Research Article

Cannabis Use During Early Pregnancy and Child Diagnoses of Depressive and Anxiety Disorders

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ABSTRACT

Objective: Prenatal cannabis use is associated with adverse pregnancy and neonatal outcomes, but research on its association with child anxiety and depressive disorders is limited. This study aimed to test the hypothesis that prenatal cannabis use is associated with child anxiety or depressive disorder diagnoses. **Method:** Population-based retrospective birth cohort study of children (N= 115,553) born between 1/1/2011 –12/31-2017 to pregnant individuals (N = 97,376) universally screened for prenatal cannabis use. Cox proportional hazards regression models examined associations between cannabis use during early pregnancy (at ~8-10 weeks gestation based on self-reported use or a positive urine toxicology test for delta-9-tetrahydrocannabinol [THC]) and child anxiety and depressive disorders from ages 6 to 13 years based on diagnosis codes, adjusting for maternal sociodemographic and clinical characteristics. **Results:** The median age at pregnancy onset was 31 (inter quartile range [IQR] = 6) years. Most pregnancies (61.4%) were to non-White individuals; 4.4% screened positive for any cannabis use; 3.7% had a positive toxicology test and 1.9% self-reported use. Overall, 9,230 children were diagnosed with an anxiety disorder at median age of 8 (IQR = 3) years and 1,224 with depressive disorder at median age of 9 (IQR = 3) years. Prenatal cannabis use was associated with a lower risk of child anxiety disorders (aHR:0.84, 95%CI: 0.75-0.95), which remained significant when defined by a toxicology test but not by self-report. Maternal prenatal cannabis use was not associated with child depressive disorders (aHR:1.15, 95%CI: 0.85-1.54). **Conclusions:** Prenatal cannabis use during early pregnancy was not associated with an increased risk of offspring early onset anxiety or depressive disorders.

Key words: = mental health; depression; anxiety; marijuana; cannabis; pregnancy

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Rates of cannabis use during pregnancy are increasing in the US (Volkow et al., 2019)·(Young-Wolff, Chi, et al., 2024), paralleling the growing accessibility, social acceptability, and legalization of cannabis (DISA Global Solutions; Young-Wolff et al., 2022). Despite national guidelines advising against prenatal cannabis use ("Committee Opinion No. 722: marijuana use during pregnancy and lactation," 2017), pregnant individuals report using cannabis to manage morning sickness and mental health symptoms (Bayrampour et al., 2019; Chang et al., 2019; Foti et al., 2023).

Prenatal cannabis use crosses the placenta (Blackard & Tennes, 1984; Lee & Chiang, 1985) and is associated with increased risk of adverse neonatal outcomes, including low birth weight, small-for-gestational-age offspring, and preterm birth (Avalos, Adams, et al., 2024; Baia & Domingues, 2022; Lo et al., 2023). Emerging evidence also suggests an association between prenatal cannabis use and increased risk of adverse maternal outcomes and childhood outcomes, including attention and behavioral difficulties, although results remain mixed (Avalos, Oberman, et al., 2024; Avalos, Shenkute, et al., 2024; Bandoli et al., 2021; Chabarria et al., 2016; Cioffredi et al., 2022; Corsi et al., 2020; Corsi et al., 2019; De Genna et al., 2022; Fried & Watkinson, 1988, 1990; Fried et al., 1992; Garrison-Desany et al., 2022; Grant et al., 2020; Koto et al., 2022; Paul et al., 2021; Paul et al., 2023; Petrangelo et al., 2019; Sharapova et al., 2018; Sujan et al., 2022; Tchuente et al., 2022; Torres et al., 2020; Warshak et al., 2015; Young-Wolff, Adams, et al., 2024; Young-Wolff et al., 2025).

