to ethical considerations, there are no randomised controlled trials (RCTs) that prospectively investigate the safety and efficacy of antidepressants in pregnant women who have depression.[36] Therefore, observational studies are primarily used to determine the association of antidepressants and adverse outcomes in infants and children. These studies are often susceptible to methodological biases[37] such as small sample sizes, attrition bias and recall bias, including: reliance on maternal self-report for exposures to illegal drugs and substances, reliance on retrospective recall for medication exposures and inability to account for severity of depression.[38] In observational studies, it is also often difficult to control for confounding factors that may alter the relationship between the development of adverse neonatal and childhood outcomes, such as socioeconomic status (SES), maternal nutrition, comorbid mental and physical illness, prenatal substance use and the use of other medications, including those with and without psychiatric indications.

A major limitation of existing observational studies is the challenge distinguishing between the effects of medication exposure and the effects of maternal mental illness itself on the developing fetus.[39] Maternal depression, anxiety and mood disorders have been shown to have adverse effects on the mother and infant.[35] Recent systematic reviews show an increase in the risk of preterm birth and low birth weight, growth restriction, disrupted emotional regulation and impaired cognitive development in childhood.[40–42] Along with the risks to the fetus, untreated maternal depression carries harm towards the mother, as mental illness can affect a mother's ability to obtain adequate prenatal care, necessary nutrition, increase risk of smoking and alcohol use, increase risk of emotional withdrawal and increase risk of self-injurious, psychotic and impulsive behaviours.[43–49] Depression during pregnancy is also a risk factor for postnatal depression, which is linked to adverse child and maternal outcomes.[40 42] Thus, clinicians and patients must carefully weigh the risks and benefits of exposing a fetus to untreated maternal mental illness against exposing the fetus to antidepressant medications.[14 37]

Furthermore, while there is a substantial body of literature investigating the effects of prenatal antidepressant use (PAU) on neonatal outcomes, the same cannot be said for studies of longer term developmental outcomes in childhood. The literature base investigating longer term outcomes in children exposed to antidepressants in utero consists of studies utilising small sample sizes, providing non-statistical, or weak evidence for motor and language delays in childhood,[50–53] neurodevelopmental behaviour outcomes, including disruptive social behaviour, motor activity, habituation and sleep,[54] and cognitive development.[55] A recent sibling-controlled study found an increased risk in anxiety symptoms at 3 years of age.[56] Few studies to date have investigated associations between in utero antidepressant exposure and neurodevelopmental disorders and these have found conflicting results.[57–65] Two recent systematic reviews suggest that prenatal exposure to antidepressants may increase the risk of autism spectrum disorder (ASD) in children.[59 66] However, authors of both reviews caution interpretation of these results due to the following biases: confounding by indication, lack of clinical validation, difficulty identifying women who took the prescribed medications during pregnancy, no assessment of severity of depression and lack of information about unhealthy behaviours.[59] Authors of almost all studies included in the reviews indicate that further research must be performed that delineates the effect of untreated maternal depression versus the effects of antidepressant exposure on the onset of ASD in children.

There are considerable methodological limitations in studies investigating longer term childhood outcomes, including small sample sizes, relatively short follow-up

durations (mostly under 3 years) and failure to account for important confounding variables such as maternal prenatal substance use, SES, education and comorbid maternal mental illness. Thus, more high-quality research utilising larger sample sizes and longer follow-up time is needed regarding the effects of prenatal antidepressant exposure on cognitive and behavioural outcomes in children. Furthermore, the few studies investigating the effect of antidepressant use during pregnancy on the onset of neurodevelopmental disorders have indicated that there may be an association. Therefore, there is a pressing need to investigate neurodevelopmental disorders (including ASD, attention deficit hyperactivity disorder (ADHD)) using longitudinal, large population-based samples and methodologies that can account for confounding factors and maternal mental illness.

