

Influence of cannabis exposure in pregnancy on childhood health outcomes: a population-based birth cohort

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Abstract

Cannabis use in pregnancy has increased, and many women continue to use it throughout pregnancy. With the legalization of recreational cannabis in many jurisdictions, there is concern about potentially adverse childhood outcomes related to prenatal exposure.⁴ Using the provincial birth registry containing information on cannabis use during pregnancy, we will assemble a large, population-based cohort of children born to mothers in Ontario, with and without prenatal exposure to cannabis from birth to 10 years of age. A series of investigations will examine the health effects of prenatal cannabis exposure on child outcomes using novel methods to address confounding. We will link pregnancy and birth data to provincial health administrative databases to ascertain child neurodevelopmental outcomes. The unique aspect of our proposed research is that we plan to utilize an existing population-based perinatal registry combined with administrative datasets for long-term follow up of children using a rich set of covariates and potential confounders to assess the association with cannabis exposure on pregnancy and perinatal outcomes and into childhood.

Introduction

1. INTRODUCTION AND RATIONALE

1.1 Current trends in cannabis use

Cannabis is the most widely used illicit drug in Canada, and the prevalence has been increasing in recent years following a period of decline from 2004-2011.¹ The 2015 Canadian Tobacco, Alcohol and Drugs Survey indicated that the overall prevalence of past-year cannabis use was 12% of the population (3.6 million individuals)¹ and the prevalence will likely increase with forthcoming legislation to allow the legal consumption, sale and distribution of cannabis for non-medical uses. This has the potential to increase overall usage with the concern of this occurring in pregnancy and among more vulnerable segments of society. Trends in prevalence among women have already shown an increase from 6.2% in 2011 to 10% in 2015, and prevalence was 21% among young men and women 15 to 19 years of age.²

Canadian data closely align with trends in the United States, which has demonstrated an increase in cannabis use from 2002 to 2014 among both pregnant and non-pregnant women of reproductive-age.³ Among 200,510 women aged 18-44 who responded to the US National Survey on Drug Use and Health from 2002 to 2014, the prevalence of last-month cannabis use for pregnant women increased from 2.4% in 2002 to 3.9% in 2014, with adjusted prevalence of 7.5% among those aged 18-25.³ For non-pregnant women, a similar increasing trend was observed, from 6.3% last-month use in 2002, to 9.3% in 2014.³ Across the literature, the prevalence of self-reported cannabis use during pregnancy varies between 1 and 6%, and may vary by trimester.⁴

1.2 Cannabis exposure and pregnancy outcomes

The results from numerous international studies that have attempted to examine the health effects of prenatal cannabis exposure using observational cohort and case-control designs have been inconsistent.⁵⁻¹⁰ The findings from two systematic reviews of the observational studies published in 2016, were also inconsistent.^{11, 12} This was likely due to methodological differences across the included studies. Although the first review found statistically significant associations between cannabis use during pregnancy with low birth weight (pooled odds ratio [pOR 1.77]) and increased neonatal intensive care unit (NICU) admissions (pOR 2.02)¹², the second review did not find maternal cannabis use to be independently associated with low birth weight or preterm delivery after adjusting for tobacco use and other confounding factors.¹¹

Other studies, both dated and recent, failed to find statistically significant associations between prenatal exposure and adverse neonatal outcomes following adjustment for confounding factors.^{9, 13} A possible reason for older studies not finding an association is that concentrations of delta-9-tetrahydrocannabinol (THC) (the primary psychoactive cannabinoid in cannabis) in cannabis plant material has risen three-fold, from 4% in 1995 to 12% in 2014 which further underscores the urgency for contemporary studies on this topic.¹⁴

1.2.1 Lack of follow-up data on children exposed to cannabis during pregnancy.

Data on long-term follow up of children who have been exposed to cannabis in utero is limited and comes primarily from several small cohorts all of which had sample sizes of less than 350 women with exposure to cannabis in pregnancy.^{15, 16} Although the findings have indicated associations with decreased concentration and attention, increased impulsivity and hyperactivity in childhood among offspring of mothers with cannabis exposure in pregnancy,¹⁶ replication is required using larger cohorts and appropriate methods to control for confounding. The unique aspect of our proposed research is that we plan to utilize an existing population-based perinatal registry combined with administrative datasets for long-term follow up of children using a rich set of covariates and potential confounders to assess the association with cannabis exposure on pregnancy and perinatal outcomes and into childhood.

