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Maternal cannabis use in pregnancy and child neurodevelopmental outcomes

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Cannabis use in pregnancy has increased[1,2], and many women continue to use it throughout pregnancy[3]. 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 perform a retrospective analysis of all live births in Ontario, Canada, between 1 April 2007 and 31 March 2012. We link pregnancy and birth data to provincial health administrative databases to ascertain child neurodevelopmental outcomes. We use matching techniques to control for confounding and Cox proportional hazards regression models to examine associations between prenatal cannabis use and child neurodevelopment. We find an association between maternal cannabis use in pregnancy and the incidence of autism spectrum disorder in the offspring. The incidence of autism spectrum disorder diagnosis was 4.00 per 1,000 person-years among children with exposure compared to 2.42 among unexposed children, and the fully adjusted hazard ratio was 1.51 (95% confidence interval: 1.17–1.96) in the matched cohort. The incidence of intellectual disability and learning disorders was higher among offspring of mothers who use cannabis in pregnancy, although less statistically robust. We emphasize a cautious interpretation of these findings given the likelihood of residual confounding.

Cannabinoids, including tetrahydrocannabinol, readily cross the placenta and can enter the fetal bloodstream[5]. Exposure to cannabinoids while in utero can disrupt the fetal endogenous cannabinoid signaling system, which has several roles in embryo development[5]. Human and animal studies suggest that disruption of endocannabinoid signaling may lead to defects in neuronal wiring, and have implications for fetal neurodevelopment[6,7].

Data on long-term follow-up of children with exposure to cannabis in utero are currently limited[8,9]. Previous studies indicate decreases in concentration and attention among offspring of mothers with cannabis use in pregnancy compared to those without[9]. There is a need for larger studies that can adequately control for confounding in cannabis–outcome associations[10]. Here we aimed to assess whether there is an association between cannabis exposure in pregnancy and neurodevelopmental outcomes in childhood using the birth registry (BORN) from Ontario, Canada with nearly complete capture of every pregnancy and birth.

A total of 689,071 births in Ontario were registered by BORN between 1 April 2007 and 31 March 2012. Following exclusions, the final cohort was based on 508,025 births. Children who lost Ontario Health Insurance eligibility or died before 18 months ($n = 4{,}960$) or 4 years ($n = 10{,}204$) of age were excluded from the primary analyses of autism spectrum disorder (ASD) and secondary analyses of neurodevelopmental outcomes, yielding analytical cohorts of 503,065 and 497,821, respectively (Supplementary Table 1). The mean age of mothers was 30.1 years (s.d. = 5.6), the mean gestational age at delivery was 38.9 weeks (s.d. = 1.7) and 51.4% of children were male. The rate of reported cannabis use in pregnancy was 0.6%. An analysis comparing excluded records to the analytical cohort indicated some modest differences by maternal age, area-level income, parity, maternal health conditions, rural residence and drug and medication use in pregnancy (Supplementary Table 2). An analysis by year of birth indicates that the rates of exclusion were lower among the cohort born after 2010 (Supplementary Table 3). Maternal cannabis use was lower among excluded records (0.3%). The first prenatal consultation, where cannabis use information is collected, occurred at a median of the 79th gestational day (11 weeks and 2 d) overall, and the 94th day (13 weeks and 3 d) among women with reported cannabis use.

Significant imbalance in covariates was identified between cannabis users and nonusers. The L_1 statistic, a global measure of imbalance, was 0.77 in the unmatched cohort, but this was reduced to 0.02 following coarsened exact matching (CEM). Imbalance in the distribution of baseline covariates was reduced in the matched cohort (standardized mean difference (SMD) < 1% for all covariates except placental abruption (SMD = 5.4%)). The matched analytical cohort comprised 173,035 records, of which 2,364 were cannabis users and 170,671 were cannabis nonusers (Table 1). The sample distribution was similar in the 4-year analytical cohort (Supplementary Table 4).

Association between prenatal cannabis use and ASD. In the 18-month cohort, 7,125 (1.4%) children were diagnosed with ASD by the end of follow-up (median length of follow-up, 7.4 years). The rate of ASD diagnosis was 2.2% among children with in utero cannabis exposure. The incidence of ASD diagnosis was 4.00 per 1,000 person-years (95% confidence interval (CI): 3.65–4.38) among children exposed to cannabis compared to 2.42 (95% CI: 2.39–2.44) among unexposed children, and the crude hazard ratio (HR) was 1.63 (95% CI: 1.29–2.06). In the CEM-matched cohort, the HR for ASD associated with cannabis exposure was 1.53 (95% CI: 1.18–1.98), and 1.51 (95% CI: 1.17–1.96) in unadjusted and fully adjusted models (Table 2).

