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Is in-utero exposure to cannabis associated with the risk of attention deficit with or without hyperactivity disorder? A cohort study within the Quebec Pregnancy Cohort

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ABSTRACT

Importance and objective Prenatal cannabis effect on attention deficit with or without hyperactivity disorder (ADHD) remains to be determined. Our aim is to quantify the impact of in-utero exposure to cannabis on the risk of ADHD.

Design Cohort study.

Setting Questionnaires were mailed to women sampled from the Quebec Pregnancy Cohort (QPC). Data from questionnaires were then linked with their QPC (built with administrative health databases, hospital patient charts and birth certificate databases).

Participants Respondents who gave birth to a singleton live born between January 1998 and December 2003 and were continuously enrolled in the Régie de l'assurance maladie du Québec (RAMQ) medication insurance plan for at least 12 months before the first day of gestation and during pregnancy.

Exposure In-utero cannabis exposure was based on mothers' answers to the question on cannabis use during pregnancy (yes/no) and categorised as occasionally, regularly exposed and unexposed if they chose one of these categories.

Outcomes ADHD was defined by a diagnosis of ADHD through the RAMQ medical services or MedEcho databases or a prescription filled for ADHD medication through RAMQ pharmaceutical services between birth and the end of the follow-up period. Follow-up started at the birth and ended at the index date (first diagnosis or prescription filled for ADHD), child death (censoring), end of public coverage for medications (censoring) or the end of study period, which was December 2015 (censoring), whichever event came first.

Results A total of 2408 children met the inclusion criteria. Of these children, 86 (3.6%) were exposed to cannabis in-utero and 241 (10.0%) had an ADHD diagnosis or medication filled. After adjustments for potential confounders, no significant association was found between in-utero cannabis exposure (occasional (1.22 (95% CI 0.63 to 2.19)) or regular (1.22 (95% CI 0.42 to 2.79))) and the risk of ADHD in children.

Conclusions In-utero exposure to cannabis seemed to not be associated with the risk ADHD in children.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Self-reported questionnaire data were linked to administrative health databases, hospital patient charts and birth certificate databases; this allowed the analyses of pregnancies with detailed information regarding exposure, outcomes and potential confounders.
⇒ The Quebec Pregnancy Cohort has 17 years of follow-up, which provides data and no recall bias possible for our outcome.
⇒ The selection method, which was not entirely random, could have limited the generalisability of our results compared with the general population of Quebec.
⇒ Our study might be underpowered when stratifying on exposure frequency, which might explain our non-significant results.

INTRODUCTION

Cannabis is the most commonly illicit drug used in the world, with a prevalence of 3.98% in 2019, for the population aged 15–64 years old.[1] Among the European Union inhabitants aged 15–34 years old, the last year prevalence of cannabis use ranged from 3.4% in Hungary to 21.8% in France, based on a survey undertook between 2015 and 2020.[2] In Canada, cannabis is among the most commonly substance used.[3] The annual Canadian prevalence of cannabis use has increased from 12.0% in 2013 to about 15.0% in 2017 among the general population aged 15 and older[3]; young adults (20–24 years old) had the highest prevalence of cannabis use (33.2%), followed by youth (15–19 years old) with 19.4%.[3] Cannabis was legalised in Canada in October 2018, which resulted in an 21.0% prevalence of use in 2019 in people aged 15 years or older.[4] As for Canadian provinces, Novia Scotia had the highest

prevalence of cannabis use with 33.1% and Quebec had the lower with 17.6% in 2019.[4 5] In 2019, 5% of pregnant Canadian women reported using cannabis during their last pregnancy.[4] In Quebec, Canada, the annual prevalence of cannabis use among the general population aged 15 and older has increased from 14.0% in 2018 to 19.7% in 2020.[6] In Ontario, Canada, the prevalence of cannabis use in pregnancy has increased from 1.2% in 2012 to 1.8% in 2017[7]; and the prevalence of cannabis use in pregnancy has increased from 2.2% in 2008 to 3.3% in 2015 in British Columbia, Canada.[8] The prevalence of cannabis use during pregnancy increased from 3.4% in 2015 to 7.1% in 2017 in the USA.[9]

Tetrahydrocannabinol (THC) is the compound predominately responsible for the psychoactive effects of cannabis.[10] The THC content of herbal cannabis has increased markedly over the past several decades in North America and Europe, from approximately 5% to more than 15%.[11] Some studies showed that cannabis components such as THC or cannabidiol (CBD) are able to cross the placental barrier.[12–15] In fact, THC leads to a decreased of the uptake of fetal folic acid, which is important for embryo's development[16 17] and alters the system regulating emotions[17] and the prefrontal cortex.[16 17] Also, Merlob *et al*[18] observed that exposure to cannabis during pregnancy may disrupt the migration and the release of the synaptic neurotransmitter in the fetus brain, which can alter the motor control, memory and neurobehavior. In addition, CBD might interact with some common medications (eg, amitriptyline, which is an antidepressant medication).[19] In short, these studies have observed different impacts that components of cannabis might have on infant's neurobehavioral.

