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ORIGINAL RESEARCH ARTICLE

Cannabis exposure during pregnancy and perinatal outcomes: A cohort study

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Abstract

Introduction: Cannabis potency and its use during pregnancy have increased in the last decade. The aim of this study was to investigate the impact of antenatal cannabis use on fetal growth, preterm birth and other perinatal outcomes.

Material and methods: A propensity score-matched analysis was performed in women with singleton pregnancies attending a tertiary care site in Barcelona. Women in the cannabis group were selected based on the results of a detection test. Primary outcomes were small for gestational age at birth (SGA), low birthweight and preterm birth. Secondary outcomes were other biometric parameters (neonatal length and head circumference), respiratory distress, admission to the neonatal intensive care unit and breastfeeding at discharge. A second propensity score-matched analysis excluding other confounders (use of other recreational drugs and discontinuation of cannabis use during pregnancy) was performed.

Results: Antenatal cannabis was associated with a higher odds ratio of SGA (OR 3.60, 95% CI: 1.68–7.69), low birthweight (OR 3.94, 95% CI: 2.17–7.13), preterm birth at 37 weeks (OR 2.07, 95% CI: 1.12–3.84) and 32 weeks of gestation (OR 4.13, 95% CI: 1.06–16.11), admission to the neonatal intensive care unit (OR 1.95, 95% CI: 1.03–3.71), respiratory distress (OR 2.77, 95% CI: 1.26–6.34), and lower breastfeeding rates at discharge (OR 0.10, 95% CI: 0.05–0.18). When excluding other confounders, no significant association between antenatal cannabis use and SGA was found.

Conclusions: Antenatal cannabis use increases the risk of SGA, low birthweight, preterm birth and other adverse perinatal outcomes. However, when isolating the impact of cannabis use by excluding women who use other recreational drugs and those who discontinue cannabis during pregnancy, no significant association between antenatal cannabis use and SGA birth was found.

Abbreviations: LBW, low birthweight; NICU, neonatal intensive care unit; PSM, propensity score-matched; SGA, small for gestational age; THC, Δ9-tetrahydrocannabinol.

Maia Brik and Miguel Sandonis contributed equally to the study.

KEYWORDS
birthweight, cannabis, fetal growth, preterm birth, recreational drugs, small for gestational age

1 | INTRODUCTION

Cannabis is the recreational drug with the highest use rate among pregnant women. Although the amount of data on pregnant women is too limited to estimate the actual use rate, in a study, analyses of meconium from neonates showed the presence of cannabis in 5.3% of cases,[1] similar to the figure reported in other studies (4.5%).[2] In addition, in the last two decades there has been an increase in the cannabis potency.[3] Cannabis treatment is also common among epileptic women of childbearing age with a good safety profile.[4] Cannabis is an increasingly accepted recreational drug and has become widely available following cannabis liberalization. In this context, regulations and prevention programs addressed at pregnant women remain inadequate.

Pregnant women may justify cannabis use for treating nausea, vomiting, pain, and other pregnancy symptoms.[5,6] Nevertheless, cannabis use during pregnancy is a public health concern, since it increases adverse perinatal outcomes[7] as well as childhood developmental, and mental disorders.[8] Antenatal cannabis use may lead to a higher risk of mood and behavioral disorders, affective mental disorders, depression symptoms, and attention deficit and hyperactivity disorder in the infant and later in life.[7–9]

Cannabis use during pregnancy can impact fetal development and, although this impact may be subtle at first and may not be detectable for months to years after birth, its physical and psychopathological consequences on adult life may be severe. Evidence of the impact of antenatal cannabis use on the infant is ample, but unclear.[5]

Antenatal cannabis use has been suggested as a contributing factor for low birthweight and admission to the neonatal intensive care unit (NICU). However, published data on fetal growth and preterm birth associated with antenatal cannabis use are inconsistent.[5,7,8,10] In studies focused on cannabis use, several confounders may have biased the results. The most relevant confounders are the use of other recreational drugs, tobacco or alcohol, discontinuation of cannabis during pregnancy, and frequency of cannabis use. In addition, the control-selection bias is a relevant fact that should be controlled.[5]

The aim of this study was to add new data to the potential association between antenatal cannabis use and adverse perinatal outcomes, such as fetal growth and preterm birth.