Using linked administrative data to address the evidence gaps: We propose a comprehensive, longitudinal (over the last 20 years) and rigorous investigation into short-term and long-term outcomes of infants and children exposed in utero to SSRIs or selective serotonin norepinephrine reuptake inhibitors (SNRIs) compared with infants and children exposed in utero to untreated mood and/or anxiety disorder, using linked administrative health and social data housed at the Manitoba Centre for Health Policy (MCHP) (a population health research unit within the University of Manitoba, Canada). The Population Health Research Data Repository (herein referred to as the 'Repository') consists of population-wide administrative data from health and social service agencies throughout Manitoba, education institutions and Canadian census. The longitudinal nature of the data allows us to conduct novel investigation into longer term outcomes in early childhood and adolescence, which include diagnoses of mental disorders, neurodevelopmental disorders (eg, ADHD, ASD), learning disabilities and educational challenges. We will also be able to disaggregate exposures to antidepressants and to mood/anxiety disorders according to whether exposure was in early, or late pregnancy. Moreover, we will conduct a sensitivity analysis between SSRIs and SNRIs; the latter are a newer class of antidepressants that are being increasingly prescribed to patients with mood/anxiety disorders.[67] These analyses have potential implications on prescribing practices. Furthermore, the vast array of social, education and demographic variables available in the Repository for all women giving birth in Manitoba allow us to use Propensity Score Matching and Inverse Probability Treatment Weights (IPTWs) to control for key maternal baseline variables that may confound the association between antidepressants and outcomes.

The purpose of this protocol paper is to: (1) provide dissemination of our research activity to prevent duplication of work and encourage collaboration; (2) provide a citation for a detailed study methodology that can be referenced for future papers produced from this research to enhance transparency.

Research questions

1. Is prenatal exposure to SSRIs or SNRIs associated with adverse birth and neonatal outcomes, including: preterm birth, low birth weight, low Apgar scores, respiratory distress, congenital malformations and persistent pulmonary hypertension compared with untreated prenatal mood/anxiety disorders?
2. Is prenatal exposure to SSRIs or SNRIs associated with adverse early childhood outcomes, including: early childhood educational challenges, diagnosis of neurodevelopmental disorders (eg, autism, ADHD) and diagnosis of mental disorders compared with untreated prenatal mood/anxiety disorders?
3. Do exposure effects differ between types of antidepressants prescribed, specifically between SSRIs and SRNIs?
4. Do exposure effects differ between gestation timing of exposure to antidepressants, that is, exposure to antidepressants throughout pregnancy, versus first trimester only, versus second and third trimesters?

METHODS AND ANALYSIS

Description of data sources

The MCHP Repository has been widely validated for the use of population health and social services research.[68–75] Key studies that utilised the Repository to investigate health services, pharmaceutical use and outcomes pertaining to maternal and child health will lay the methodological foundation for this study.[76 77] Several databases containing demographic, SES, social, educational, medical claims data and drug data will be linked together for this study. See table 1 for a description of each data set, years of data that will be used and the types of data that will be retrieved from each data set.

Description of data linkage: Deidentified health records are transferred to MCHP from Manitoba Health, Seniors and Active Living (MHSAL, the government department that administers the universal health insurance programme for the province) and contain scrambled identifiers that allow for linkages across the multiple databases described above and across years of data. MHSAL acts as a third party for other non-health data providers, to develop cross-walk files allowing individual-level linkages across different data sectors. Linkages are performed using deidentified personal health identification numbers (PHINs) which are unique nine-digit numeric identifiers assigned by MHSAL to every person registered for health insurance in Manitoba. We will identify the study population through linking women with a record of a live birth in Manitoba occurring between 1996 and 2014, and a diagnosis of mood/anxiety disorder 3 months prior to conception to their child using the 'Hospital Newborn to Mother linkage' which is an existing Registry file in the Repository. This file contains basic demographic and hospital data on newborns born in a hospital in Manitoba from 1984/1985 onward and their mothers. This file includes all live and stillbirths to

Table 1 Description of data sets used for analysis and types of information retrieved