Some studies have investigated the impact of prenatal cannabis use on children neurodevelopment.[14 15 18 20–27] Previous studies indicate an increased hyperactivity[13 14 18 20 25 28] and an increased of attention problems[14 15 20 21 25 26 29] among children who were exposed to cannabis in-utero. These studies usually used a questionnaire to define attention problems and hyperactivity an indirect association between the increase of DRD4 associated with cannabis use and the fact that the increase of DRD4 has been associated to attention deficit with or without hyperactivity disorder (ADHD) symptoms.[29] However, another study has shown that cannabis exposure during pregnancy was not associated with increased risk of attention deficits problems at 18 months old in general, but showed a significant increased risk of attention problems in girls.[24] Moreover, Corsi *et al*, in Ontario, Canada, studied the impact of overall cannabis use during pregnancy and the risk of ADHD and they found no significant association (HR 1.11 (95% CI 0.98 to 1.25)), using a diagnosis of ADHD.[22]

Given the expanding legalisation status of cannabis worldwide, more studies on the possible effects of in-utero cannabis exposure on neurodevelopment outcomes are needed to aid clinical practice and pregnant women themselves. Therefore, our study aimed to quantify the association between in-utero overall cannabis exposure and the risk of ADHD in children, and by stratifying on frequency of use (occasional use, regular use and no use).

METHODS

Data sources

We obtained data from the Quebec Pregnancy Cohort (QPC) and a self-administered questionnaire linked to the QPC using the patient's unique anonymous identifier.

The Details of QPC are described elsewhere.[30] Briefly, the QPC is a population-based cohort built through the linkage of the Regie de l'assurance maladie du Québec (RAMQ), the Quebec hospitalisation archives (MedEcho) and the Institut de la Statistique du Québec (ISQ). The QPC contains data on all pregnancies of women who are covered by the Quebec's public prescription drug insurance plan enrolled for at least 12 months before their first day of the last menstrual period (first day of gestation) and during pregnancy. All medical services and pharmaceutical coverage are provided by the RAMQ. The MedEcho database records data on all hospitalisation and demographic information (for mothers, fathers and newborns), birth weight and gestational age for live births and stillbirths are collected in the ISQ database. Pregnancies are identified through RAMQ and MedEcho databases and the first day of gestation is defined using data on gestational age.[31] Data in the QPC are available until December 2015.

The self-administered questionnaire was designed to collect information not present in the QPC, such as lifestyle variables before and during pregnancy (physical activity, tobacco use, alcohol use, soft and hard drug use, etc), sociodemographic information, pregnancy history, weight and height at the beginning and during pregnancy, natural health product use, folic acid intake, and medical history. A total of 8505 pregnancies ending with a live birth between January 1998 and 31 December 2003 were selected and the mothers were asked to fill a self-administered standardised questionnaire. The data from the self-administered questionnaire were then linked with each women data in the QPC using their unique anonymous identifier. A copy of the questionnaire is available in online supplemental appendix 1.

Study population

Multiple pregnancies ending with twins and triplets were excluded as well as pregnancies with missing values on in-utero cannabis exposure. Moreover, we excluded all premature babies as well as all infants with a diagnosis of autism spectrum disorder (ASD). Premature babies were excluded because the critical phase of neurodevelopment usually happens during the second and third trimesters of pregnancy. We removed ASD from our main analysis because infants with ASD often have some form of ADHD. The date of entry was the date of birth of each newborn.

Exposure

The self-administered questionnaire includes information on cannabis use during pregnancy. In-utero cannabis exposure was based on mothers' answers to the question on the use of soft drugs, as cannabis, during pregnancy (yes/no) and categorised as occasionally exposed, regularly exposed and unexposed (reference category) if mothers chose one of these categories in the questionnaire (online supplemental appendix 1).

Outcomes

ADHD was defined by a diagnosis of ADHD (ICD-9 code 314.0 or ICD-10 code F90.9) through the RAMQ medical services or MedEcho databases or a prescription filled for ADHD medication (dexamphetamine, methylphenidate, amphetamine, atomexetine, lisdexamfetamine and guanfacine) through RAMQ pharmaceutical services between birth and the end of the follow-up period. The first diagnosis or prescription filled for ADHD medication was defined as the index date. Follow-up started at birth and ended at the index date, child death (censoring), end of public coverage for medications (censoring) or the end of the study period, which was December 2015 (censoring), whichever event came first.

Covariates

We selected potential covariates based on their association with cannabis or ADHD a priori. Maternal sociodemographic characteristics included maternal age on first day of gestation, education level, household annual income, living alone, area of residence, race, previous children and prepregnancy body mass index. Maternal lifestyle characteristics during pregnancy included smoking status, alcohol intake, coffee intake, cocaine use and physical activity. Gestational age at delivery was identified through the MedEcho database and have previously been validated against patient charts.[31] Maternal comorbidities such as diabetes, hypertension, asthma and thyroid disorders were identified through ICD-9 diagnosis codes and through prescription filled for these medical conditions (online supplemental table S1). Maternal depression/anxiety included affective disorders (depressive disorder), anxiety and bipolar disorder were obtained using ICD-9 diagnostic codes or data on filled prescription of antidepressants as well as maternal diagnostic codes for ADHD (online supplemental table S1). Moreover, we included maternal psychiatric disorders other than maternal affective disorders such as schizophrenia, schizotypal and delusional disorders; disorders of adult personality and behaviour; dissociative and conversion disorders; phobic disorders; obsessive–compulsive disorder; dysthemic disorder; neurasthenia; depersonalisation disorder; somatoform disorder; unspecified non-psychotic mental disorder); drug dependence expect for cannabis dependence obtained using ICD-9 diagnostic codes or data on filled prescription related to those disorders (online supplemental table S1). In addition, we also included maternal pain as a covariate, identified using ICD-9 diagnosis codes of chronic pain and for most diseases that can induce pain and for which medical cannabis[32] can be used (online supplemental table S2). All maternal comorbidities were obtained 1 year prior to or during pregnancy. Infant characteristics included sex and calendar year of birth.