Key Message

The novel finding of this propensity score-matched study is that cannabis use during pregnancy in women that are not using other recreational drugs is associated with an increased risk of preterm birth.

2 | MATERIAL AND METHODS

2.1 | Study design and population

This was a retrospective cohort study, including a propensity score matched (PSM) analysis. The eligibility criteria were singleton pregnancies with at least one ultrasound scan performed at Vall d'Hebron Hospital from January 2013 to December 2021 (9-year period), and complete follow-up data. Data was recorded while performing the ultrasound scan and after birth. Data included information about the pregnancy, delivery and the immediate postpartum.

From all eligible women ($n = 23\,522$), those who delivered from 24 to 42 weeks of gestation were selected, and those with uncomplete data, fetal death, late termination of pregnancy or late miscarriage ($n = 10\,884$) were excluded. Therefore, the total study population included a total of 12 638 participants. Our hospital, being a tertiary care site, performs many ultrasound scans for women that give birth at different sites across the country; therefore, it is difficult to obtain birth data for all patients.

The following patient characteristics were recorded: maternal age, maternal body mass index before pregnancy, parity, ethnicity (Caucasian, non-Caucasian), use of other recreational drugs (cocaine, opioids), and alcohol use. The use of other recreational drugs was defined either as self-reported during pregnancy or by using a urine analysis determination.

Two populations were included in the study: (1) antenatal cannabis users, and (2) controls. To establish cannabis use, a quantitative analysis of Δ9-tetrahydrocannabinol (THC) in a urine sample using an enzyme immunoassay was performed in those who self-reported cannabis use. This test is routinely performed with the consent of the pregnant woman whenever cannabis use is self-reported at any point during the pregnancy. Individuals who did not report antenatal cannabis use during the first trimester were included in the control group.

The main outcome variables were small for gestational age (SGA) at birth, low birthweight (LBW) and preterm birth. SGA was defined as a birthweight below the 10th percentile,[11] LBW was defined as a birthweight below 2500 g, and preterm birth was defined as delivery before 37 weeks of gestation, with cutoff points at 32 and 28 weeks of gestation.

Secondary outcome variables included gestational age at delivery, cesarean section, birthweight, neonatal length and head circumference, 5-min Apgar score, admission to the NICU, respiratory distress and breastfeeding at discharge. These data were collected after the PSM analysis, which included data for cannabis users and controls.

Neonatal length and head circumference percentiles were calculated adjusting for gender and gestational age at delivery, following the Spanish pediatric population calculator.[12] Breastfeeding rates after delivery were recorded at hospital discharge.

A second PSM analysis was performed where participants who used other recreational drugs and those who discontinued cannabis use during pregnancy were excluded. Cannabis discontinuation was confirmed by a negative THC urine test in the third trimester or at birth. The aim of this second PSM analysis excluding confounders was to isolate the effect of antenatal cannabis use on the main outcomes.

2.2 | Data sources/measurement

Data were obtained using the Viewpoint software (GE®) for obstetrics ultrasound and cross-matched with the electronic medical records (SAP®). For pregnant women who did not give birth at our site, data was collected from the shared medical history system at Institut Català de la Salut, if available. A case record data was created at the local hospital Information Technology system for data management. Participant's names were codified and only study researchers had access to the files and codes.

2.3 | Statistical analyses

Descriptive data are expressed as the mean, standard deviation and interquartile range and as percentages (absolute and relative frequencies). Comparisons between the groups were performed using the Mann–Whitney U test or the two-tailed chi-squared test, as appropriate.

As the aim of the study was to investigate the effect of antenatal cannabis use on perinatal outcomes, and patient characteristics were different between the study groups, we used a PSM analysis to compare risk of perinatal outcomes in groups with and without antenatal cannabis use after controlling for potential confounders related with the outcome that were unequally distributed among the cannabis and non-cannabis group. In brief, for the PSM analysis, we first calculated the probability of a patient to use cannabis during pregnancy according to several characteristics of the patient. This probability is calculated using a multivariate logistic regression with "use of cannabis" as the outcome and all available potential confounders as covariates (parity, ethnicity, maternal age, gravidity and body mass index). These variables were firstly selected because of their association with preterm birth and fetal growth. The regression analysis is shown in Appendix S1. Each cannabis user was matched with two controls (ratio 1:2) from the general population sample who had the same probability of being a cannabis user. We also accepted cases only if the difference in the propensity score between matched cases was small (caliper of 0.1). The distribution of confounders was compared before and after matching, showing an excellent balance between cannabis and non-cannabis cases. A conditional logistic regression was performed to calculate the relationship between matched and non-matched cases. A total of 330 participants were matched. After matching we compared the main outcomes using a univariate logistic regression analysis fitted by generalized estimating equations for paired samples to account for matched data.