Name of data set	Description of data set	Years of data	Information retrieved
Population Registry	A registry maintained by the provincial department of health of all Manitobans eligible to receive health services since 1970 (updated semiannually) and includes demographic information and six-digit residential postal code	1970/1971 to June 2013	Maternal and child demographics: region of residence
Canada Census Information: Socioeconomic Factor Index (SEFI-2)	Social data based on the Statistics Canada Population Census. These data were used to derive a composite measure of area-level SES, comprising information on employment, education, lone-parent and income.[83] Scores <0 indicate more favourable socioeconomic conditions, while scores >0 indicate less favourable socioeconomic conditions[83]	1996, 2001, 2006, 2013	Maternal and child socioeconomic status
Employment and Income Assistance Data	Data from the Social Assistance Management Information Network that provide information on Manitoba residents who receive provincial employment and income assistance, a programme that provides financial assistance for meeting the basic needs of living	1995/1996 to 2012/2013	Maternal and child socioeconomic status
Education data: Enrolment, Marks and Assessments	Education data maintained by the provincial department of education that provides information on enrolment, marks, provincial standards tests, high school completion and special funding. Special education funding is provided to children with moderate to profound disabilities, with the category of disability (eg, autism) specified	1995/1996 to 2012/2013	Maternal and child high school completion, level of special education funding Outcome data: childhood educational outcomes
Early Developmental Instrument Data set	Data from the Early Development Instrument, a questionnaire that is filled out by kindergarten teachers on their students' developmental health across five domains of development to measure population-level development in early childhood	2006–2013	Outcome data: childhood educational outcomes
Baby First/Families First Screening Programme data	Data collected as part of a universal screening programme conducted by Healthy Child Manitoba. The screen is filled out by Public Health Nurses on all families with newborns in Manitoba and captures data on biological, social and demographic risk factors, including alcohol use during pregnancy	2003–2013=Families First 2000–2002=Baby First	Maternal alcohol and drug use during pregnancy Maternal education
Healthy Baby Prenatal Benefit and Healthy Baby Community Support Programme	Data from the Healthy Baby programmes, which provide financial benefits to help women meet nutritional needs during pregnancy and connect women to programmes and resources in their area	2001 to 2011/2012	Maternal demographic and socioeconomic status Maternal programme participation
Hospital Abstracts	Health data maintained by provincial department of health consisting of all hospitalizations in Manitoba, including up to 16 ICD-9-CM diagnostic codes for discharges before 1 April 2004 and up to 25 ICD-10-CM diagnostic codes for discharges on or after April 1, 2004	1984 to 2012/2013	Outcome data: maternal and child physical and mental health diagnoses Antenatal hospitalisations

Continued

Table 1 Continued

Name of data set	Description of data set	Years of data	Information retrieved
Medical/Physician reimbursement claims	Health data maintained by provincial department of health consisting of all ambulatory physician visits in Manitoba and include a single ICD-9 diagnostic code associated with each visit, coded to the third digit	1984 to 2012/2013	Exposure data: maternal mood/anxiety disorders Exposure data: maternal physical and mental health diagnoses and physician visits Maternal prenatal care Childhood outcome data: diagnoses in the neonatal period Childhood outcome data: Medical diagnosis in childhood
Prescription claims data: Drug Programme Information Network	Data maintained by provincial department of health containing all prescription drug claims from the Drug Programme Information Network (DPIN, an electronic, online, point-of-sale prescription drug database that connects department of health and all pharmacies in Manitoba). Contains information on all prescription drugs dispensed in Manitoba	1995/1996 to 2012/13	Exposure data: maternal mood/anxiety disorders Exposure data: maternal antidepressants Exposure data: maternal prescription drugs Childhood outcome data: physical and mental health diagnoses
Vital Statistics data	A longitudinal population-based registry maintained by Manitoba's Vital Statistics Agency that includes all Manitobans who have died since January 1970 to present and the cause	1970 to 2012/2013	Maternal and child cause of death or suicide completion
Child and Family Services Information System (CFSIS)	A data management system that supports case tracking and reporting of services provided to children and families as they pass through the Manitoba child welfare system. This database includes information on children in care as well as information of families receiving protective and support services	1992/1993 to 2012/2013	Demographic information: maternal or child involvement with child and family services

Manitoba residents, and babies born out of province to Manitoba residents, if reported to MHSAL. Babies not included are those: born out of hospital, born in Manitoba hospitals to out-of-province residents, those born out of province to Manitoba residents not reported to MHSAL. A baby's birth record is matched to the mother's obstetrical delivery record using PHINs.