Association between prenatal cannabis use and neurodevelopmental disorders. In the 4-year cohort, the rates of secondary

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Table 1 | Characteristics of reported cannabis users and nonusers in the study cohort and matched cohort, Ontario 2007–2012

Characteristic	Cohort by maternal cannabis use			CEM cohort by maternal cannabis use		
	Nonusers	Users		Nonusers	Users	
	n = 499,917	*n* = 3,148		*n* = 170,671	*n* = 2,364	
	n (%) or mean ± s.d.		SMD	Percentage or mean ± s.d.		SMD
Maternal age, mean ± s.d.	30.1 ± 5.5	23.7 ± 5.6	1.16	23.5 ± 5.4	23.4 ± 5.4	0.0196
Maternal age (categories, years)						
<20	17,914 (3.6)	822 (26.1)	0.67	27.5	27.5	<0.0001
20–24	62,730 (12.5)	1,155 (36.7)	0.58	37.9	37.9	<0.0001
25–29	136,927 (27.4)	695 (22.1)	0.12	20.9	20.9	<0.0001
30–34	172,135 (34.4)	313 (9.9)	0.62	9.1	9.1	<0.0001
35+	110,211 (22.0)	163 (5.2)	0.51	4.6	4.6	<0.0001
Maternal education, mean ± s.d.[a]	0.51 ± 0.1	0.43 ± 0.1	0.63	0.43 ± 0.1	0.43 ± 0.1	<0.0001
Maternal education (quartiles)[a]						
1 (lowest)	118,124 (23.6)	1,426 (45.3)	0.47	47.5	47.5	<0.0001
2	129,593 (25.9)	875 (27.8)	0.04	27.5	27.5	<0.0001
3	15,772 (3.2)	68 (2.2)	0.06	1.7	1.7	<0.0001
4 (highest)	232,453 (46.5)	708 (22.5)	0.52	22.0	21.8	0.0039
Missing	3,975 (0.8)	71 (2.3)	0.12	1.4	1.5	0.0134
Preexisting maternal conditions						
Diabetes	10,586 (2.1)	52 (1.7)	0.03	0.8	0.8	<0.0001
Hypertension	13,920 (2.8)	27 (0.9)	0.14	0.6	0.6	<0.0001
Asthma	22,973 (4.6)	391 (12.4)	0.28	10.7	10.7	<0.0001
Heart disease	2,698 (0.5)	23 (0.7)	0.02	0.3	0.3	<0.0001
Maternal psychiatric disorders						
Mood/anxiety disorders	135,169 (27.0)	1,398 (44.4)	0.37	41.0	41.0	<0.0001
Substance use disorder	7,611 (1.5)	572 (18.2)	0.58	11.2	11.2	<0.0001
Maternal prenatal substance use						
Alcohol	437 (0.1)	120 (3.8)	0.27	0.8	0.8	<0.0001
Cocaine	625 (0.1)	422 (13.4)	0.55	3.2	3.2	<0.0001
Hallucinogens	55 (0.0)	76 (2.4)	0.22	0.0	0.0	<0.0001
Methadone	1,067 (0.2)	140 (4.4)	0.28	1.6	1.6	<0.0001
Opioids	469 (0.1)	161 (5.1)	0.32	0.6	0.6	<0.0001
Prescription medication	14,795(3.0)	356 (11.3)	0.33	7.0	7.0	<0.0001
Rurality			0.24			<0.0001
Urban	450,294 (90.1)	2,573(81.7)		84.1	84.1	
Rural	49,586 (9.9)	574 (18.2)		16.0	16.0	
Income quintile						
1 (lowest)	104,669 (20.9)	1,403 (44.6)	0.52	46.4	46.4	<0.0001
2	98,341 (19.7)	715 (22.7)	0.07	23.0	23.0	<0.0001
3	103,156 (20.6)	412 (13.1)	0.20	12.9	12.9	<0.0001
4	107,704 (21.5)	337 (10.7)	0.30	10.0	10.0	<0.0001
5 (highest)	83,606 (16.7)	227 (7.2)	0.30	6.6	6.6	<0.0001
Missing	2,441 (0.5)	54 (1.7)	0.12	1.1	1.1	<0.0001
Parity						
Nulliparous	212,178 (42.4)	1,821 (57.8)	0.31	61.9	61.9	<0.0001
Primiparous	180,740 (36.2)	701 (22.3)	0.31	21.3	21.3	<0.0001
Multiparous	103,874 (20.8)	615 (19.5)	0.03	16.6	16.5	0.0024
Missing	3,125 (0.6)	11 (0.3)	0.04	0.2	0.3	0.0186
Prenatal care provider						