Statistical analyses were conducted by the Statistics and Bioinformatics Unit (UEB) of Vall d'Hebron Research Institute (VHIR). All analyses were performed with the R statistical software (Foundation for Statistical Computing, Vienna, Austria). The MatchIt R package was used for matching. A type I error of 5% was assumed.

3 | RESULTS

3.1 | Main outcome of the study population

From 12 638 pregnant individuals, 12 504 did not use cannabis during pregnancy, and 134 used cannabis during pregnancy. Figure 1 shows the patient's flow diagram. Therefore, the prevalence of cannabis use in the study population was 1.06%. Maternal characteristics and main outcomes of the study population, according to cannabis use during pregnancy, are shown in Table 1. Among women using cannabis, 24.6% (33/134, 95% CI: 17.6–32.8) used other recreational drugs, such as cocaine or opioids, or alcohol. Also, among women using cannabis during pregnancy in the first trimester, 23.1% (31/134, 95% CI: 16.3–31.2) discontinued use during pregnancy.

3.2 | Propensity score matching

In the cannabis group, 111 participants were included in the PSM matching. For one case, no controls matched were found, and for one case, only 1 control matched was found. In the PSM analysis, 111 participants from the cannabis group and 219 in the control group were included.

Figure 2 shows the standardized differences between cases (cannabis use) and controls groups before and after matching. Standardized differences for all covariates were significantly reduced after matching. Therefore, PSM analysis significantly improves the comparability between the case and controls.

3.3 | Estimating the association of antenatal cannabis use with small for gestational age, low birthweight and preterm birth after matching

Table 2 shows statistical data for the main outcomes in cases and controls, before and after matching. Antenatal cannabis use was associated with a higher odds ratio of SGA (OR 3.60, 95% CI: 1.68–7.69), LBW (OR 3.94, 95% CI: 2.17–7.13), preterm birth at 37 weeks of