Study design and population

This is a retrospective, matched-cohort study based on all children born between 1996 and 2014 of mothers diagnosed with prenatal mood/anxiety disorders in Manitoba. Based on a study on the perinatal health of women in Manitoba, 7.5% of women were diagnosed with prenatal psychological distress (including depression) out of 15 000 births in 2008/2009.[77] This will give us ~21 375 women diagnosed with prenatal psychological distress during our study period. Based on previous studies, the majority of these mothers (>90%) will be linkable to their children, obtaining the largest Canadian sample to date of children exposed to prenatal antidepressants and/or prenatal mood/anxiety disorders.

Identifying exposures

Exposure to mood/anxiety disorder: A woman is considered to have prenatal mood/anxiety disorders if in the 3 months prior to giving birth she had: one or more hospitalisations with a diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction OR one or more physician visits with a diagnosis for depressive disorder, affective psychoses or adjustment reaction, OR one or more hospitalisations with a diagnosis for anxiety disorders, anxiety states, phobic disorders or obsessive–compulsive disorders OR two or more physician visits with a diagnosis for anxiety disorders. See online supplementary appendix 1 for specific ICD codes. This definition was developed and used in a 2012 MCHP Report investigating Perinatal Services and Outcomes in Manitoba.[77]

Exposure to antidepressants will be defined if at least two prescriptions were filled at any time during pregnancy, or if a prescription was filled that overlapped the first day of gestation.

Antidepressants will be identified by utilising prescription drug data and the WHO's Anatomical Therapeutic

Table 2 Short-term and long-term study outcomes

Short-term outcomes	Long-term outcomes
Neonatal outcomes ▶ Neonatal mortality ▶ Infant mortality ▶ Preterm birth—gestational age <37 weeks ▶ Post-term birth—gestational age of 42 or more completed weeks of pregnancy ▶ Small for gestational age—birth weight <10th centile for its gestational age and sex using a Canadian standard (Kramer *et al*, 2001) ▶ Large for gestational age—birth weight is above 90th centile for their gestational age and sex using Canadian standard (Kramer *et al*, 2001) ▶ Low birth weight ▶ High birth weight ▶ Apgar scores—5 min Apgar score of 7 or less ▶ Length of stay in hospital >3 days ▶ Neonatal intensive care unit admissions ▶ Neonatal readmissions ▶ Breastfeeding initiation ▶ Persistent pulmonary hypertension of the newborn *Postnatal adaption syndrome*: including: respiratory distress syndrome (RDS), convulsions of newborn, feeding difficulties, jaundice, hypoglycaemia, Apgar scores—5 min Apgar score of 7 or less *Congenital anomalies*: Down syndrome, neural tube defects, congenital heart defects (ventricular septal defects and atrial septal defects) *Severe neonatal morbidity* (including: neonatal sepsis, hypoxic–ischaemic encephalopathy (HIE), brachial plexus injury/palsy, persistent fetal circulation, neonatal hypertension, Grade III or IV intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), intubation, gastroschisis, omphalocele, diaphragmatic hernia)	Social outcomes: ▶ Teen pregnancy ▶ Child taken into care Neurodevelopmental disorders: ▶ Autism spectrum disorder (ASD) ▶ Fetal alcohol spectrum disorder (FASD) ▶ ADHD Other disorders and disabilities: ▶ Motor disorders: developmental coordination disorder, stereotypic movement disorder, Tourette syndrome ▶ Communication, speech and language disorders ▶ Asthma ▶ Diabetes ▶ Epilepsy ▶ Vision/hearing disability ▶ Learning disabilities Educational outcomes: ▶ Special education funding ▶ Grade repetition ▶ Successful education outcomes—EDI, grade 3 assessment in reading and numeracy, grade 7 assessments in math and school engagement, grade 8 assessment in reading and writing, grade 12 standard tests—language arts and math ▶ High school completion Mental health: ▶ Mood and anxiety disorders ▶ Substance use disorders ▶ Personality disorders ▶ Conduct disorder ▶ Suicide attempts and completion