The endocannabinoid system (ECS) plays a critical role in healthy brain development and the regulation of emotional responses. ECS receptors (e.g., CB1 and CB2) are involved in neurotransmitter release and neural development. Cannabinoids, including tetrahydrocannabinol (THC) can interact with these receptors, and prior studies suggest that exposure to cannabis in utero may alter ECS and affect neural circuit development involved in stress regulation (Mulligan & Hamre, 2023). Importantly, while considerable research has focused on the relationship between prenatal cannabis exposure and neonatal outcomes or externalizing behaviors and attention-related issues in children, the association between prenatal cannabis and childhood anxiety and depressive disorders has been overlooked. A recent meta-analysis of initial studies found no association between prenatal cannabis use and child depression (adjusted pooled odds ratio [OR] = 0.72, 95% CI 0.11-4.57) or anxiety (adjusted pooled OR = 1.34, 95% CI 0.79-2.29; (Bassalov et al., 2024). Studies to date have limitations, including the use of older data, self-reported cannabis use, or a combined measure of prenatal and postpartum cannabis use. Furthermore, studies have relied on parent or child self-reported mental health symptoms rather than clinician-documented diagnoses.

Given potential underreporting of prenatal cannabis use (Young-Wolff et al., 2020) and the increasing strength of cannabis products (ElSohly et al., 2016), research that uses both self-report and toxicology testing to assess how prenatal cannabis use relates to clinician-documented diagnoses of child anxiety and depressive disorders is critically needed. In this large, retrospective cohort study, we tested the hypothesis that maternal prenatal cannabis use was associated with the development of early onset of anxiety and depressive disorders in their children born between 2011 and 2017, using data from pregnant individuals universally screened for cannabis use through self-report and urine toxicology testing.

METHODS

Setting and Sample

This study took place in Kaiser Permanente Northern California (KPNC), an integrated healthcare delivery system providing healthcare to >4.6 million patients representative of the insured population in the region. IRB approval was obtained from KPNC and the state of California (governing the use of birth certificate data) with a waiver of consent. STROBE reporting guidelines for cohort studies were followed.

We conducted a retrospective, longitudinal cohort study of pregnant individuals and their singleton children born at a KPNC facility between 1/1/2011–12/31/2017. Eligibility criteria included continuous KPNC enrollment 1-year before pregnancy onset through delivery (allowing for <3-month gaps), attendance at ≥1 KPNC prenatal visit, a response to the question about prenatal

cannabis use, and a prenatal toxicology test for THC. Exclusion criteria included a prenatal prescription fill for a teratogenic, antineoplastic, or antiepileptic drug and missing parity or address data. Children not enrolled in KPNC at age 6 were excluded (eFigure 1). Individuals with >1 pregnancy during the study contributed >1 child to the analysis.

Measures

Data were from the electronic health record (EHR) unless otherwise specified.

Prenatal cannabis use. Pregnant individuals receiving care in KPNC are screened for prenatal cannabis use at entrance to prenatal care (at ~8-10 weeks gestation) via a self-administered questionnaire that assesses frequency of use since pregnancy ("none," "monthly or less," "weekly," and "daily") and a urine toxicology test to which they consent (Young-Wolff et al., 2017). The primary exposure was any cannabis use during early pregnancy based on self-reported prenatal cannabis use or a positive toxicology test (eAppendix 1). As a secondary exposure, we also examined frequency of prenatal cannabis use (never, monthly or less, weekly, daily, or unknown [no self-reported use and a positive toxicology test]).

Child anxiety and depressive disorders. Anxiety (F40, F40.X, F41, F41.X, F43, F43.X, F94, F94.X) and depressive disorders (F32, F32.X, F33, F33.X) were based ICD-10 diagnostic codes (eAppendix 4). The earliest diagnosis date was used to determine each outcome, requiring a diagnosis during follow-up when the child was ≥6 years old between 1/1/2017–12/31/2023.

Covariates

Maternal socio-demographics. This includes self-reported race and ethnicity (Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and Other/unknown, included as a social construct due to differences in prenatal cannabis use and child depressive and anxiety disorder prevalence by race and ethnicity), maternal age at pregnancy onset (<18, 18-24, 25-30, 31-35, 36+), parity (0, 1, 2+), insurance type (Medicaid vs. non-Medicaid), education (high school or less, some college, college graduate, and graduate school), maternal neighborhood deprivation index (NDI; categorized into quartiles(Messer et al., 2006) and infant birth year. Maternal race/ethnicity, parity, and education were supplemented with birth certificate data if missing from the EHR.