1.3 The BORN database and cannabis exposure

The Better Outcomes Registry and Network (BORN) is a comprehensive perinatal registry in the province of Ontario and encompassing nearly 40% of all live births in Canada.¹⁷ It contains robust data on prenatal screening, pregnancy complications, intrapartum events, admission to neonatal intensive care, newborn screening, and data on maternal exposures including substance use. Together with the historical perinatal database (Niday), there are over one million registered births and more than 10,000 women with exposure to cannabis in pregnancy. This sample size is at least 20 times larger than any published report and has the added value of being population-based. Furthermore, linkage to existing administrative data sets in the Institute for Clinical Evaluative Sciences (ICES) allows us to study longitudinal aspects of growth and development of children.

2. AIM AND STUDY OBJECTIVES

The overall aim of our study is to assemble a large, population-based cohort of children born to mothers in Ontario, with and without prenatal exposure to cannabis from birth to 10 years of age. A series of investigations will examine the health effects of prenatal cannabis exposure on child outcomes using novel methods to address confounding, with the following objectives:

Primary objective: To estimate and compare rates of neurodevelopmental problems including cognitive, emotional, and behavioural disorders in children born to mothers with and without cannabis use in pregnancy.

Secondary objective 1: To compare rates of health service utilization in exposed and non-exposed children utilization from birth to 10 years of age.

Secondary objective 2: To determine the association between in utero exposure to cannabis and neurodevelopmental vulnerability at the age of 5 using the Early Development Instrument (EDI).^{18, 19}

3. BACKGROUND

3.1 Canadian and international data on prevalence of cannabis in pregnancy

The US National Survey on Drug Use and Health from 2002-2014 which included 4,971 pregnant women showed that 3.9% reported last-month cannabis use, with the highest prevalence of use in the first trimester of 7.4%.²⁰ A prospective study based in Australia which recruited nulliparous women (n=5,628) and followed them throughout pregnancy had a rate of self-reported cannabis use during pregnancy of 5.6%.⁷ A substance use survey conducted 2-3 days postpartum among mothers in France (n=13545) found a self-reported rate of 1.2% for cannabis use in pregnancy.⁶ A retrospective cohort study in Australia (n=24,874) showed the prevalence of ever-use cannabis to be 9.5%, and while in pregnancy to be 2.6%.⁸ Data from the National Birth Defect Prevention Study (n=10,241) reported a prevalence of 5% among pregnant women.²¹ The longitudinal Generation R Study from Rotterdam, Netherlands (n=7,452) had 2.9% of women (n=214) who self-reported cannabis use before and during first trimester of pregnancy, and of those 214 women, 41 (19%) continued to use cannabis throughout pregnancy.¹⁰

3.2 Longer term health outcomes in children including developmental and cognitive

Three longitudinal studies following children with prenatal cannabis exposure have demonstrated decreased concentration and attention, increased impulsivity and hyperactivity in childhood and adolescence, and lowered abstract and verbal reasoning in adolescence.¹⁶ These three studies include the Ottawa Prenatal Prospective Study (OPPS), initiated in 1978 in Ottawa; the Maternal Health Practices

and Child Development Study (MHPCD), initiated in 1982 in Pittsburgh; and Generational R study, initiated in 2002 in Rotterdam, Netherlands.¹⁶