Continued

Table 1 | Characteristics of reported cannabis users and nonusers in the study cohort and matched cohort, Ontario 2007–2012

Characteristic	Cohort by maternal cannabis use			CEM cohort by maternal cannabis use		
	Nonusers	Users		Nonusers	Users	
	n = 499,917	*n* = 3,148		*n* = 170,671	*n* = 2,364	
	n (%) or mean ± s.d.		SMD	Percentage or mean ± s.d.		SMD
No	2,849 (0.6)	91 (2.9)	0.18	0.9	0.9	<0.0001
Yes	480,216 (96.1)	2,954 (93.8)	0.10	97.3	97.3	<0.0001
Missing	16,852 (3.4)	103 (3.3)	0.01	1.8	1.8	<0.0001
Maternal smoking						
No	418,097 (83.6)	583 (18.5)	1.72	75.9	75.9	<0.0001
Yes	58,182 (11.6)	2,452 (77.9)	1.79	2.8	2.8	<0.0001
Missing	23,638 (4.7)	113 (3.6)	0.06	21.2	21.2	<0.0001
Variables not used in matching						
Gestational age at delivery			0.22			0.1169
<37 weeks	30,355 (6.1)	389 (12.4)		7.7	11.1	
37 weeks and more	469,562 (93.9)	2,729 (87.6)		92.3	88.9	
Obstetric complications						
Placental abruption	2,636 (0.5)	40 (1.3)	0.08	0.7	1.3	0.0532
Placenta previa	3,204 (0.6)	16 (0.5)	0.02	0.4	0.5	0.0106
Preeclampsia	9,519 (1.9)	61 (1.9)	0.00	1.9	2.0	0.0131
Eclampsia	172 (0.0)	≤5 (0.1)	0.01	0.1	0.0	0.0089
Gestational diabetes	23,674 (4.7)	82 (2.6)	0.11	2.7	2.5	0.0170
Gestational hypertension	17,340 (3.5)	102 (3.2)	0.01	3.8	3.0	0.0465

[a]Measured using census data as the neighborhood proportion of people with a post-secondary education degree. Percentages rounded to the nearest decimal place. Area-level median family income quintiles were extracted from the Canadian Census using patient postal codes mapped to standard geographical units for census tracts and dissemination areas[26]. Substance use was captured as 'yes, use of substance' or 'no' for the current pregnancy. Gestational age was estimated by first-trimester ultrasound or menstrual dating. We excluded 56,967 records (8.3%, *n* = 21,707 infants and *n* = 33,664 mothers) due to invalid or missing identification numbers, mismatched dates of birth or other errors that prevented linkage between BORN and health administrative databases (*n* = 1,596), and these records were considered lost to follow-up. 71,151 (10.3%) observations were excluded due to non-Ontario residency at birth (*n* = 658) and/or ineligibility for Ontario's Health Insurance Plan coverage at the time of birth (*n* = 9,549 infants) or in a continuous 2-year period before birth (*n* = 60,944 mothers). We further excluded stillbirths (*n* = 155), multifetal pregnancies (*n* = 22,473), mothers >50 years of age (*n* = 52), infants with missing gestational age (*n* = 53) and mothers with missing cannabis use information (*n* = 30,195). Children who lost Ontario Health Insurance eligibility or died before 18 months (*n* = 4,960) or 4 years (*n* = 10,204) of age were excluded. See Methods for additional details.

Table 2 | Hazard ratios and 95% CIs for the association between prenatal cannabis exposure and study outcomes

Outcome	Crude HR (95% CI)	Adjusted HR (95% CI)[c]	Additionally adjusted HR (95% CI)[c,d]
Primary outcome			
ASD[a]	1.63 (1.29–2.06)	1.53 (1.18–1.98)	1.51 (1.17–1.96)
Secondary outcomes[b]			
Intellectual disability and learning disorders	2.04 (1.68–2.49)	1.23 (0.97–1.55)	1.22 (0.97–1.54)
ADHD	2.60 (2.35–2.86)	1.11 (0.99–1.25)	1.11 (0.98–1.25)

[a]Diagnosed after 18 months of age, *n* = 503,065 children. [b]Diagnosed after age 4 years, *n* = 497,821 children. [c]Models adjusted using CEM method: *n* = 173,035 children for primary outcome, *n* = 170,271 children for secondary outcomes. [d]Adjusted for placental abruption, placenta previa, preeclampsia, eclampsia, gestational diabetes, gestational hypertension and preterm birth.