Maternal prenatal use of other non-cannabis substances. Substance-use was assessed at entrance to prenatal care and included alcohol, nicotine, opioids, stimulants, anxiolytics/sedatives, selective serotonin reuptake inhibitors (SSRIs), and non-SSRI antidepressants (eAppendix 1).

Prenatal care initiation. The Kotelchuck Month of Initiation Index (Kotelchuck, 1994) was used, with categories for adequate plus (month 1-2), adequate (month 3-4), intermediate (month 5-6) and inadequate (month 7+).

Maternal comorbidities. Diagnoses based on ICD-9/ICD-10 were used for nausea and vomiting between pregnancy onset and first prenatal visit; asthma, thyroid disorders, chronic pain disorders, hypertension disorders in the year before pregnancy onset through first prenatal office visit; and diabetes mellitus diagnosed in the 2 years before pregnancy onset through first prenatal visit. Maternal anxiety, depressive, and other psychiatric disorders were defined using diagnoses during the year before pregnancy onset through the first prenatal visit (eAppendix 2).

Statistical Analysis

Marginal Cox proportional hazards regression models with a cluster term at the maternal level and robust standard errors to account for correlated observations (i.e., multiple pregnancies nested within individuals) were fit to estimate the association between prenatal cannabis use and outcomes. Follow-up time began when children were 72 months old (6 years), and age of child in months was used as the time scale. Children were followed until the earliest of outcome occurrence (first diagnosis), end of KPNC enrollment (>3-month gap in enrollment), no pediatric or mental health department visit within a required age window (see below), death, or end of the study period (December 31, 2023), with a maximum follow-up age of 13 years. Attendance at ≥1 pediatric or mental health visit during the intervals (age 6-9 and 9-12) was required to

ensure that clinicians had the opportunity to recognize and diagnose anxiety and depressive disorders (eAppendix 3).

Inverse probability of censoring weights (IPCW) was applied to account for the potential impact of informative censoring due to any differences in healthcare visits or membership loss among children of individuals with versus without prenatal cannabis use (Howe et al., 2016). Time-varying stabilized weights were generated for 3 censoring time intervals (months 72-107, 108-143, and 144-155).

Child anxiety and depressive disorders were modeled separately. For each outcome, a series of analyses sequentially adjusted for sets of covariates to examine the degree of confounding. Model 1 did not include any covariates. Model 2 adjusted for maternal sociodemographic characteristics, Model 3 additionally adjusted for other prenatal non-cannabis substance use, Model 4 additionally adjusted for prenatal care initiation, Model 5 additionally adjusted for maternal medical comorbidities, and Model 6 additionally adjusted for maternal mental health comorbidities. All models adjusted for child's age using age as the time scale.

For both the primary and secondary exposures, sensitivity analyses were conducted that: 1) tested for interactions by child sex on the primary exposure and outcomes, 2) excluded children born to individuals with any non-cannabis prenatal substance use, and 3) stratified by maternal anxiety disorder (for child anxiety disorder models) or by maternal depressive disorder (for child depressive disorder models), and 4) defined prenatal cannabis use by a) only self-report and b) only urine toxicology.

Analyses were performed using SAS, version 9.4 and R, version 4.0.2, and two-sided P values <.05 were considered statistically significant.

RESULTS

Of the 115,533 pregnancies (from 97,376 unique individuals), 27.0% were Asian/Pacific Islander, 5.8% non-Hispanic Black, 24.7% Hispanic, and 38.5% were non-Hispanic White; 11.9% were aged ≤24 years, 4.3% were insured by Medicaid, and 15.6% were to individuals with ≤high school education (Table 1). The median gestational age at substance use screening was 8.0 (inter-quartile range [IQR]=2.6) weeks. Overall, 4.4% screened positive for cannabis use by self-report or urine toxicology testing (0.4% daily, 0.5% weekly, 1.0% monthly, and 2.5% unknown frequency); 0.7% were positive by self-report only, 2.5% were positive by urine toxicology testing only, and 1.2% were positive on both.