The OPPS is a longitudinal study which followed 190 children selected from 698 predominantly healthy, Caucasian, middle-class women who agreed to participate in the study.²² Of the 190 children, 140 were exposed to cannabis, cigarettes, or alcohol use prenatally, and 49 of those had documented prenatal cannabis exposure. These neonates were found to have increased startle response, tremors, and poor habituation to visual stimuli compared with neonates who were not exposed²². Follow-up studies at 4 years of age showed significantly lower scores on verbal and memory domains of McCarthy Scales of Children's Ability²³, but no effects were subsequently found at age 5-6, 6-9, 9-12, and 13-16 after adjusting for home environments.^{24, 25}

There are limitations to ascertaining causality between intrauterine environment (including exposure to cannabis), to later childhood outcomes due to various study designs, variable outcome measurements, and possibly divergent socioeconomic circumstances in childhood.²⁶ Given these caveats, it has been shown that children in OPPS with exposure to prenatal cannabis were more likely to use cannabis themselves (OR 2.76), and to both initiate cigarette use (OR 2.58) and to use cigarettes daily (OR 2.36) in the teenage years compared to non-exposed children in the study.²⁷

The Maternal Health Practices and Child Development Study (MHPCD) randomly selected and interviewed 1360 women from an inner-city clinic in Pittsburgh, Pennsylvania, and all women who reported >2 joints per month of cannabis use during first trimester of pregnancy were enrolled in the study and followed; with a random sample of women who used less cannabis than that enrolled to serve as controls (n=763).²⁸ The cannabis exposure was stratified to exposure in each trimester. The women were around 50% African-American, and 50% Caucasian; they were mostly single and low income.²⁸ At 3 years of age, there were significant negative effects of prenatal cannabis exposure on the performance of the Stanford-Binet Intelligence Scale. The effects were associated with exposure during the first and second trimesters of pregnancy.²⁹ Second trimester exposure was also associated with increased impulsivity, hyperactivity and delinquency; and decreased concentration, IQ score, verbal and visual reasoning at 6 and 10 years of age.³⁰

The Generational R study from Rotterdam, Netherlands initiated in 2002, with enrollment until 2006.³¹ At 18-months follow-up, found that among the children born to mothers who reported cannabis use during pregnancy,(n=88), the girls had significant increase in attention problems and increased aggression.³¹ This is a relatively new study so the results from later childhood and teenage years are not yet available. However, it does utilize a novel analytical tool of including information on paternal cannabis use, which should allow the researchers to better ascertain causality between intrauterine exposure, and post-birth exposure.²⁶

3.3 Mechanisms of effects of cannabis exposure on embryological development

THC, the primary psychoactive cannabinoid in cannabis, readily crosses the placenta and can enter the fetal bloodstream.³² Animal studies indicate that THC is detectable in fetal plasma within 15 minutes of maternal exposure and equilibrated to maternal levels within 3 hours.³² The lipophilic nature of THC together with a half-life of approximately 8 days in fat deposits results in slow fetal clearance of THC and fetal exposure is therefore prolonged even after maternal consumption is discontinued.³³ THC exposure during pregnancy can disrupt the complex fetal endogenous cannabinoid signaling system (ECSS) which has several roles in reproduction from fertilization to embryo development.³² Alterations to this system may have differential effects depending on the stage of pregnancy and the impacts are not fully understood. Human and animal studies suggest that deregulation of the ECSS may have range of cellular effects including modulating neurodevelopment and may be associated with adverse pregnancy outcomes including miscarriage and compromised placentation.³⁴ Although biologic and animal data exist on the potential effects of cannabis exposure in utero,³²⁻³⁴ attributing causality in epidemiological research continues to be a challenge given the necessity of using observational designs and potential for confounding.

Reagents

Equipment

Procedure

4. RESEARCH METHODS

4.1 Study design

We will conduct a population-based retrospective cohort study assembled using existing provincial birth registry data from the Better Outcomes Registry & Network (BORN) Ontario BORN Information System (BIS) and the BORN-Niday perinatal database, covering all births in Ontario between April 2007 and March 2014. The study will be conducted through the Institute for Clinical Evaluative Sciences (ICES), which already houses the Niday perinatal database (2007-2012) and the BIS data from 2012-2014. We will utilize linkages between the BORN data and health administrative datasets held at ICES to provide additional exposure and outcome information around the time of birth, as well as provide up to ten years of follow-up for pediatric health outcomes for the children. For **Secondary objective 2**, data from Niday/BORN will be individually linked with neurodevelopmental data from the EDI. The population-level Ontario 2015 EDI data for children born in 2009 are now available at Institute of Clinical Evaluative Sciences (ICES).