Chemical (ATC) classification codes, specifically all drugs coded as NO6A for 'antidepressants'. We will group the antidepressants as follows:

1. SSRIs (fluoxetine, paroxetine, citalopram, fluvoxamine, sertraline, escitalopram);
2. SNRIs (effexor, xymbalta, milnacipran, levomilnacipran, desvenlafaxine).

Exclusion criteria: Women exposed to antipsychotic medications, and/or benzodiazepines, and/or opioids will be excluded from our study groups as these medications may affect child outcomes over antidepressants. Women exposed to other antidepressants including: tricyclic antidepressants (amitriotyline, nortriyline, desipramine, imiparamine), monoamine oxidase inhibitors will also be excluded.

Study population and time frame: All women with a record of a live birth in Manitoba occurring between 1996 and 2014, and a diagnosis of mood/anxiety disorder 3 months prior to conception will be identified to obtain exposed and unexposed groups. Children born in this time period will be linked to their birth mothers using mother–child linkage developed at MCHP.

Exposed group 1 (antidepressant use throughout pregnancy): Children whose mother filled at least two prescriptions for either an SSRI or an SNRI throughout the prenatal period (beginning of pregnancy until birth).

Exposed group 2 (first trimester use): Children whose mother filled at least one prescription for either an SSRI or an SNRI in her first trimester of pregnancy (prescription ≤14 weeks gestation).

Exposed group 3 (second trimester use): Children whose mother filled at least one prescription for either an SSRI or an SNRI in her second trimester of pregnancy (prescription 15–26 weeks gestation).

Exposed group 4 (third trimester use): Children whose mother filled at least one prescription for either an SSRI or an SNRI in her third trimester of pregnancy (prescription ≥27 weeks gestation).

Unexposed group: Children whose mothers had a diagnosis of mood/anxiety disorder during pregnancy but did not use any antidepressants during the prenatal period. This comparison group will be generated by extracting women diagnosed with mood/anxiety disorder at any point from 3 months prior to pregnancy

but who did not fill prescriptions for antidepressants. This group will be used to assess the effects of untreated prenatal mood/anxiety disorder compared with in utero antidepressant use.

Analysis plan: research questions 1 and 2

STEP 1: Creation of indicator variables and univariate analysis: Indicator variables for adverse birth and neonatal outcomes, and childhood outcomes using existing algorithms and validated definitions from MCHP will be created. Descriptive statistics including frequencies and means will be used to describe the variables/outcomes (table 2) for each study group (see appendix 1 for definitions for each outcome as well as corresponding ICD9 and ICD10 codes).

STEP 2: Propensity score matching will be used to control for confounding baseline maternal characteristics that may affect neonatal or childhood outcomes. Propensity scores will be estimated using multiple logistic regression, with exposure to antidepressants during pregnancy as the dependent variable and outcome variables listed in table 2. We will use the estimated propensity scores to construct IPTW. IPTWs will be applied to the data to balance differences in observed characteristics between the mothers who took antidepressants during pregnancy and those who did not. After applying IPTWs, we will compare women who were prescribed antidepressants during pregnancy and women who were not on observed covariates. We will test whether or not the measured covariates were balanced using standardised differences, set at an a priori 10% difference.[78] Once we have achieved balance in measured covariates, IPTWs will then be applied to all outcome models to estimate the adjusted association between exposure to antidepressants during pregnancy and the outcomes. Dichotomous outcomes will be modelled using generalised linear models with a binomial distribution. We will use the log-link function to estimate the risk ratio associated with exposure to maternal antidepressants during pregnancy for each outcome. We will first model the crude risk ratios, and then model propensity score-adjusted risk ratios by applying the IPTWs to our dichotomous outcome models. Non-dichotomous outcomes, such as count outcomes, will be modelled using generalised linear models with a negative binomial distribution.