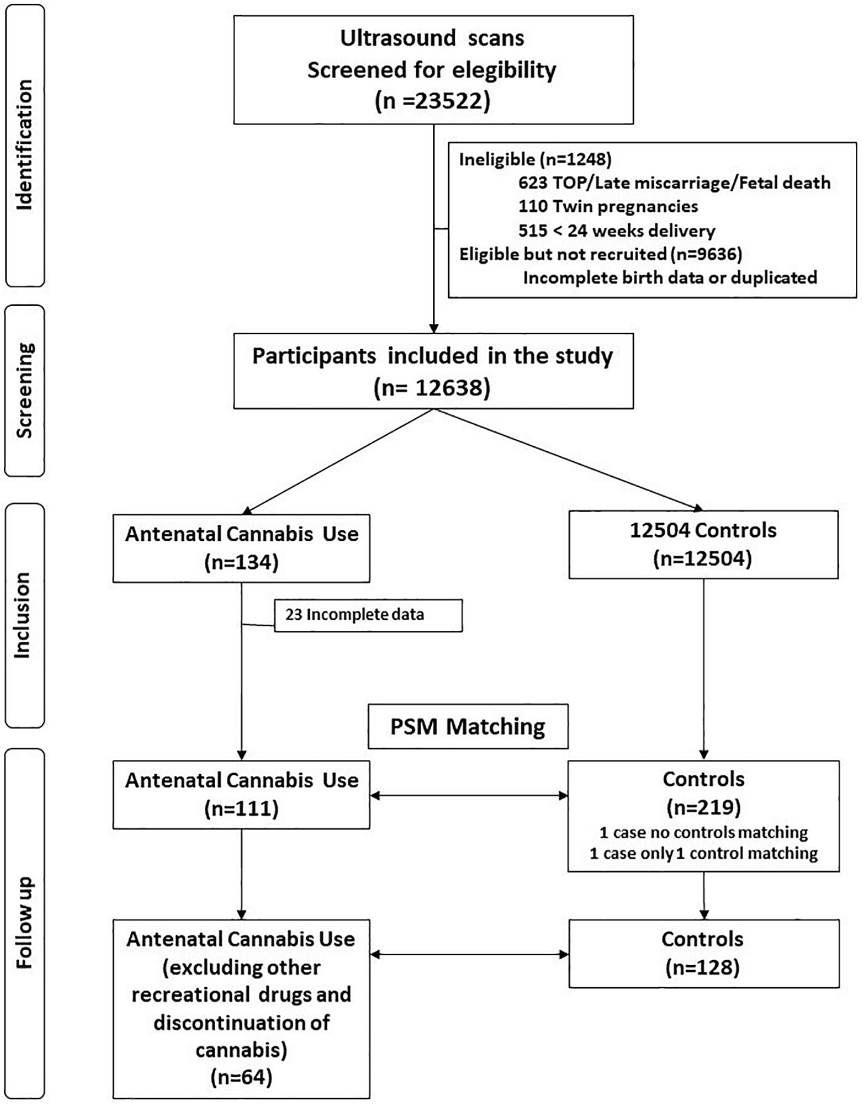

FIGURE 1 Patient flow diagram.

gestation (OR 2.07, 95% CI: 1.12–3.84), and preterm birth at 32 weeks of gestation (OR 4.13, 95% CI: 1.06–16.11), as shown in Figure 3.

3.4 | Subgroup analysis

In order to investigate the isolated effect of cannabis use, a second PSM analysis, which excluded participants who discontinued cannabis use during pregnancy and those who used other recreational drugs, was performed. Subsequently, after excluding these confounders, standardized differences between the cases and controls before and after matching were calculated (Appendix S2).

Table 2 shows statistical data for the main outcomes in the cannabis and control groups, before and after matching. In the PSM analysis, 64 participants in the cannabis group and 128 from the control group were included. Antenatal cannabis use was associated with a higher odds ratio of preterm birth at 37 weeks of gestation (OR 2.47, 95% CI: 1.04–5.88) and LBW (OR 3.71, 95% CI: 1.67–8.27). No significant association between cannabis use and SGA was found.

3.5 | Estimating the association of antenatal cannabis use with other perinatal outcomes after matching

Antenatal cannabis use was associated with an increased odds ratio of admission to the NICU (OR 1.95, 95% CI: 1.03–3.71), respiratory distress (OR 2.77, 95% CI: 1.26–6.34), and lower breastfeeding rates at discharge (OR 0.10, 95% CI: 0.05–0.18). In addition, antenatal cannabis use is a predictor for lower biometric parameters (birthweight, length and head circumference), and lower gestational age at delivery (Table 3).

4 | DISCUSSION

First, cannabis use during pregnancy increases the risk of SGA, LBW, and preterm birth. Second the effect of antenatal cannabis use on SGA risk is confounded by the use of other recreational drugs and cannabis discontinuation use during pregnancy. Third, antenatal cannabis use increases the risk of NICU admission, respiratory distress and formula feeding at discharge.

TABLE 1 Maternal characteristics and main outcomes in the study population according to cannabis use before matching ($N = 12\,638$).

	Control group ($n = 12\,504$)	Cannabis group ($n = 134$)	p
Maternal age	31.3 (6.1) [31.2; 31.4]	28.2 (5.9) [27.2; 29.3]	<0.001
Parity			
Nulliparous	6634 (53.1%) [52.2; 53.9]	69 (51.5%) [42.7; 60.2]	
Multiparous	5870 (46.9%) [46.1; 47.8]	65 (48.5%) [39.8; 57.3]	0.784
Ethnicity			
Caucasian	10 793 (86.3%) [85.7; 86.9]	110 (82.1%) [74.5; 88.2]	
Non-Caucasian	1711 (13.7%) [13.1; 14.3]	24 (17.9%) [11.8; 25.5]	0.198
Body mass index before pregnancy	12 504 25 (5.1) [24.9; 25.1]	114 22.6 (5.7) [21.5; 23.6]	<0.001
Birthweight (g)	3171.3 (588.8) [3160.9; 3181.6]	2723.6 (664.7) [2610; 2837.2]	<0.001
Small for gestational age	1141 (9.1%) [8.6; 9.6]	28 (20.9%) [14.4; 28.8]	<0.001
Low birthweight <2500 g	1337 (10.7%) [10.2; 11.2]	45 (33.6%) [25.7; 42.2]	<0.001
Preterm birth at 37 weeks of gestation	1227 (9.8%) [9.3; 10.3]	31 (23.3%) [16.4; 31.4]	<0.001
Preterm birth at 32 weeks of gestation	193 (1.5%) [1.3; 1.8]	9 (6.8%) [3.1; 12.5]	<0.001
Preterm birth at 28 weeks of gestation	48 (0.4%) [0.3; 0.5]	2 (1.5%) [0.2; 5.3]	0.097

Note: mean (SD) [95% CI mean] or *n* (%) [interquartile range].