4.2 Study population

From the BORN birth registry database, we will select all women who had a singleton pregnancy and delivered at a gestational age ≥ 20 weeks or birth weight ≥ 500 grams born in an Ontario hospital between April 2007 and March 2014.

4.3 Data sources

The databases required to carry out this study already exist within ICES. ICES along with members of our study team (which includes an ICES Scientist) have developed the capacity to conduct data linkage between Niday/BORN and other administrative datasets which will be used in this study.

4.3.1 Better Outcomes Registry & Network (BORN) Ontario Birth Registry: The BORN Ontario birth registry captures all hospital births ≥ 500 grams or ≥ 20 weeks' gestation occurring in the province. The routine data collection includes information on maternal demographics and health behaviours, pre-existing health problems, obstetric complications and birth outcomes. Data are collected from medical records, clinical forms and patient interview when a woman is admitted to hospital to give birth. An ongoing program of data quality checks and formal training sessions assures a high level of data quality.¹⁷

4.3.2 Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD): The CIHI-DAD is a service-based, national health care administrative database, administered by CIHI. Following each discharge from an acute care hospital, trained coders abstract relevant information from the medical chart using standardized methods and submit a hospital separation abstract to CIHI. Each abstract contains demographic information, medical diagnosis codes for the most responsible diagnosis and up to 24 additional diagnoses codes, up to 20 medical interventions received during the hospital admission, and other data elements. Medical diagnoses are coded using the Canadian implementation of the International Classification of Diseases, 10th Revision (ICD-10-CA) and medical interventions are coded using the Canadian Classification of Health Interventions (CCI).^{35,36}

4.3.3 ICES Registered Persons Database: ICES maintains a master registration file for all Ontario residence with a valid provincial health card. These files contain demographic data for anyone who has received an Ontario health card number and indicate the eligibility period for individuals to receive provincially-funded health care, accounting for deaths or migration out of province. This database contains the ICES Key Number (IKN), an encrypted identification variable to enable linkage between administrative databases at ICES. Registration files will be used to determine the follow-up period for children and for linkage between datasets.

4.3.4 Ontario Health Insurance Plan (OHIP) Claims Database: ICES maintains a database for all physician claims reimbursed by the Ontario Ministry of Health. This database records the underlying reason for physician visit on each claim using and ICD diagnostic codes and OHIP fee service codes are applied for diagnostic and clinical consultation services. This database will be used for ascertainment of childhood outcomes using validated diagnostic codes and case-finding algorithms for determining outcomes.

4.3.5 Canadian Institute for Health Information (CIHI) National Ambulatory Care Reporting System: The National Ambulatory Care Reporting System is also a national database administered by CIHI, with annual transfer of Ontario records to ICES. NACRS captures data originating from urgent visit to emergency departments in Ontario and contains up to 10 clinical diagnoses on each abstract using the ICD-10-CA classification.

4.3.6 Early Development Instrument (EDI) for Secondary Objective 2

Early development from birth to age five represents a critical time to shape future productivity.³⁷ Indicators of child development at this age have been shown to be predictive of both school performance and later life economic potential and human capital.^{38,39} The EDI is a validated measure of child development used in Canada and several countries internationally and has been demonstrated to be robust marker of child development and future school performance.⁴⁰ It is a 103-item teacher-completed assessment of children in kindergarten who will be entering primary school (conducted at 5 to 6 years of age). It captures a teachers' view of the development and achievement skills of the children in their classroom using questions about noticeable markers of brain development for this age.⁴¹ We will examine the domain scores for "language and cognitive development", which has been identified as the strongest predictor of later school performance.^{19, 42-45} The EDI is administered by the Offord Centre for Child Studies at McMaster University and data collection has been undertaken in all publically funded Ontario schools in multiple cycles from 2004 and 2015.⁴⁶ Data for the 2015 cycle, covering children born in 2009 are now available at ICES and our team has successfully completed linkages to other health data sources using identifiers for date of birth, sex, and postal code.