Statistical analyses

Maternal and newborn characteristics were compared according to the three categories of in-utero exposure to cannabis. We used t-test for continuous variables and χ^2 or Fisher exact test (when samples are less than 5) for categorical variables to determine statistically significant differences, comparing exposed and unexposed groups.

We calculated crude and adjusted HRs with 95% CI to quantify the association between in-utero cannabis exposure and ADHD using Cox proportional hazard models. For our multivariate models, we included an intermediated model to adjust only for children sex and age of the mother. Moreover, adjustments were made for all potential confounders listed above. In order to deal with our missing data, we use a multiple imputation technique.

We performed several sensitivity analyses. First of all, we restricted our analysis to children of at least 4 years of age because infants less than 4 years old were less likely to have a diagnosis of ADHD or receive ADHD medications given the short period of follow-up. Moreover, we restricted our classification of children with ADHD to only those having a diagnosis of ADHD confirmed by a specialist (psychiatrist or neurologist) or a prescription filled for an ADHD medication to account for the severity of ADHD. Moreover, we included preterm babies as another sensitivity analyses. In addition, to account for a potential social desirability bias, we considered children whose mothers had missing information on exposure as exposed to cannabis during pregnancy. We also, included ASD children in another sensitivity analysis as ADHD since both disorders are often comorbid.

Statistical analyses were performed using SAS V.9.4 (SAS Institute).

Patient and public involvement state

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this study.

RESULTS

Of the 8505 women to whom a questionnaire was mailed, 3354 returned their completed questionnaires, of which 3320 were linked to the QPC. Of these pregnancies, 77 were twins or triplets and therefore excluded from the current study. We further excluded 76 pregnancies due to missing values on cannabis status. In addition, we excluded premature babies (N=597) and any child with a diagnosis of ASD (N=62). Thus, 2408 children were included in the final main cohort (figure 1).

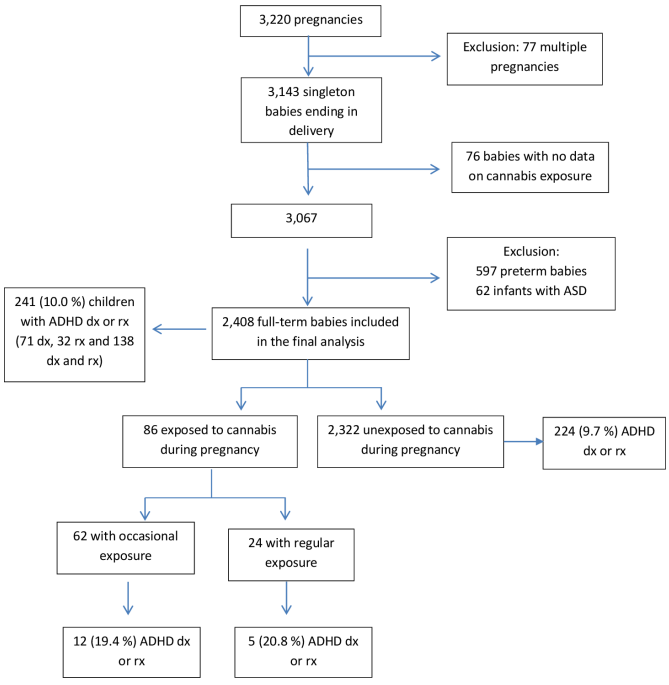

Figure 1 Flow chart of study population according to in-utero cannabis exposure status and ADHD. ADHD, attention deficit with or without hyperactivity disorder; ASD, autism spectrum disorder; Dx, diagnosis; rx, prescription of a medication.

Compared with the unexposed to cannabis group, mothers of the cannabis occasionally exposed in-utero were younger (25.5 vs 27.6 years old), less educated (12 (19.7 %) for Collège d'Enseignement Général et Professionnel (CEGEP) and University versus 923 (39.2 %)), more likely to have a lower income (39 (67.3) for ≤18 000 vs 736 (32.5 %)) and living alone during their pregnancy (24 (38.7%) vs 349 (32.5%)) (table 1). In addition, mothers of occasionally and regularly exposed in-utero to cannabis were more likely to be smoking (38 (71.7%) for occasionally exposed and 17 (81.0%) for regular exposed versus 787 (34.6%) for the unexposed group) and alcohol consumers (26 (41.9%) for occasionally exposed and 9 (39.1%) for regular exposed versus 509 (22.0%) for the unexposed group) compared with mothers of the unexposed in-utero (table 1). Moreover, mothers of the occasionally exposed in-utero were more likely to have comorbidities such as asthma (28 (45.2%) vs 503 (21.7%)), depression/anxiety/bipolar disorder (39 (62.9%) vs 1056 (45.5%)) and other psychiatric disorders (22 (35.5%) vs 521 (22.4%)) than mothers if the unexposed in-utero (table 1).

Of the 2408 children within this cohort, 86 (3.6%) were exposed to cannabis in-utero, of which 62 (72.1%) were occasionally exposed and 24 (27.9%) were regularly exposed (table 1). Of the 2408 full-term infants, 241 (10.0%) had a diagnosis of ADHD or a prescription filed for ADHD medication, of which 71 were diagnoses only, 32 were prescription filed only and 138 were both diagnoses and prescription filed. In the occasional exposure group, 12 children (19.4%) had a diagnosis of ADHD or a prescription filling for ADHD medication, while five children (20.8%) had an ADHD diagnosis or a prescription filling for ADHD medication in the regular exposure group, and 224 children (9.7%) in the unexposed group (table 1).