outcomes were 1.7% for intellectual and learning disorders and 5.7% for attention deficit, hyperactivity and conduct disorders (ADHD). Rates were higher among children with prenatal cannabis exposure. The unadjusted incidence of intellectual disability and learning disorders was 10.3 (95% CI: 9.4–11.2) per 1,000 person-years among children with prenatal exposure compared to 4.9 (95% CI: 4.80–4.93) among unexposed children. The incidence of ADHD was 45.0 (95% CI: 42.2–48.1) per 1,000 person-years among children born to women who reported cannabis use in pregnancy and 17.1 (95% CI: 16.90–17.2) among unexposed children. In crude analyses, the HR was 2.04 (95% CI: 1.68–2.49) for intellectual disability and learning disorders and 2.60 (95% CI: 2.35–2.86) for ADHD. In the matched cohort, the HR was 1.23 (95% CI: 0.97–1.55) for intellectual disability and learning disorders and 1.11 (95% CI: 0.99–1.25) for ADHD. Following additional adjustment, the estimates for intellectual disability and learning disorders (HR = 1.22 (95% CI: 0.97–1.54)) and ADHD (HR= 1.11 (95% CI: 0.98–1.25)) were attenuated and no longer statistically significant (Table 2).

A sensitivity analysis among women who reported cannabis use in pregnancy but no other substance use (*n* = 485,289, 2,203 cannabis users) resulted in a crude HR of 1.83 (95% CI: 1.41–2.39) for ASD (Table 3). The use of CEM in this cohort (*n* = 168,843, 2,006 cannabis users) with additional covariate adjustment attenuated the association to 1.54 (95% CI: 1.17–2.03). For secondary analyses in the matched cohort, the HR was 1.35 (95% CI: 1.05–1.73) for intellectual disability and learning disorders. We also analyzed the overall cannabis–ASD association stratified by income. This analysis indicated similar effects across income strata with no evidence of effect modification ($P_{interaction} = 0.94$), although the association was less statistically reliable in the higher-income strata. The HR for CEM-adjusted association was 1.51 (95% CI: 1.11–2.06) in income quintiles 1 and 2 (lower income) compared to 1.54 (95% CI: 0.95–2.49) in income quintiles 3, 4 and 5 (higher income). To account for preterm birth, we analyzed the primary outcome stratified by deliveries occurring before 37 weeks' and ≥37 weeks' gestation. Among

Table 3 | Hazard ratios and 95% CIs for the association between prenatal cannabis exposure and outcomes in subgroups

Subgroup/outcome	Crude HR (95% CI)	Adjusted HR (95% CI)[d]	Additionally adjusted HR (95% CI)[d,e]
Prenatal cannabis only[a]			
ASD[b]	1.83 (1.41–2.39)	1.57 (1.19–2.07)	1.54 (1.17–2.03)
Intellectual disability and learning disorders[c]	2.01 (1.58–2.55)	1.38 (1.07–1.77)	1.35 (1.05–1.73)
ADHD[c]	2.32 (2.05–2.63)	1.11 (0.98–1.26)	1.11 (0.97–1.26)
Income	1.67 (0.80–3.51)	1.73 (0.82–3.66)	1.76 (0.83–3.72)
ASD[b]			
Income quintiles 1 and 2	1.50 (1.13–1.98)	1.52 (1.11–2.07)	1.51 (1.11–2.06)
Income quintiles 3, 4 and 5	1.58 (1.01–2.48)	1.56 (0.96–2.52)	1.54 (0.95–2.49)
P value for interaction between cannabis use and income quintiles	0.84	0.94	0.96
Preterm birth			
ASD[b]			
Preterm birth (<37 weeks gestation)	1.42 (0.78–2.57)	1.98 (1.05–3.71)	1.97 (1.05–3.71)
Full-term birth (≥37 weeks gestation completed)	1.61 (1.25–2.09)	1.45 (1.09–1.93)	1.44 (1.08–1.91)
P value for interaction between cannabis use and preterm birth	0.69	0.37	0.36

[a]Cohort restricted to mothers who did not use other substances such as alcohol, tobacco, cocaine, hallucinogens, methadone, opioids or prescription drugs. [b]Diagnosed after 18 months of age, $n = 485{,}289$ children. [c]Diagnosed after age 4 years, $n = 480{,}334$ children. [d]Models adjusted using CEM method: $n = 171{,}533$ children for primary outcome, $n = 168{,}843$ for secondary outcomes. [e]Adjusted for placental abruption, placenta previa, preeclampsia, eclampsia, gestational diabetes and gestational hypertension.

women with preterm deliveries (6% of the cohort, $n = 30{,}744$), the CEM-adjusted HR was 1.97 (95% CI: 1.05–3.71) compared to 1.44 (95% CI: 1.08–1.91) in full-term deliveries ($P_{\text{interaction}} = 0.36$). For secondary outcomes, the associations were attenuated in the preterm sample. With fewer events, estimates of these associations were less precise (Supplementary Table 5). To address potential bias arising from the exclusion of children younger than 18 months or 4 years of age, we repeated the analyses, including everyone starting from birth. These findings were nearly identical to the 18-month and 4-year follow-up cohorts (Supplementary Table 6).