4.4 Database linkages and access

The methodology to link the BORN-Niday perinatal data (2007-2012) with administrative databases at ICES has been successfully developed in a previous study led by members of our Research Team⁴⁷ and the linked files and methodologies are available for this current project. The record linkage of the BIS data from 2012-2014 will be carried out by an ICES analyst. The linked study files will be developed and used in accordance with provincial privacy legislation to ensure that linked database files are de-identified, stored, accessed and analyzed within a secure network environment.

4.5 Exposure variables

Prenatal exposure to cannabis will be measured by physician documentation, which is collected in BORN during antenatal and/or intrapartum visits. Maternal drugs and substance exposures are likely to be underreported in BORN and therefore two additional approaches will be carried out to increase the sensitivity to identify women who have used cannabis in pregnancy. A chart and medical record review will be carried out on a random sample of patients at The Ottawa Hospital who did and did not report use of cannabis to determine the sensitivity and specificity of self-reporting in BORN. The methodology for the validation study will be detailed in a supplemental protocol. In addition, we will search for relevant

maternal (ICD-10 codes F12 and subcodes for cannabis) and stillbirth/newborn diagnostic codes (ICD-10 codes P04.4 and P96.1 for neonatal withdrawal syndrome and concomitant use of cannabinoids) in the CIHI-DAD to identify additional exposed mothers and we will conduct a review of a sample of these records to determine accuracy. Analyses of BORN data from 2012-13 and 2013-14 indicated that the self-reported prevalence of prenatal cannabis use was approximately 1.5-2%.⁴⁸

4.6 Outcome variables

Study outcomes will be ascertained from the linked database which contains information on child outcomes including standard diagnostic codes to document primary diagnoses.

Primary Objective: The primary outcome of the study will be child autism spectrum disorder diagnosed after age 2. Autism spectrum disorder is defined as at least 2 outpatient diagnoses by either a pediatrician or psychiatrist or at least 1 diagnosis in hospital databases after the age of 2 years, or both. This definition has been used previously in studies conducted by ICES,⁴⁹ and had a positive predictive value of 87% when used in US insurance data.⁵⁰ Follow-up will be to maximum age of 10 years and median age of autism spectrum disorder diagnosis is approximately 4.6 years.⁵¹

Secondary outcomes will include intellectual disability and learning disorders; and emotional and behavioural disorders with onset occurring in childhood⁵² including: attention deficit and hyperactivity disorders, depression, anxiety, oppositional defiant and conduct disorders.

Secondary Objective 1: Rates of health service utilization for pediatric mental health is an important indicator⁵³ but limited data exist in the cannabis-exposed population. Utilization of health services in children will be measured as rates of primary care visits (including family physicians and pediatricians), visits to psychiatrists, emergency department visits, walk-in clinics or other urgent care centres, and in-patient hospitalizations to identify diagnoses with the highest frequency and associated costs.^{54, 55} Visits will be converted to costs from the time of prenatal care through the first 10 years of life for exposed and unexposed infants.

Secondary Objective 2: Childhood neurodevelopment assessed in the EDI. Cannabis exposure in pregnancy will be related to binary outcomes for scores falling below the 10th percentile on the language and cognitive development domain and emotional maturity subdomains for attention/hyperactive, anxious, and aggressive behaviour of the EDI. Secondary analyses will also analyze the continuous EDI scores

4.7 Confounding variables

Based on the literature and our previous work on perinatal use of tobacco, electronic cigarettes, and other substances,^{26, 56-59} we have identified a number of health, behavioural, socioeconomic and demographic

characteristics potentially associated with cannabis use and study outcomes.⁶⁰ These factors include maternal age, comorbid health conditions (including pre-eclampsia⁶¹) and psychiatric disorders, previous history of trauma, income, cigarette smoking, alcohol consumption, parity, relationship status, geographic identifiers (health region, urban/rural location, census geographic information obtained from postal codes), antenatal care provider, marital status, season of conception⁶², historical use of health services, familial diagnoses of neurodevelopmental disorders, and use of other substances during pregnancy.