After adjusting for all potential confounders, the overall HR for cannabis in-utero exposure was 1.22 (95% CI 0.70 to 2.02). After adjusting for potential confounders and stratifying of exposure frequency, the HR for occasional in-utero cannabis exposure was 1.22 (95% CI 0.63 to 2.19) and 1.22 (95% CI 0.42 to 2.79) for regular in-utero cannabis exposure (table 2).

Moreover, overall in-utero cannabis exposure was not associated with the risk of ADHD (HR 1.22 (95% CI 0.70 to 2.02); 17 exposed cases) (table 3).

Sensitivity analyses results

When we restricted the cohort to infants who were at least 4 years of age, no association was found between occasional (HR 1.51 (95% CI 0.56 to 2.15)) or regular (HR 1.38 (95% CI 0.48 to 3.17)) in-utero cannabis exposure and ADHD (online supplemental table S3). In addition, there was no association between in-utero exposure (occasional HR 1.14 (95% CI 0.53 to 2.21); regular HR 1.53 (95% CI 0.52 to 3.56)) to cannabis and the risk of ADHD, when redefining our outcome as ADHD diagnosed by a specialist (psychiatrist or neurologist) or having a filled prescription for ADHD medication (online supplemental table S4). We also found no significant association, when considering children whose mothers had missing information on exposure as exposed to cannabis in-utero, with the risk of ADHD (HR 1.06 (95% CI 0.67 to 1.60)) (online supplemental table S5). In addition, when including preterm babies in our analysis, we found no significant association between occasional exposure (HR 0.85 (95% CI 0.48 to 1.42)) and regular exposure (HR 1.16 (95% CI 0.52 to 2.24) and the risk of ADHD (online supplemental table S6). Finally, when included ASD children in our sensitivity analysis as ADHD, we found similar results as the others sensitivity analyses (HR 1.02 (95% CI 0.52 to 1.79) for occasional exposure and HR 1.31 (95% CI 0.51 to 2.77) for regular exposure) (online supplemental table S7).

DISCUSSION

In this study, we assessed the association between in-utero exposed to cannabis and the risk of ADHD. Moreover, we stratify the exposure into the subgroups: unexposed, occasionally exposed and regularly exposed to assess whether the frequency of exposure might have an impact on the risk of ADHD. Overall, 3.6% (N=86) of children were exposed to cannabis in-utero within our cohort of 2408 full-term newborns, of which 72.1% (N=62) were occasionally exposed and 27.9% (N=24) were regularly exposed. After adjustments, when stratifying on the frequency of in-utero cannabis exposure (occasionally

Table 1 Characteristics of study participants according to in-utero cannabis exposure patterns

	No exposure	Overall exposure	P value	Occasional	Regular	
	N=2322 (96.4 %)	N=86 (3.6 %)		N=62 (2.6 %)	N=24 (1.0 %)	P value
Maternal characteristics						
Maternal age at 1DG, years, mean (SD)	27.6 (5.5)	25.3 (5.6)	0.0001	25.5 (6.1)	24.9 (4.2)	0.0006
Maternal age at 1DG, years			<0.0001			0.0002
<18	43 (1.8)	6 (7.0)		6 (9.7)	0 (0.0)	
18–24	782 (33.7)	**43 (50.0)**		**29 (46.7)**	14 (58.3)	
25–34	1237 (53.3)	**31 (36.0)**		**21 (33.9)**	10 (41.7)	
≥35	260 (11.2)	**6 (7.0)**		**6 (9.7)**	0 (0.0)	
Gestational age at delivery, weeks, mean (SD)	39.2 (1.1)	39.3 (1.3)	0.5033	39.3 (1.3)	39.3 (1.3)	0.7722
Education			**0.0004**			**0.0025**
Secondary school	1106 (47.0)	55 (66.3)		39 (63.9)	16 (72.7)	
CEGEP or University	923 (39.2)	**16 (19.3)**		**12 (19.7)**	**4 (18.2)**	
Others	323 (13.8)	12 (14.4)		10 (16.4)	2 (9.1)	
Missing	53	3		1	2	
Household annual income, $C			**<0.0001**			**<0.0001**
≤18 000	736 (32.5)	53 (65.5)		39 (67.3)	14 (60.9)	
18 001–30 000 000	643 (28.3)	**21 (25.9)**		**15 (25.9)**	6 (26.1)	
30 001–46 000 000	462 (20.4)	**3 (3.7)**		**2 (3.4)**	**1 (4.3)**	
≥46 001	426 (18.8)	**4 (4.9)**		**2 (3.4)**	**2 (8.7)**	
Missing	55	5		4	1	
Marital status—*living alone*	349 (15.0)	**31 (36.1)**	**<0.0001**	**24 (38.7)**	**7 (29.2)**	**<0.0001**
Area of residence—rural	596 (25.7)	24 (27.9)	0.6409	20 (32.3)	4 (16.7)	0.2986
Race—*caucasian*	2116 (93.8)	83 (96.5)	0.3076	59 (95.2)	24 (100.0)	0.6405
Missing	67	0		0	0	
Prepregnancy body mass index, kg/m^2, mean (SD)	23.5 (5.1)	23.3 (5.1)	0.7359	23.5 (5.5)	22.7 (4.3)	0.7816
Missing	338	8		7	1	
Weight gain during pregnancy, kg, mean (SD)	16.3 (5.7)	16.7 (5.5)	0.5403	16.2 (5.4)	17.9 (5.5)	0.4312
Missing	460	20		17	3	
Maternal lifestyle during pregnancy						
Smoking	787 (34.6)	**55 (74.3)**	**<0.0001**	**38 (71.7)**	**17 (81.0)**	**<0.0001**
Missing	49	12		9	3	
Alcohol	509 (22.0)	**35 (41.2)**	**<0.0001**	**26 (41.9)**	**9 (39.1)**	**0.0002**
Missing	8	1		0	1	
Cocaine use	14 (0.6)	0 (0.0)	1	0 (0.0)	0 (0.0)	1
Coffee	1641 (72.4)	64 (78.1)	0.2588	46 (78.0)	18 (78.3)	0.5284
Missing	55	4		3	1	
Multivitamins use	2019 (87.0)	72 (83.7)	0.3843	54 (87.1)	18 (75.0)	0.2263
OTC medications use	956 (43.9)	34 (42.0)	0.7299	25 (43.1)	9 (39.1)	0.8937
Missing	145	5		4	1	
Physical activity	1865 (80.7)	**79 (91.9)**	**0.0094**	56 (90.3)	23 (95.8)	**0.029**
	11	0		0	0	
Maternal comorbidities in the year prior to or during pregnancy						
Chronic/gestational diabetes*	241 (10.4)	11 (12.8)	0.4731	9 (14.5)	2 (8.3)	0.5432