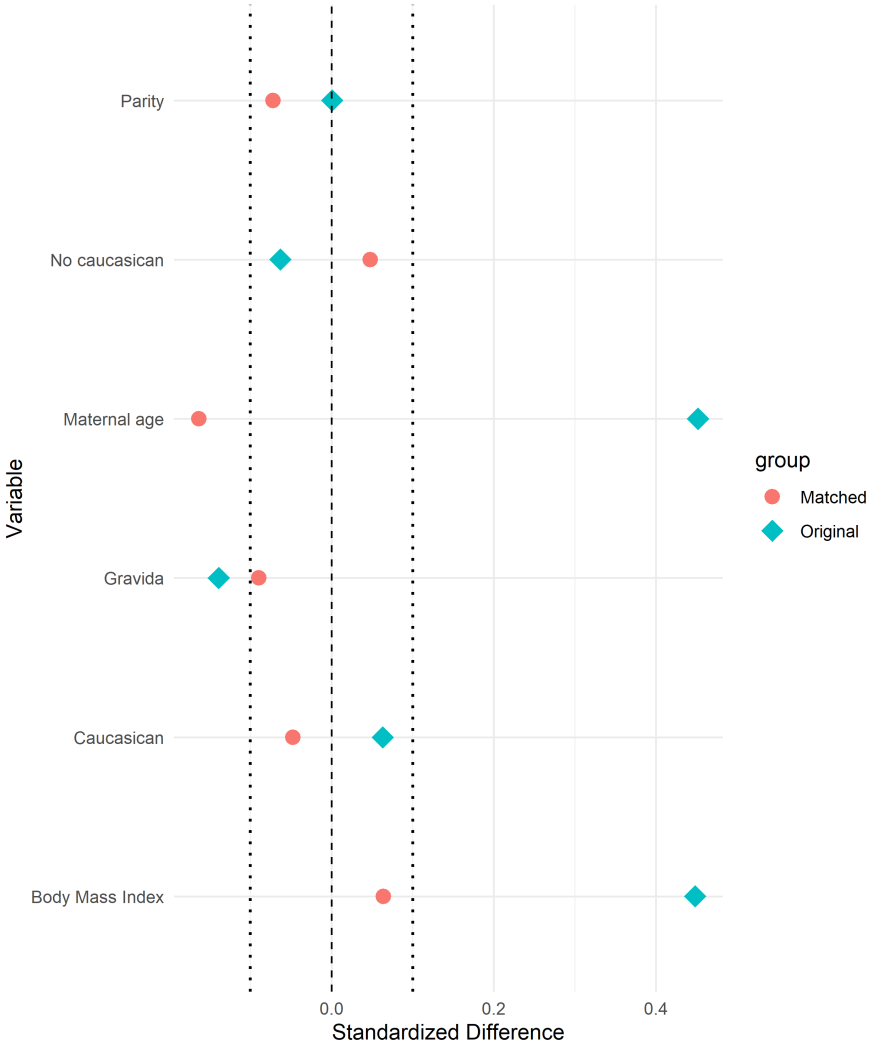

FIGURE 2 Standardized differences between the cannabis and control groups before and after propensity score matching.

TABLE 2 Antenatal cannabis exposure and perinatal outcomes (preterm birth, low birthweight below 2500 g and small for gestational age) after the propensity score matching analysis.