IPTW reduces the effects of confounding to accurately estimate treatment effects by developing a statistical model using markers or variables that predict antidepressant use during pregnancy. The model assigns scores to each women based on how well her characteristics matched those that predicted antidepressant use during pregnancy to the unexposed and exposed groups. The score is used to then adjust or weight the results for each outcome examined, using weights termed 'the average treatment effect'. For the evaluation cohort (the children of those women who took antidepressants during pregnancy), those with a higher score will contribute less to the analysis of outcomes than those with a lower score, and for the comparison cohort, the reverse will occur. A logistic regression model including these weights and whether or not women received antidepressants will be run that allows us to estimate the rates of the outcomes between groups, resulting in relative risks for the evaluation cohort, relative to the comparison cohorts.

The following maternal characteristics will be used for propensity scoring: *SES (taken from Census data, using SEFI-2); mother's age; history of teen birth; mother's education level; receipt of community prenatal support programmes; receipt of prenatal income supplement; adequacy of prenatal care; comorbid chronic illness; prenatal alcohol/substance use*. We will attempt to control for severity of mood/anxiety disorder by including proxy measures of disease severity in the propensity scoring including: *number of visits to a physician; number of hospitalisations; number of visits to a psychiatrist, number of times diagnosed with a mood/anxiety disorder; number of times diagnosed as having another mental disorder, excluding mood/anxiety disorder; comorbid mental illness; history of mood/anxiety disorders; history of mental illness; history of suicide attempts; number of prescriptions for antidepressant medications*.

Additional covariates that will be taken into consideration include known or suspected risk factors for certain outcomes; for example, known risk factors for congenital cardiac malformation include: multiple gestation, maternal hypertension, diabetes, renal disease, use of other psychotropic medications. Moreover, specifically in the investigation of ADHD or ASD in children, we will control for maternal ADHD or ASD, as there is a possibility of genetic heritability for these disorders. A unique model will be built for each outcome that takes into account important risk factors and covariates.

Sensitivity analysis: Sensitivity to unmeasured confounding can be assessed using γ sensitivity analysis. This analysis allows us to examine how strong an unmeasured confounder would have to be to invalidate any statistically significant findings.[79] Examples of such confounders that may differ between our study groups and be associated with childhood outcomes could include maternal diet, exercise and genetic factors. Using established convention,[79] we present an example of a dichotomous confounding variable. Equations 1 and 2 will be used to illustrate this sensitivity analysis. Equation 1 represents the estimated relationship between PAU and autism, and equation 2 represents the true relationship between PAU and autism, given the unmeasured confounder: β represents the true relationship between PAU and autism and γ represents the unaccounted for relationship between the confounder and autism. Sensitivity analyses identify the minimum strength of γ that would result in a non-statistically significant β; that is, the minimum γ that would produce a null-effect. These sensitivity analyses are outlined in detail, elsewhere.[79]

$$\text{Autism} = \hat{\beta} \times \text{PAU} \quad (1)$$

$$\text{Autism} = \beta \times \text{PAU} + \gamma \times \text{Confounder} \quad (2)$$

Analysis plan: research questions 3 and 4: To assess whether the treatment effect differs between types of

antidepressants, analysis for each research question above will be stratified by the type of antidepressant prescribed. Specifically, a sensitivity analysis will be performed on SRRIs versus SNRIs. Second, to determine if treatment effect differs between gestational timing of exposure to antidepressants, our research design includes the use of four exposed groups of children: exposure throughout pregnancy, exposure during first trimester, exposure during second trimester and exposure during third trimester.