Continued

Table 1 Continued

	No exposure	Overall exposure	P value	Occasional	Regular	
	N=2322 (96.4 %)	N=86 (3.6 %)		N=62 (2.6 %)	N=24 (1.0 %)	P value
Chronic/gestational hypertension*	223 (9.6)	3 (3.5)	0.0562	3 (4.8)	0 (0.0)	0.1273
Asthma*	503 (21.7)	**32 (37.2)**	**0.0007**	**28 (45.2)**	4 (16.7)	**<0.0001**
Thyroid disorders*	123 (5.3)	4 (4.7)	1	3 (4.8)	1 (4.2)	1
Maternal psychiatric disorders in the year prior to or during pregnancy						
Depression/anxiety/bipolar disorder†	1056 (45.5)	**53 (61.6)**	**0.0032**	**39 (62.9)**	14 (58.3)	**0.012**
Other psychiatric disorders‡	521 (22.4)	**29 (33.7)**	**0.0144**	**22 (35.5)**	7 (29.2)	**0.0411**
Maternal pain in the year prior to or during pregnancy§	696 (30.0)	20 (23.3)	0.1807	16 (25.8)	4 (16.7)	0.2889
Maternal ADHD in the year prior to or during pregnancy	6 (0.3)	0 (0.0)	1	0 (0.0)	0 (0.0)	1
Previous pregnancies ending with a live birth	93 (4.1)	5 (5.8)	0.3964	4 (6.5)	1 (4.2)	0.4929
Pregnancy history in the year prior 1DG						
Spontaneous abortion	20 (0.9)	0 (0.0)	1	0 (0.0)	0 (0.0)	1
Planned abortion	50 (2.2)	0 (0.0)	0.26	0 (0.0)	0 (0.0)	0.7829
Premature birth	2 (0.1)	1 (1.2)	0.1034	1 (1.6)	0 (0.0)	0.1034
Infant characteristics						
Infant sex—*male*	1253 (54.0)	52 (60.5)	0.2346	**42 (67.7)**	10 (41.7)	**0.0461**
Birth weight, g, mean (SD)	3392.1 (487.0)	3308.4 (434.6)	0.1162	3336.6 (442.7)	3235.4 (413.1)	0.1999
ADHD	224 (9.7)	**17 (19.8)**	**0.0021**	**12 (19.4)**	5 (20.8)	**0.0088**
ADHD confirmation (n=241—no exposure=224; overall exposure=17; occasional exposure=12; regular exposure=5)						
Diagnosis only	69 (30.8)	2 (11.8)	**0.0243**	2 (16.7)	0 (0.0)	0.1438
Prescription filed only	32 (14.3)	0 (0.0)		0 (0.0)	0 (0.0)	
Both diagnosis and prescription filed	123 (54.9)	15 (88.2)		10 (83.3)	5 (100.0)	

All bold numbers have a significant difference (p<0.05) when comparing to the unexposed group.
Italic characters represent reference category of each characteristic.
P values represent the statistic test comparing exposure groups (occasional or regular) to the unexposed group.
*Based on ICD-9 diagnostic codes and prescription filled for diabetes/hypertension/asthma/thyroid disorders medication.
†Based on ICD-9 and ICD-10 diagnostic codes for affective disorders (unipolar depressive disorder), anxiety or bipolar disorder and data on filled prescription of antidepressants.
‡Schizophrenia, schizotypal and delusional disorders; disorders of adult personality and behaviour; dissociative and conversion disorders; phobic disorders; obsessive–compulsive disorder; dysthemic disorder; neurasthenia; depersonalisation disorder; somatoform disorder; unspecified non-psychotic mental disorder; and drug dependence except for cannabis dependence based on ICD-9 diagnostic codes and prescription filled for antipsychotic and other psychotropic medications.
§Based on ICD-9 diagnostic codes of chronic pain, cancer, epilepsy/seizures, glaucoma, muscles spasm, arthritis, nausea and vomiting.
ADHD, attention deficit with or without hyperactivity; CEGEP, Collège d'Enseignement Général et Professionnel; 1DG, first day of gestation; OTC, Over-The-Counter.

and regularly), we observed that the regular exposure to cannabis was associated with a higher risk of ADHD; however, no significant association was found when comparing the unexposed group to each of the exposure groups. Moreover, the overall exposure to cannabis during pregnancy was not associated with ADHD. In the sensitivity analyses considering only children aged four and older, we obtained similar results. Moreover, we did not find any significant association in our other sensitivity analyses.