We will use high-dimensional propensity score methods (HDPS) as an approach to account for confounding arising from the identified covariates and as a proxy for unobserved confounders.⁶³ An ICES-developed HDPS algorithm will incorporate multiple surrogate variables including diagnostic and procedure codes, billing codes and drug claims available from ICES-linked databases to represent the unobserved confounding structure.⁶⁴ Alternate approaches will explore and assess the possibility of confounding and bias in the exposure-outcome relationship dataset including negative control⁶⁵ analyses using different outcomes and exposures. For example, examining the use of prenatal folic acid as an exposure which is not causally related to preterm birth⁶⁶ or outcomes but that is within the study dataset could be used to assess the confounding structure and robustness of the cannabis-outcome associations.

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5. STATISTICAL ANALYSES AND STUDY POWER

5.1 Statistical analyses

Descriptive analyses will be conducted to compare mothers who used cannabis during pregnancy and those who did not across maternal demographic and socioeconomic characteristics using means, medians, and frequencies and corresponding statistical tests (t-tests, chi-squared tests) and standardized differences to with absolute differences of >10% considered indicative of a meaningful difference.

To test for associations between cannabis use in pregnancy and childhood outcomes, for each outcome we will compare women who used cannabis to those who did not. We will utilize HDPS methods to account for the potential effects of unmeasured confounding on the cannabis-outcome relationship. An available HDPS algorithm will be implemented to select a large set of target covariates from the linked databases and data dimensions will be identified from diagnostic coding systems.⁶³ A temporal window of 12 months prior to delivery will be specified and within each dimension the most prevalent codes will be rank ordered and top n most prevalent codes will be selected and converted into a numeric score based on recurrence.⁶³ Covariates will then be prioritized and selected based on exposure-confounder and confounder-outcome associations. The probability of exposure will be calculated for each covariate and a certain number (up to $n=500$ covariates) will be used for HDPS estimation. Other prespecified confounders deemed to be important, a priori, including maternal age, baby sex, income, use of cigarettes, alcohol or other drugs will be retained as part of the final propensity score (PS). Following estimation of

the PS, inverse probability of treatment weighting⁶⁷ will be implemented and balance assessed among measured covariates between the exposed and unexposed groups.

Once the data have achieved covariate balance, we will use log-binomial regression to assess the association between prenatal cannabis exposure and autism spectrum disorder and secondary outcomes. Cox proportional hazards models will be used to allow for censoring and proportional hazards assumptions in models will be assessed using log-log survival curves and residual plots. Rates of urgent and in-patient health service utilization will be modeled using Poisson regression.

5.2 Study power

Data will come from the linked BORN-ICES dataset with a fixed sample size. For the primary outcome, autism spectrum disorder, assuming a rate of 5% in the study population, we will have 90% power based on a chi-squared test to detect a relative risk of 1.25 for the cannabis-autism association assuming a 1% prevalence of prenatal cannabis use. Therefore, the study will be sufficiently powered and we have prespecified the magnitude of clinically important effects to be 1.5 or higher.

For **Secondary Objective 2**, EDI data are available on approximately 125,000 children aged 5. Assuming a minimum 0.6% prevalence of prenatal opioid use, and a minimum 85% linkage rate with BORN, we will have 80% power to detect a difference of 3.5% in the prevalence of language and cognitive developmental vulnerability (13.5% vs 10% in controls). For continuous analyses of EDI domain scores, we will have >90% power to detect less than a 0.25 difference in mean scores between exposed and unexposed groups for EDI domains, with a difference of this magnitude considered meaningful.¹⁹

Troubleshooting

Time Taken

Anticipated Results

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