In this large retrospective cohort, we found that children with mothers who reported cannabis use in pregnancy were at higher risk for ASD diagnosis. Children with prenatal cannabis exposure had an increase of 50% in the risk of an autism diagnosis over the study period, and these associations were robust after controlling for confounding. Also, children with prenatal cannabis exposure appeared to have some increased risk for developing intellectual disabilities, learning disorders and ADHD compared to unexposed children. However, these associations were smaller in magnitude (11–22% increase) and did not attain statistical significance at conventional levels after matching and covariate adjustment. The primary association between maternal cannabis use and ASD persisted in sensitivity analyses by other substance use, income and preterm birth. Although findings of an increased risk for childhood neurodevelopmental disorders are of substantive interest, we emphasize a cautious interpretation given the likelihood of residual confounding.

Prenatal exposure to drugs may impact fetal central nervous system development and subsequent behavior[11]. Animal data support that prenatal insults to the developing central nervous system continue to affect fetal, neonatal, infant and childhood development[12]. Neuroimaging studies have demonstrated region- and gene-specific neural changes associated with prenatal exposure to cannabis[13]. Fetal brain development occurs throughout pregnancy, including in the first trimester. Prenatal insults during this period show an association with anomalies of the central nervous system and neurodevelopmental disorders[14]. Furthermore, animal data indicate that the fetal endocannabinoid type 1 receptor, through which cannabis primarily affects the brain, is expressed at the equivalent of 5–6 weeks of gestation in humans[15]. Associations between prenatal cannabis exposure and potential neurodevelopmental outcomes in children may be complex and subject to confounding or mediation. Factors including individual genetic profile, prematurity, fetal and postnatal environment, dose and type of substance of exposure and environmental factors may be involved[16], thus limiting our ability to ascertain causality between in utero cannabis exposure and later childhood outcomes[17].

Subgroup analyses among women who reported cannabis use, but no use of other substances in pregnancy, were consistent with the overall findings, particularly for ASD. These analyses suggest that the observed associations were not likely to be confounded by the use of other substances. However, some of the estimates were less statistically reliable due to a smaller number of cannabis-only users. In addition, stratified analyses by socioeconomic status revealed that the association between reported cannabis use and incidence of ASD was similar between lower- and higher-socioeconomic-status groups. The association remained stable in the subgroup analyses of full-term births, suggesting that the cannabis–ASD association was not driven by preterm birth.

This study has several limitations. First, the prevalence of cannabis use was lower than reported elsewhere, although data were collected before recent increases in use[1,18]. Cannabis users may be misclassified as nonusers in the birth registry, probably due to underreporting, which may arise from social stigma or fear of involvement of child protective services[19–21]. Data on the use of cannabis in pregnancy are self-reported and collected through disclosure to prenatal care providers using standardized perinatal care forms. The use of cannabis is a combination of therapeutic and recreational use. Cannabis use data in BORN are highly accurate when validated against clinical records, although similar biases may exist in both sources[22]. Second, data on frequency, trimester and duration of use are not available. Data from a UK cohort indicated that about 2.6% of the cohort used cannabis in the first trimester of pregnancy, which was higher than the rate in the second trimester (2.1%)[23]. US data from 2017 also indicate that the prevalence of regular cannabis use declines in pregnancy, from 5.3% in the first trimester to 2.5% in the second and third trimesters[3]. In this cohort, although some women may have quit using cannabis, we have data only on exposure at any time in pregnancy.

Third, although self-reporting of cannabis use is moderately reliable for use in epidemiological studies compared to biomarkers[24], misclassification can occur. Pregnant women may underreport cannabis use, but we do not anticipate that this will have a significant effect on the magnitude of the findings. Because exposure information was collected before outcome ascertainment, and the degree of underreporting is probably similar between women with a child who has experienced the outcome and those whose children did not, misclassification is likely to be nondifferential. Nondifferential exposure misclassification would bias the reported associations

towards the null. A second reason is that the exposure is rare in this cohort, and the unexposed group is substantially larger. With a rare exposure, low sensitivity in identifying cannabis users would not lead to bias, and our previous work indicates that the specificity of exposure is high[22]. Therefore, the net result of exposure misclassification is likely to underestimate the potential risks of cannabis consumption in pregnancy, although we expect this to be minimal.