Data on the impact of cannabis use during pregnancy on children neurodevelopment such as ADHD are still limited. Our results are consistent with the study of Corsi *et al*,[22] which did not find any association between overall prenatal cannabis exposure and the risk of ADHD in children. Paul *et al*, in their cross-sectional study with 5.7% exposed children to cannabis prenatally, observed a higher risk of psychopathology characteristics such as attention problems associated with cannabis exposure after knowledge of pregnancy compared with the unexposed group.[26] Moreover, prenatal marijuana exposure during the first and third trimesters was associated with increased hyperactivity, impulsivity and inattention at age 10.[25] Unlike our study, these studies used a questionnaire

Table 2 Association between in-utero patterns of exposure to cannabis and the risk of ADHD in children

	Total infants, N=2408	Infants with ADHD, N=241	ADHD Follow-up no. of person-years	Unadjusted HR (95% CI)	Model 1—adjusted HR* (95% CI)	Model 2—adjusted HR† (95% CI)	Model 3—adjusted HR‡ (95 % CI)
Exposure patterns							
No exposure	2322	224	1502	Reference	Reference	Reference	Reference
Occasional use of cannabis	62	12	88	1.37 (0.73 to 2.35)	1.24 (0.65 to 2.12)	1.04 (0.54 to 1.80)	1.22 (0.63 to 2.19)
Regular use of cannabis	24	5	32	1.32 (0.47 to 2.88)	1.26 (0.45 to 2.77)	1.08 (0.38 to 2.41)	1.22 (0.42 to 2.79)
Maternal age at 1DG, years, mean (SD)	27.6 (5.5)	**26.3 (6.0)**	1622	**0.97 (0.95 to 0.99)**	**0.97 (0.95 to 0.99)**	**0.97 (0.95 to 0.99)**	**0.98 (0.95 to 1.00)**
Gestational age at delivery, weeks, mean (SD)	39.2 (1.1)	39.0 (1.2)	1622	0.90 (0.81 to 1.01)	–	–	**0.89 (0.80 to 0.99)**
Education							
Secondary school	1134	166	1167	Reference	Reference	Reference	Reference
CEGEP or University	948	45	258	**0.60 (0.42 to 0.83)**	–	0.86 (0.59 to 1.22)	0.79 (0.54 to 1.13)
Others	326	30	197	0.98 (0.65 to 1.43)	–	1.05 (0.70 to 1.53)	1.05 (0.69 to 1.54)
Household annual income, $C							
≤18 000	810	169	1223	Reference	Reference	Reference	Reference
18 001–30 000 000	679	40	242	**0.60 (0.42 to 0.85)**	–	**0.69 (0.48 to 0.98)**	0.70 (0.48 to 1.01)
30 001–46 000 000	483	21	107	**0.58 (0.35 to 0.90)**	–	0.87 (0.52 to 1.39)	0.87 (0.52 to 1.41)
>46 000	436	11	50	**0.35 (0.18 to 0.62)**	–	**0.51 (0.25 to 0.93)**	**0.49 (0.24 to 0.92)**
Marital status—*living alone*	380	82	614	1.26 (0.96 to 1.65)	–	–	0.91 (0.67 to 1.24)
Area of residence—*rural*	620	44	298	**1.46 (1.06 to 2.05)**	–	–	**1.43 (1.03 to 2.04)**
Race—*caucasian*	2263	224	1495	1.08 (0.68 to 1.84)	–	–	1.25 (0.76 to 2.20)
Previous pregnancies ending with a live birth	98	16	100	**2.00 (1.15 to 3.20)**	–	1.67 (0.95 to 2.75)	1.71 (0.96 to 2.85)
Prepregnancy body mass index, kg/m^2, mean (SD)	23.5 (5.2)	24.2 (6.8)	1622	1.02 (1.00 to 1.04)	–	–	**1.02 (1.00 to 1.05)**
Maternal lifestyle during pregnancy							
Smoking	869	110	794	1.03 (0.80 to 1.33)	–	–	0.83 (0.63 to 1.11)
Alcohol	546	48	319	0.95 (0.69 to 1.30)	–	–	1.00 (0.71 to 1.38)
Cocaine use	14	3	15	1.37 (0.34 to 3.58)	–	–	1.11 (0,26 to 3.13)
Coffee	1745	179	1205	0.91 (0.69 to 1.23)	–	–	0.90 (0.66 to 1.24)
Multivitamins use	2091	216	1452	1.32 (0.89 to 2.04)	–	–	1.40 (0.93 to 2.19)
Physical activity	1953	205	1381	1.11 (0.79 to 1.62)	–	–	1.03 (0.72 to 1.50)
Maternal comorbidities in the year prior to or during pregnancy							
Chronic/gestational diabetes§	252	28	194	1.05 (0.69 to 1.53)	–	–	0.98 (0.64 to 1.46)