DISCUSSION

The MCHP Repository offers a novel approach to investigation in this field that fills gaps in the research literature and addresses methodological concerns of previous studies by employing a rigorous observational study design including:

(1) A large population-based sample and clinically relevant comparison groups: It is difficult to ascertain and follow large groups of women who have anxiety/mood disorders during pregnancy and their children using primary data collection due to challenges of attrition and length of follow-up time needed to obtain long-term outcomes of children. It is even more difficult to distinguish between women who are untreated for maternal mood/anxiety disorders during pregnancy due to issues with recall bias and inaccurate pharmacological exposure information. The Repository allows us to generate a large population-based group of all women diagnosed with prenatal mood/anxiety disorders in Manitoba since 1996, generating the largest Canadian sample to date of children exposed to prenatal antidepressants and/or prenatal mood/anxiety disorders. Moreover, the use of hospital, physician and pharmaceutical claims data allows us the ability to accurately distinguish between women who have been diagnosed with prenatal mood/anxiety disorders and who are and are not treated with medications, a major limitation in previous studies. Furthermore, the large sample sizes generated will allow us the statistical power necessary to conduct advanced statistical analyses that control for underlying maternal mood/anxiety disorders and illness.

(2) Accurate exposure data and the ability for sensitivity analysis: By using a provincially regulated prescription database, we have eliminated recall bias that is often present in observational studies collecting primary data from patients, especially data regarding the dose and exposure of medications. The prescription data at our disposal greatly increase the accuracy of information regarding antidepressant exposure in this proposed study. Moreover, the significant level of detail in the pharmacological data allows us the ability to stratify analysis for different types of antidepressants.

(3) Accurate, validated and novel longitudinal health, social and education data for outcome measures: While other studies have utilised administrative health data to study prenatal antidepressant exposure, the unique ability to link together health, education and social data using the MCHP Repository allows us to examine broader and longer term outcomes in later childhood that have not been examined at a population level, including the onset of chronic illness such as diabetes, asthma and epilepsy. Unique educational outcomes that are exclusive to our data include: learning disabilities, grade repetition, results from the provincially administered Early Development Instrument at age 5, and results from math and reading assessments in primary and middle school. We can also comprehensively examine the onset of mental disorders in childhood and adolescence, including mood and anxiety disorders, ADHD and conduct disorder.

(5) Powerful statistical methodology to control for important confounding variables: Historically, it has been difficult to control for potential confounding factors in this research area, as there are only observational studies conducted of pregnant women who take antidepressants during pregnancy. RCTs are considered the gold standard approach for estimating the effect of treatments on outcomes, as randomisation ensures that treatment status will not be confounded with either measured or unmeasured baseline characteristics. However, in observational studies, treatment selection is often influenced by baseline characteristics; thus, the characteristics of treated participants often systematically differ from those of untreated participants. Therefore, in observational studies evaluating the treatment effect of medications, one must account for systematic differences in baseline characteristics between the exposed and unexposed participants. The most commonly used approach to control for baseline covariates in recent years has been the use of propensity scores, especially in pharmacoepidemiology studies.[80] A propensity score is a balancing score that ensures that the distribution of measured baseline covariates is similar between treated and untreated participants.[78] Therefore, in a set of participants who have the same propensity score, the distribution of observed baseline covariates will be the same between the treated and untreated participants. The propensity score is a powerful tool to control for confounding variables in observational data analysis; studies have demonstrated that the distributions of variables included in propensity scores between medication users and non-users matched on the propensity score is more balanced than if the drug allocation was randomised.[81] However, it is important to note that randomisation balances unmeasured confounders as well as measured confounders, while propensity scores do not account for unmeasured confounding variables. There are several propensity score methods used for removing the effects of confounding variables when estimating the effects of treatment on outcomes. The most commonly used method in investigating the effects of in utero exposure to antidepressants on infants and children is Propensity Score Matching, which entails forming matched sets of treated and untreated participants who share a similar