Fourth, observational studies are often beset by residual confounding bias. Despite employing a robust matching strategy to achieve balance in our cohort across critical potential confounders, residual confounding due to unmeasured confounders may remain. The interpretation of the associations should be cautious. Finally, ASD and other outcomes, including ADHD, can be misdiagnosed. Although we used validated case-finding algorithms that are accurate for population-level comparisons[25], identification of these conditions is likely to be correlated with access to care and identification within the school system.

Among pregnant women in Ontario, cannabis use was associated with an increased risk of neurodevelopmental disorders by age 10. Further study is needed on the amount and timing of cannabis use in pregnancy and childhood health outcomes and following the legalization of cannabis in many jurisdictions. Moreover, novel analytical approaches to addressing potential residual confounding bias in this area are required.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-020-1002-5.

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Methods

We follow Strengthening the Reporting of Observational Studies in Epidemiology to report the methodology of this retrospective cohort study.

Ethical approval and record linkage. Research ethics board approval for this study was obtained from the Ottawa Health Science Network Research Ethics Board and the Children's Hospital of Eastern Ontario. We designed the study cohort using a linkage between Ontario's provincial birth registry with health administrative databases. Analyses were conducted at the Institute for Clinical Evaluative Sciences (ICES), an independent organization for evaluating and improving Ontario's health care services. ICES holds legal status under Ontario's health information privacy law to collect and analyze health care and demographic data without consent. ICES acts as a secure repository for Ontario's perinatal database and provincial health administrative databases, with the ability to deterministically link individual patient health information across databases using unique encoded identifiers to protect privacy and confidentiality.

Data sources. The BORN Ontario birth registry captures all hospital births >500 g or >20 weeks' gestation occurring in the province. The routine data collection includes information on maternal demographics and health behaviors, preexisting health problems, obstetric complications and birth outcomes. Data are collected from medical records, clinical forms and patient interviews when a woman is admitted to the hospital to give birth. An ongoing program of data quality checks and formal training sessions assures a high level of data quality.

The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) is a service-based, national healthcare 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 data, 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.

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

The Ontario Health Insurance Plan (OHIP) Claims Database, maintained by ICES, includes all physician claims reimbursed by the Ontario Ministry of Health. This database records the underlying reason for physician visit on each claim, and ICD diagnostic codes and OHIP fee service codes are applied for diagnostic and clinical consultation services. This database was used to ascertain childhood outcomes using validated diagnostic codes and case-finding algorithms for determining outcomes.

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

Study design and participants. The study is a population-based, retrospective cohort design. The study population includes singleton live births between 1 April 2007 and 31 March 2012, born to women between the ages of 16 and 50 years who were continuously eligible for Ontario health insurance in the 2 years before pregnancy. Children born to non-Ontario residents, those without a valid health card number and those who died before the age of 18 months (4 years for secondary outcomes) were excluded.

Exposure. BORN collects information on cannabis use in pregnancy during routine prenatal care for mothers. A standardized perinatal record is completed for all pregnant women in Ontario by their obstetrician, family physician or midwife. At the first prenatal visit (usually occurring between 8 and 12 weeks' gestation), women are asked about any substance use in the current pregnancy. The question is recorded as 'yes, use of cannabis' or 'no' for the current pregnancy. Data from the perinatal record are abstracted into the birth registry. Cannabis exposure is also captured from clinical histories obtained from patients at admission to the hospital for labor/delivery and recorded in the birth registry. Our previous analyses found that reported cannabis use in the birth registry had a sensitivity of 97% (95% CI: 93–99) and a specificity of 94% (91–96) compared to clinical records, and the positive predictive value was 90% (85–94)[22].

Outcomes. All diagnoses were taken from ICES databases. We used definitions of outcomes undertaken and validated in ICES studies for ASD, ADHD and intellectual disabilities and learning disorders[25,27–31]. Because diagnoses would not typically be made in the first few years of life, we considered children at risk for ASD only after 18 months of follow-up, and only after 4 years for secondary outcomes. This approach has been taken in other population-based cohort studies of neuropsychiatric outcomes using follow-up in health administrative registries[32].