Continued

Table 2 Continued

	Total infants, N=2408	Infants with ADHD, N=241	ADHD Follow-up no. of person-years	Unadjusted HR (95% CI)	Model 1—adjusted HR* (95% CI)	Model 2—adjusted HR† (95% CI)	Model 3—adjusted HR‡ (95 % CI)
Chronic/gestational hypertension§	226	26	174	1.12 (0.73 to 1.65)	–	–	1.03 (0.66 to 1.53)
Asthma§	535	101	709	**2.07 (1.60 to 2.67)**	–	**1.83 (1.39 to 2.39)**	**1.76 (1.34 to 2.32)**
Thyroid disorders§	127	8	43	0.74 (0.34 to 1.40)	–	–	0.70 (0.31 to 1.34)
Maternal psychiatric disorders in the year prior to or during pregnancy							
Depression/anxiety/bipolar disorder¶	1109	144	997	**1.46 (1.13 to 1.90)**	–	1.11 (0.82 to 1.51)	1.12 (0.82 to 1.52)
Other psychiatric disorders**	550	84	605	**1.40 (1.07 to 1.83)**	–	1.16 (0.84 to 1.59)	1.19 (0.86 to 1.65)
Maternal ADHD	6	3	22	**5.24 (1.29 to 13.88)**	–	2.17 (0.52 to 6.06)	3.01 (0.69 to 9.04)
Maternal pain††	716	90	637	**1.34 (1.03 to 1.73)**	–	1.11 (0.85 to 1.46)	1.08 (0.82 to 1.42)
Infant sex—*male*	1305	148	958	**1.61 (1.24 to 2.09)**	**1.62 (1.25 to 2.10)**	**1.68 (1.29 to 2.20)**	**1.84 (1.41 to 2.43)**
Calendar year of delivery	–	–	–	**1.15 (1.05 to 1.25)**	–	1.05 (0.96 to 1.16)	1.04 (0.95 to 1.15)

Italic characters represent reference category of each characteristic.
All bold numbers have a significant difference ($p<0.05$).
*Adjusted for only maternal age and infant sex.
†Adjusted for variables that have an unadjusted HR significant ($p<0.05$).
‡Adjusted for all variables included in the table.
§based on ICD-9 and ICD-10 diagnostic codes and prescription filled for diabetes/hypertension/asthma/thyroid disorder medications.
¶Based on ICD-9 and ICD-10 diagnostic codes for affective disorders (unipolar depressive disorder), anxiety or bipolar disorder and data on filled prescription of antidepressants.
**Schizophrenia, schizotypal and delusional disorders; disorders of adult personality and behaviour; dissociative and conversion disorders; phobic disorders; obsessive–compulsive disorder; dysthemic disorder; neurasthenia; depersonalisation disorder; somatoform disorder; unspecified non-psychotic mental disorder; and drug dependence except for cannabis dependence, based on ICD-9 diagnostic codes and prescription filled for antipsychotic and other psychotropic medications.
††Based on ICD-9 diagnostic codes of chronic pain, cancer, epilepsy/seizures, glaucoma, muscles spasm, arthritis, nausea and vomiting.
ADHD, attention deficit with or without hyperactivity; CEGEP, Collège d'Enseignement Général et Professionnel; 1DG, first day of gestation.

Table 3 Association between overall cannabis exposure and risk of attention deficit with or without hyperactivity disorder in children

	Total infants, N=2408	Infants with ADHD, N=241	ADHD Follow-up no. of person-years	Unadjusted HR (95% CI)	Model 1—adjusted HR* (95% CI)	Model 2—adjusted HR† (95% CI)	Model 3—adjusted HR‡ (95 % CI)
Exposure patterns							
No exposure	2322	224	1502	Reference	Reference	Reference	Reference
Overall exposure	86	17	120	1.36 (0.80 to 2.16)	1.24 (0.73 to 1.98)	1.05 (0.61 to 1.70)	1.22 (0.70 to 2.02)
Maternal age at 1DG, years, mean (SD)	27.6 (5.5)	26.3 (6.0)	1622	**0.97 (0.95 to 0.99)**	**0.97 (0.95 to 0.99)**	**0.97 (0.95 to 0.99)**	**0.98 (0.95 to 1.00)**
Gestational age at delivery, weeks, mean (SD)	39.2 (1.1)	39.0 (1.2)	1622	0.90 (0.81 to 1.01)	–	–	**0.89 (0.80 to 0.99)**
Education							
Secondary school	1134	166	1167	Reference	Reference	Reference	Reference
CEGEP or University	948	45	258	**0.60 (0.42 to 0.83)**	–	0.86 (0.59 to 1.22)	0.79 (0.54 to 1.13)
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Marital status—*living alone*	380	82	614	1.26 (0.96 to 1.65)	–	–	0.91 (0.67 to 1.24)
Area of residence—*rural*	620	44	298	1.46 (1.06 to 2.05)	–	–	1.43 (1.03 to 2.04)
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Continued

Table 3 Continued

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Infant sex—male	1305	148	958	**1.61 (1.24 to 2.09)**	**1.62 (1.25 to 2.10)**	**1.68 (1.29 to 2.20)**	**1.84 (1.41 to 2.43)**
Calendar year of delivery	–	–	–	**1.15 (1.05 to 1.25)**	–	1.05 (0.96 to 1.16)	1.04 (0.95 to 1.15)