	Control	Antenatal cannabis	Antenatal cannabis			
	N = 12 504	*N* = 134	Original sample		Sample after matching	
	n/frequency		Crude OR	95% CI	Adjusted OR*	95% CI
PTB37	1227 (9.8)	31 (23.3)	2.75	1.73–2.41	2.07	1.12–3.84
PTB32	19.3 (1.5)	9 (6.8)	4.21	1.76–8.53	4.13	1.06–16.11
LBW	1337 (10.7)	45 (33.6)	4.40	2.95–6.47	3.94	2.17–7.13
SGA	1141 (9.1)	28 (20.9)	2.54	1.57–3.97	3.60	1.68–7.69
Subgroup analysis (excluding other recreational drugs and discontinuation of cannabis during pregnancy)						
	N = 12 504	*N* = 76	Original sample		Sample after matching	
	n/frequency		Crude OR	95%CI	Adjusted OR*	95% CI
PTB37	1227 (9.8)	19(25)	2.70	1.46–4.70	2.47	1.04–5.88
PTB32	193 (1.5)	7(9.2)	5.23	1.81–11.93	6.61	0.72–60.86
LBW	1337 (10.7)	27(35.5)	4.47	2.64–7.36	3.71	1.67–8.27
SGA	1141 (9.1)	14(18.4)	1.99	0.99–3.67	1.11	0.51–2.41

Abbreviations: CI, confidence interval; LBW, low birthweight below 2500 g; OR, odds ratio; PTB32, preterm birth below 32 weeks; PTB37, preterm birth below 37 weeks; SGA, small for gestational age at birth, defined as birthweight below 10th centile.