value of the propensity score.[78] The treatment effect can be estimated by directly comparing outcomes between the treated and untreated participants in the matched sample. However, this method has several limitations, primarily that these matching algorithms often omit a significant proportion of the population when comparison groups are constructed, thus limiting the sample size and generalisability of results.[82] This is a particular drawback when rarer outcomes are being observed. We will be the first study in this field that utilises an alternative to matching called IPTWs. This technique makes more complex use of observational data, as it requires fewer distributional assumptions about the underlying data, and can incorporate time-dependent covariates and deal with censored data.[82] The breadth of the data, including social and education measures, allows us to identify potential confounding variables that we can use in propensity scoring to balance differences between women who took antidepressants during pregnancy and those who did not.

Limitations: We acknowledge that conducting research in this area is extremely complex, and there are potential limitations that will warrant our careful consideration, including: lack of data on non-pharmaceutical treatment of mood/anxiety disorders (eg, cognitive–behaviour therapy given by psychologists); lack of information on maternal BMI; limited information on disease severity and potential for unmeasured confounding. Despite our efforts in controlling for confounding by indication, women who take medications during pregnancy may have a more severe form of illness, and no amount of statistical adjustment using information from administrative data claims can eliminate this type of confounding. Furthermore, some women may also have a greater biological risk for mental disorders, and thus their children may have an increased biological risk for adverse childhood outcomes, such as neurodevelopmental disorders and psychiatric disorders. Our study may not fully be able to isolate the effect of antidepressants from genetic risk, despite controlling for family history. Moreover, as with all studies utilising administrative data claims, the diagnoses are reliant on the accuracy of physician data. As well, we are utilising an aggregate definition of mood and anxiety disorders due to limitations of the data and the diagnostic capabilities of the providers diagnosing the majority of patients taking antidepressants. There are high rates of comorbidities between mood and anxiety disorders and given that only one diagnosis is entered in the administrative database, women having one disorder or another would be frequently incorrect as patients often have both. Also, given that most patients are seen in primary care settings where the accuracy of diagnosis in sorting between these two disorders is questionable, a panel of experts in Manitoba has decided that it is more accurate to use this aggregate definition in our work. However, we acknowledge that antenatal untreated mood and anxiety disorders may be associated with different impacts on neonatal impacts and will conduct sensitivity analysis using a disaggregated definition for key outcomes to assess if there is a difference between women with one or the other diagnosis. Furthermore, as with all studies utilising drug data, we do not know if women actually took the medications they were prescribed, or if they stopped taking their medications after they filled their prescription. To help account for this possibility, we have only included women who have more than one prescription throughout their pregnancy. We also cannot account for the confounding effect of illicit drugs or illegally obtained prescription drugs. Also, while we have excluded women who were prescribed antipsychotic medications, benzodiazepines and antidepressants other than SSRIs and SNRIS, this exclusion criterion is not exhaustive. We cannot be sure that women are not taking other psychiatric drugs that may cause confounding; however, we will try to account for this through sensitivity analysis. Finally, due to the exploratory nature of this study, there are multiple comparisons being performed and we acknowledge the potential for an inflated type 1 error, which is a limitation of this work. Future research should be conducted that corroborates the results from this proposed study.

Study implications: There is extensive public and professional debate over PAU. Conducting research in this area is extremely complex, and absolute conclusions over the use of antidepressants during pregnancy cannot be made based solely on observational studies. While the databases brought together for this study and the results produced will generate high-quality evidence that addresses the methodological concerns of past studies, this study is intended to be an additional piece of evidence to add to the knowledge base that physicians and patients may draw on when making decisions about prescribing or taking medications during pregnancy. Ultimately, providers must evaluate the evidence and guide each individual woman, weighing the risk of the medications against the underlying maternal depression and the options of non-pharmacological versus pharmacological treatments. Patients must also be made aware of the strengths and limitations of current evidence in order to make informed decisions.

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