Italic characters represent reference category of each characteristic.
All bold numbers have a significant difference (p<0.05).
*Adjusted for only maternal age and infant sex.
†Adjusted for variables that have an unadjusted HR significant (p<0.05).
‡Adjusted for all variables included in the table.
§Based on ICD-9 and ICD-10 diagnostic codes and prescription filled for diabetes/hypertension/asthma/thyroid disorder medications.
¶Based on ICD-9 and ICD-10 diagnostic codes for affective disorders (unipolar depressive disorder), anxiety or bipolar disorder and data on filled prescription of antidepressants.
**Schizophrenia, schizotypal and delusional disorders; disorders of adult personality and behaviour; dissociative and conversion disorders; phobic disorders; obsessive–compulsive disorder; dysthemic disorder; neurasthenia; depersonalisation disorder; somatoform disorder; unspecified non-psychotic mental disorder; and drug dependence except for cannabis dependence, based on ICD-9 diagnostic codes and prescription filled for antipsychotic and other psychotropic medications.
††Based on ICD-9 diagnostic codes of chronic pain, cancer, epilepsy/seizures, glaucoma, muscles spasm, arthritis, nausea and vomiting.
ADHD, attention deficit with or without hyperactivity; CEGEP, Collège d'Enseignement Général et Professionnel; 1DG, first day of gestation.

to measure the attention, hyperactivity problems. A study showed that the use of cannabis in pregnant rats affects the dopamine activity, and that this altered activity can lead to development of attention deficit and hyperactivity disorder.[33] This might have explained the higher risk of attention problems and hyperactivity found in the previous studies. It has been showed that passive smoking during pregnancy might cause a delay in neurodevelopment in children.[34 35] In our study, unfortunately, we do not have data about passive smoking during pregnancy. It might be interesting for future studies to take in account passive smoking during pregnancy when studying prenatal cannabis use and children neurodevelopment.

Strength and limitation

Study strengths include that the self-reported questionnaire was linked to administrative health databases, hospital patient charts and birth certificate databases; this allowed for the analyses of pregnancies with detailed information regarding exposure, outcomes and potential confounders. QPC data on prescriptions filled,[36] gestational age[31] and birth weight[31] have been validated.

As for limits, our response rate was 39% (3354/8505) which is not high. However, the responders were comparable to the non-responders on the study variables present in the QPC.[37] Thus, the selection bias, if present, should not have highly impacted our results. Moreover, our questionnaire was conducted in 2006 for live births between January 1998 and December 2003, which make our data old. Cannabis was legalised in Canada in October 2018 and with our data we were not able to retrieve more information about cannabis use, since cannabis was still an illicit drug at our time frame. Also, the use of the self-administered questionnaires to collect data retrospectively on prenatal cannabis use and other lifestyle factors might lead to recall or social desirability biases, which might have affected our results. However, others have shown that women tend to remember events occurring during their perinatal period,[38] which could have limited the recall bias. Consequently, if the recall bias is present, it will be a non-differential bias equally assigned among women. To limit for the social desirability bias, we did a sensitivity analysis considering all non-responses of cannabis exposure as exposed to cannabis, and we found no significant association. Furthermore, the self-administered questionnaire used in our study was not validated, but a toll-free telephone line was set up for women requiring further information.[37] Moreover, the selection method of our study population was not entirely random, and this could have limited the generalisability of our results compared with the general population of Quebec. Thus, we did an analysis comparing the included infants and the potential responders and the characteristics were relatively similar (results are presented in online supplemental table S8). In addition, the QPC includes only women who were insured by the provincial prescription drug insurance programme during their pregnancy; however, we have previously shown these women are similar to women who are privately covered in terms of health status and medication.[39] Moreover, for children who stopped being covered by the public insurance for medication, we did not have access to the children whose public coverage for medication has ended, we can no longer follow them. Finally, our study might be underpowered when stratifying on exposure frequency (occasional and regular). In fact, we calculated the power a posteriori and found that for the overall exposure, for a power of 80%, we needed at least 193 infants in each group. For our sample of 86 overall exposed to cannabis during pregnancy, we only had a power of 46.3%. This might explain our non-significant results in our main analyses

CONCLUSION

In our study, we did not find any association between in-utero occasional or regular exposure to cannabis and the risk of ADHD in children, as well as overall exposure to cannabis and the risk of ADHD in children. Further research focusing on the timing of exposure during pregnancy (eg, first, second, third trimester), as well as using different methods for quantifying prenatal cannabis exposure (eg, biological samples), is needed to better understand the impact of cannabis use during pregnancy and developmental outcomes in children. Moreover, medical professionals should consider the interaction between cannabis components and common medication when giving advice to pregnant women about cannabis use, especially to women who have prescription for diseases such as depression, thyroid disease, since cannabis components might alter some medications.

Contributors All authors participated in the study. AB acquired the data. OS contributed to the study design, data collection. VT contributed to analysis of data and preparation of the final document. VT, OS, J-PZ, JG, Y-HG and AB revised and corrected the article. All authors read and approved this final document. VT and AB are responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the CHU Sainte-Justine's Research Ethics Committee (#1740) and the Commission d'Accès à l'information du Québec provided authorisation for the linkage of the datasets (#2976). All participants provided informed consent for the original survey. As such, participants agreed to fill up the questionnaire and have their questionnaire's data linked to their data in the Quebec Pregnancy Cohort.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information. All data relevant to this study are included in this article or uploaded as supplementary information. In order to obtain crude underlying health data from RAMQ and data from our questionnaires, individuals need to contact data holders of the QPC which is in QC, Ethics Committee President (http://chusj.nagano.ca), CHU Ste-Justine, Montreal, QC, Canada for researchers who meet the criteria for access to confidential data.

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