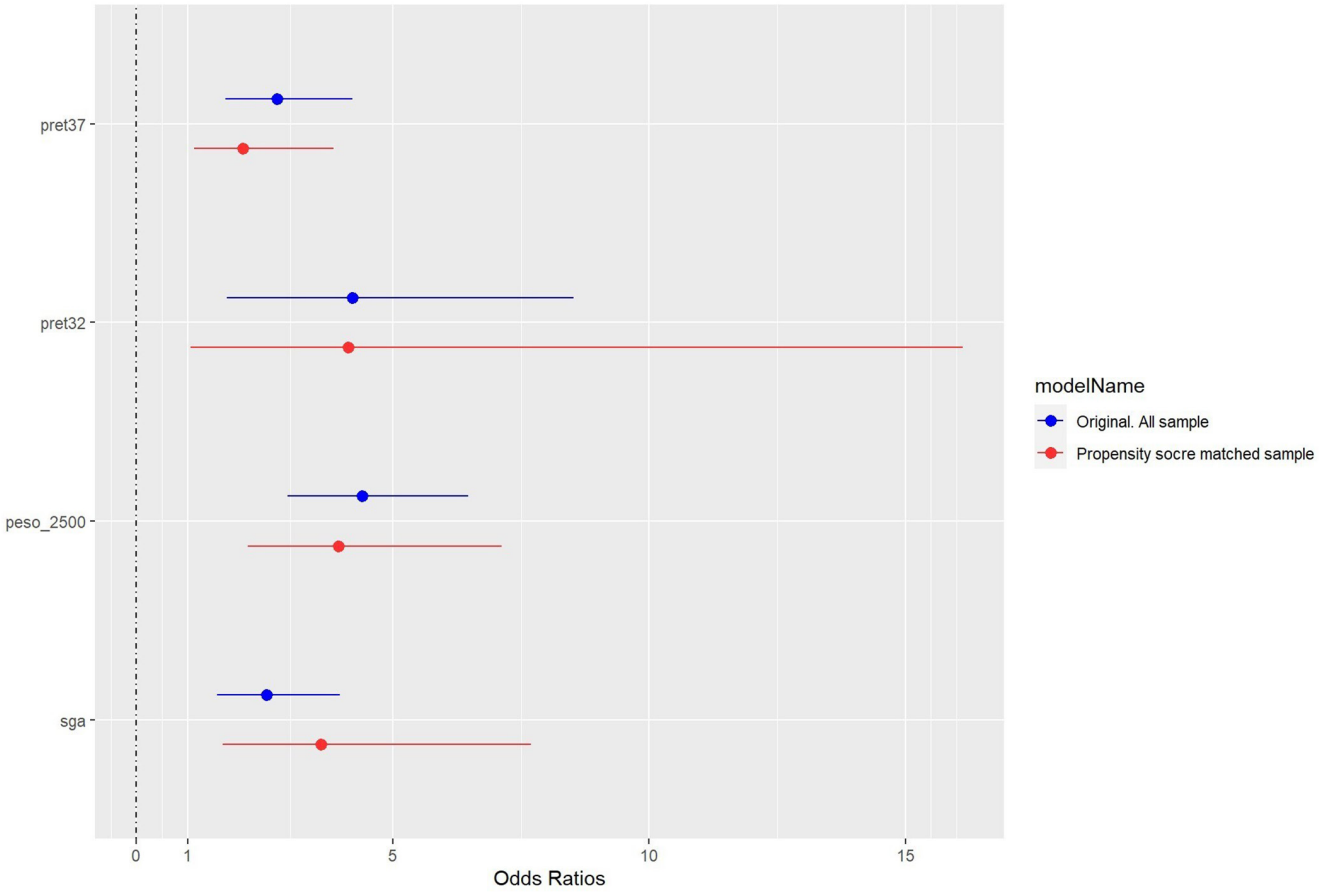

FIGURE 3 Associations between antenatal cannabis use and the main outcomes.

Women using cannabis during pregnancy differ from the general population in certain maternal characteristics.[5,13,14] In order to adjust for patient characteristics using a PSM analysis, a control group with comparable maternal characteristics, such as parity, ethnicity, body mass index and maternal age, was included. This improves the accuracy when estimating the effect of cannabis use during pregnancy.[15]

TABLE 3 Antenatal cannabis use and other perinatal outcomes after the propensity score matching analysis.

			Antenatal cannabis	
	Control	Antenatal cannabis	Sample after matching	
Perinatal outcomes	*N* = 219	*N* = 111	OR	95% CI
Gestational age at delivery	38.4 (2.2)	37.5 (2.9)	−0.91	−1.49 to −0.33
Cesarean section	57 (27.3%)	28 (25.2%)	0.90	0.53 to 1.51
Birthweight	3134 (597)	2731 (674)	−402.49	−546.76 to −258.21
Birthweight percentile	49.1 (29.2)	32.4 (28.9)	−16.76	−23.48 to −10.04
Birthweight below the 10th percentile	25 (11.9)	34 (30.6)	3.27	1.84–5.89
Neonatal length	49 (3.4)	47.5 (3.6)	−1.44	−2.32 to −0.56
Neonatal length percentile	46.4 (30.8)	36.2 (32.5)	−10.18	−18.16 to −2.20
Head circumference	33.6 (3.5)	33 (1.9)	−0.60	−1.27 to 0.07
Head circumference percentile	43 (25.2)	33.8 (28.3)	−9.19	−15.84 to −2.54
5-min Apgar score below 7	3 (1.7%)	4 (3.7%)	2.23	0.48 to 11.53
Admission to the neonatal intensive care unit (NICU)	22 (12.5%)	24 (21.8%)	1.95	1.03 to 3.71
Respiratory distress	11 (6.2%)	17 (15.6%)	2.77	1.26 to 6.34
Breastfeeding rate at discharge	156 (89.1%)	49 (44.5%)	0.10	0.05 to 0.18

Note: *n* (%), mean (SD).

Abbreviatons: CI, confidence interval; OR, odds ratio; SD, standard deviation.

Regarding preterm birth, a large meta-analysis showed no increase on preterm birth risk with antenatal cannabis use.[5,7] In addition, in a large population-based study supporting an increased risk for preterm birth with self-reported cannabis use during pregnancy, after adjusting for the use of alcohol, tobacco and other recreational drugs, antenatal cannabis use showed an association with preterm birth.[16] However, this association has not been found in cases with a positive THC test.[17] Our results shows an increased risk of preterm birth with antenatal cannabis use.

Previous studies have reported the effect of antenatal cannabis use on fetal growth, showing discrepant results.[5,7,10,18] Some meta-analyses have reported that fetal exposure to cannabis led to LBW, defined as a birthweight below 2500 g (OR 1.77; 95% CI: 1.04–3.01).[7,19] Other studies did not adjust for confounders, such as the use of other recreational drugs or cannabis discontinuation during pregnancy. In our study, when isolating the effect of cannabis use by adjusting for these confounders, the OR for LBW was higher than the value reported in the literature.[7] However, no association with SGA was found in this subgroup, which may be explained by the higher OR for preterm birth in this subgroup. We included SGA as a more accurate outcome for determining fetal growth, since SGA includes gestational age at birth and neonatal gender.