The primary outcome was ASD diagnosed after 18 months. Diagnoses were recorded up to 31 March 2017, when children could be a maximum of 10 years of age. We define ASD as at least two outpatient diagnoses by either a pediatrician or psychiatrist or at least one diagnosis in hospital databases, or both. This definition has been used previously[27], and has been shown to have a positive predictive value of up to 87% (ref. [28]). Secondary neurodevelopmental outcomes included (1) intellectual disability and learning disorders, and (2) ADHD and conduct disorders. Using methods previously validated previously[25,30], we measured secondary outcomes using diagnosis codes in hospital discharges from all acute care psychiatric and nonpsychiatric hospitals, and comprehensive outpatient databases. The specific algorithm for determining these outcomes was at least one hospital diagnosis or two or more outpatient diagnoses from a pediatrician, psychiatrist or physician after 4 years of age (associated diagnostic codes are provided in Supplementary Table 7)[25,31].

Covariates. Baseline characteristics and covariates were measured using data variables from BORN and the hospital administrative databases. Maternal age at delivery was derived from the dates of birth and delivery. Area-level income and education information was extracted from the Canadian Census based on standard geographical units assigned by postal code[26]. Preexisting maternal medical conditions (diabetes, hypertension, asthma and heart disease) were defined using validated ICES-derived cohorts[33,34]. Psychiatric disorders included any inpatient hospital or outpatient encounters occurring within 2 years before conception (Supplementary Table 1). Parity, antenatal care, smoking, alcohol use and other drug use (including cocaine, hallucinogens, methadone, opioids and prescription medication) were included as potential confounders from BORN. Drug and substance use is captured as 'yes, use of substance' or 'no' for the current pregnancy and recorded at the first prenatal visit. Pregnancy complications (gestational diabetes, gestational hypertension, preeclampsia, eclampsia, placental complications) and gestational age at birth were obtained from the BORN database. Missingness in covariates was limited, and no single covariate exceeded 5% of missing data.

Statistical analyses. We compared women who used cannabis during pregnancy with nonusers across all baseline characteristics using SMD[35], and considered SMD > 10% as indicative of a meaningful difference across groups[36]. We assessed covariate balance using the L_1 statistic[37], defined between 0 (perfect covariate balance between users and nonusers) and 1 (complete separation of covariates between users and nonusers). We used matching methods to reduce imbalance and account for potential confounding.[38] Specifically, we used CEM methods to generate a matched cohort of cannabis users and nonusers across covariates. CEM involves two steps before running statistical analyses. First, we categorized covariates as presented in Table 1. Next, we matched cannabis users to nonusers within strata representing unique combinations of the covariate categories. We excluded any strata with 0 cannabis users or 0 nonusers. We selected all available controls for matching and generated a weighted covariate distribution for nonusers normalized to match the users' distribution. The proportion of missing data in covariates was small, and no imputation was conducted. However, we modeled the missing data as a separate category within our matching algorithm, and these cases were retained in the analyses. We fit Cox proportional hazard regression models accounting for matching weights to estimate the HR for primary and secondary outcomes associated with maternal cannabis use. We report associations with 95% CIs. We used two-sided tests with the criterion for statistical significance set at $\alpha = 0.05$. Crude analyses are presented for the unmatched cohort for each outcome.

Subgroup analyses were conducted in the matched cohort, which examined the association of cannabis use on primary and secondary outcomes in a restricted sample of women who reported cannabis use but no use of alcohol, tobacco, cocaine, hallucinogens, methadone, opioids or prescription medication in pregnancy. Also, because socioeconomic status is related to substance use in pregnancy[1] and neurodevelopment outcomes[39], it may confound the cannabis–outcome association. To disentangle this potential confounder, we conducted stratified analyses by area-level income quintile and tested for statistical interaction in the association with the primary outcome across income levels. To account for prematurity, we conducted a stratified analysis of the primary outcome for deliveries occurring before 37 weeks and 37 or more weeks. Datasets were linked using unique encoded identifiers and analyzed at ICES. Statistical analyses were conducted in SAS (v.9).

Reporting Summary. Additional information on research design is available in the Nature Research Reporting Summary.

Data availability

The dataset from this study is held securely in coded form at ICES. While data-sharing agreements prohibit ICES from making the dataset publicly available,

access may be granted to those who meet prespecified criteria for confidential access, available at https://www.ices.on.ca/DAS. The full dataset creation plan is available from the authors upon request.

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Author contributions

D.J.C., M.W., D.F. and H.H. contributed to the conception, design, analysis and interpretation. D.J.C. wrote the manuscript. J.D. and E.S. performed all statistical analyses with contributions from S.H. and D.F. D.E.-C., L.B. and S.W.W. contributed to data interpretation and critical revisions of the manuscript. D.J.C. served as principal investigator.