Antenatal cannabis impacts other biometrical parameters when adjusted for gender and gestational age at birth. These results are consistent with previously reported data.[20,21]

Abnormalities in fetal growth with antenatal cannabis use are biologically plausible, since cannabinoids can freely cross the placenta. In vivo studies have demonstrated a THC fetal/maternal steady-state plasma concentration ratio below one third,[22] and about one fifth for Cannabidiol (CBD).[23] Two cannabinoid receptors have been described: CB_1 and CB_2.[24] Endogenous cannabinoids, similarly to exogenous THC, lead to a decreased vascular tone, increased blood pressure and increased vascular blood flow.[25,26] Antenatal cannabis use has been associated with an increase pulsatility index in the uterine artery blood flow during the third trimester.[27] This effect on maternal blood flow is also observed in cases with placental insufficiency associated with restricted intrauterine growth.[28]

In women using cannabis during pregnancy, health care providers should advice about the increased risk of adverse perinatal outcomes. In this scenario, strategies promoting abstinence during pregnancy by a multidisciplinary team (mental health specialists, obstetricians, midwives, neonatologists, and social workers), and a fetal growth assessment by ultrasound during pregnancy, should be offered.

The results of the presents study pave the way for future studies evaluating dishabituation strategies based on clinical data of cannabis related poor perinatal outcomes, and long-term studies on the impact of antenatal cannabis use on the infant.

The main limitation of this study was the fact that tobacco use was not included as a confounder, since data for tobacco use in cannabis users was not reliable. However, about 48% of cannabis users mix cannabis with tobacco,[29] and the impact of tobacco on fetal growth for cannabis users during pregnancy has been studied with discrepant results.[30,31] A second limitation of this study is the underestimation of cannabis use prevalence, estimated at around 5% at birth.[1] This underestimation of cannabis use prevalence may be due to use being self-reported and the retrospective nature of the study. A third limitation is that certain information about cannabis use history, such as patterns of use, type of cannabis product and

route of intake, was not included. However, a subanalysis was performed including those participants who continued to use cannabis during pregnancy.

In addition, although several confounders were considered in the PSM analysis, potential confounders such as educational level or socioeconomic status, also related to cannabis use,[32] were not considered due to lack of data.

On the other hand, we want to highlight the main strengths of the present research. First, in this study, a biological test was used for confirming cannabis use, as compared to previous studies,[5,7,8] where cannabis use was self-reported. Despite its limitations, detection of THC in urine rather than self-reported use of cannabis, is a more accurate screening method.[33]

Also, data was adjusted for confounders using PSM analysis, thus reducing the differences between cases and controls and making them more suitable for comparisons. This allowed the effect of antenatal cannabis use on perinatal outcomes. Additionally, in order to isolate the effect of cannabis use, we excluded participants who used other recreational drugs, and those who discontinued cannabis during pregnancy. Finally, another strength of our study was the fact that the research was conducted recently, which is relevant given the increased potency of cannabis in the last two decades.[3]

The findings of the study may not be applicable to women giving birth in other settings. The higher rate of missing data in mother-infant pairs may also impact the general applicability of the results.

5 | CONCLUSION

The results of the present study highlight that antenatal cannabis use increases the risk for SGA, LBW and preterm birth. However, when isolating the impact of cannabis use by excluding participants who used other recreational drugs and those who discontinued cannabis during pregnancy, no association with SGA was found.

AUTHOR CONTRIBUTIONS

Maia Brik: Conceptualization, methodology, term, investigation, data curation, drafting of the original draft, review and editing, supervision and project administration. Miguel Sandonis: Investigation, resources, drafting and edition of the review and visualization. Alina Hernández- Fleury: Investigation, resources drafting and edition of review and visualization. Judit Gil: Investigation, resources, drafting and edition of the review and visualization. Miriam Mota: Methodology, software, validation, formal analysis drafting and edition of the review. Francisco José Barranco: Resources, drafting and edition of the review and visualization. Itziar Garcia: Resources, drafting and edition of the review and visualization. Nerea Maiz: Methodology, resources, drafting and edition of the review and visualization. Elena Carreras: Methodology, resources, drafting and edition of the review, visualization, supervision and funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of Vall d'Hebron Research Institute (VHIR) on April 30, 2021 with study number PR (AMI)204/2021. Informed consent was waived since this was a retrospective study, evaluating routinely collected data, where no additional procedures or tests were performed for study purposes.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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