Competing interests

No authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to D.J.C.

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Software and code

Policy information about availability of computer code

Data collection	No commercial, custom use or open source code/software was used in this manuscript
Data analysis	Statistical analyses were performed with SAS software (version 9)

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All studies must disclose on these points even when the disclosure is negative.

Study description	This is a quantitative, population-based retrospective cohort study.
Research sample	The study population includes singleton, live births, which occurred between April 1st, 2007 and March 31st, 2012, born to women between the ages of 16 and 50 and who were continuously eligible for Ontario health insurance in the 2 years before pregnancy. Children born to non-Ontario residents, those without a valid health card number, and those who died before the age of 18 months (4 years for secondary outcomes) were excluded from primary analyses.
Sampling strategy	The sample includes birth registry data from Ontario, Canada with nearly complete capture of every pregnancy and birth in the province.
Data collection	This study was conducted at the Institute for Clinical Evaluative Sciences (ICES), a non-profit research organization with Prescribed Entity status under provincial privacy legislation. ICES acts as a secure repository for Ontario's perinatal database and provincial health administrative databases, with the ability to deterministically link individual patient health information across databases using unique encoded identifiers to protect privacy and confidentiality.
Timing	Singleton, live births, which occurred between April 1st, 2007 and March 31st, 2012, with follow-up of children until March 31, 2017.
Data exclusions	We excluded mothers outside the ages of 16 to 50 years and those who did not reside in Ontario for 2 years prior to pregnancy. Children born to non-Ontario residents, those without a valid health card number, and those who died before the age of 18 months (4 years for secondary outcomes) were excluded. We excluded participants if linkage with health administration databases was incomplete. We excluded stillbirths, multi-fetal pregnancies, and infants with missing gestational age.
Non-participation	This study used follow-up of participants through administrative data linkages, was population-based, and involved no individual-level recruitment.
Randomization	This is a retrospective study and randomization was not preformed.

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We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

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Methods

n/a	Involved in the study
☒	☐ ChIP-seq
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Population characteristics	Following exclusions, the final cohort was based on 508,025 births. Children who lost Ontario Health Insurance eligibility or died prior to 18 months (n=4,960) or 4 years (n=10,204) of age were excluded from the primary analyses of autism spectrum disorder (ASD) and secondary analyses of neurodevelopmental outcomes, yielding analytical cohorts of 503,065 and 497,821, respectively (Table B1). The mean age of mothers was 30.1 years (SD 5.6), the mean gestational age at delivery was 38.9 weeks (SD 1.7), and 51.4% of children were male. The rate of reported cannabis use in pregnancy was 0.6%.
Recruitment	This study used follow-up of participants through administrative data linkages, was population-based, and involved no individual-level recruitment.

Ethics oversight	Research ethics board approval for this study was obtained from the Ottawa Health Science Network Research Ethics Board and the Children's Hospital of Eastern Ontario.

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Clinical trial registration	n/a
Study protocol	The full study protocol and data creation plans are available from the corresponding author.
Data collection	Births occurred between April 1st, 2007 and March 31st, 2012, with follow-up of children until March 31, 2017. Data were analyzed between July 2018 and December 2019
Outcomes	All diagnoses were taken from ICES databases. We used definitions of outcomes which have been undertaken and validated in ICES studies for autism spectrum disorder, attention deficit hyperactivity and conduct disorders, and intellectual disabilities and learning disorders. As diagnoses would not typically be made in the first several years of life, we considered children at risk of for autism spectrum disorder only after 18 months of follow up, and only after 4 years for secondary outcomes. This approach has been taken in other population-based cohort studies of neuropsychiatric outcomes using follow up in health administrative registries. The primary outcome was autism spectrum disorder diagnosed after 18 months. Diagnoses were recorded up to March 31, 2017, when children could be a maximum of 10 years of age. We define autism spectrum disorder as at least two outpatient diagnoses by either a pediatrician or psychiatrist or at least one diagnosis in hospital databases, or both. This definition has been used previously, and has been shown to have a positive predictive value of up to 87%. Secondary neurodevelopmental outcomes included: 1) intellectual disability and learning disorders and 2) attention-deficit/hyperactivity and conduct disorders. Using methods which have been validated previously, we measured the secondary outcomes using diagnosis codes in hospital discharges from all acute care psychiatric and non-psychiatric hospitals, and comprehensive outpatient databases. The specific algorithm for determining these outcomes was at least one hospital diagnosis or two or more outpatient diagnoses from a pediatrician, psychiatrist, or physician after 4 years of age (associated diagnostic codes are presented in the supplemental appendix, Table B7).