The cohort of children was 51.3% male, 48.7% female. The median length of follow-up was 8.8 (IQR=3.3) years. By follow-up end, 9,230 children were diagnosed with an anxiety disorder with a first diagnosis at median age 8 (IQR=1.7) years, and 1,224 children were diagnosed with a depressive disorder with median age of first diagnosis at 9.4 (IQR=1.7) years. Most were diagnosed in a mental health specialty department (anxiety disorder: 78%; depressive disorder: 93%).

Table 1. *Characteristics of 115,533 Mother-Child Dyads Born 2011-2017, Overall and by Prenatal Cannabis Use*

		Prenatal Cannabis Use [b]	
	Pregnancies[a], *n* (%)	No, *n* (%)	Yes, *n* (%)
Total	**115,533**	**110,451**	**5,082**
Maternal sociodemographic characteristics			
Race/ethnicity			
Asian/Pacific Islander	31,239 (27.0)	30,938 (28.0)	301 (5.9)
Non-Hispanic Black	6,735 (5.8)	5,530 (5.0)	1,205 (23.7)
Hispanic	28,574 (24.7)	27,233 (24.7)	1,341 (26.4)
Non-Hispanic White	44,446 (38.5)	42,545 (38.5)	1,901 (37.4)
Other[c]/Unknown	4,539 (3.9)	4,205 (3.8)	334 (6.6)
Age			
<18	969 (0.8)	783 (0.7)	186 (3.7)
18-24	12,787 (11.1)	10,939 (9.9)	1,848 (36.4)
25-30	38,002 (32.9)	36,498 (33.0)	1,504 (29.6)
31-35	42,660 (36.9)	41,541 (37.6)	1,119 (22.0)

36+	21,115 (18.3)	20,690 (18.7)	425 (8.4)
Parity			
0	46,687 (40.4)	43,903 (39.7)	2,784 (54.8)
1	43,474 (37.6)	42,043 (38.1)	1,431 (28.2)
2+	25,372 (22.0)	24,505 (22.2)	867 (17.1)
Insurance type			
Medicaid	4,934 (4.3)	3,967 (3.6)	967 (19.0)
Non-Medicaid	110,599 (95.7)	106,484 (96.4)	4,115 (81.0)
Education level			
High School or Less	17,976 (15.6)	16,237 (14.7)	1,739 (34.2)
Some College	33,827 (29.3)	31,642 (28.6)	2,185 (43.0)
College Graduate	38,286 (33.1)	37,519 (34.0)	767 (15.1)
Graduate School	23,081 (20.0)	22,835 (20.7)	246 (4.8)
Unknown	2,363 (2.0)	2,218 (2.0)	145 (2.9)
Neighborhood Deprivation Index, Quartile			
Q1 - Least deprived	28,879 (25.0)	28,237 (25.6)	642 (12.6)
Q2	28,884 (25.0)	27,889 (25.3)	995 (19.6)
Q3	28,887 (25.0)	27,546 (24.9)	1,341 (26.4)
Q4 - Most deprived	28,883 (25.0)	26,779 (24.2)	2,104 (41.4)
Delivery year			
2011	15,164 (13.1)	14,566 (13.2)	598 (11.8)
2012	15,823 (13.7)	15,204 (13.8)	619 (12.2)
2013	16,164 (14.0)	15,512 (14.0)	652 (12.8)
2014	16,549 (14.3)	15,841 (14.3)	708 (13.9)
2015	16,627 (14.4)	15,901 (14.4)	726 (14.3)
2016	17,361 (15.0)	16,530 (15.0)	831 (16.4)
2017	17,845 (15.4)	16,897 (15.3)	948 (18.7)
Prenatal substance use[d]			
Alcohol use	10,645 (9.2)	9,572 (8.7)	1,073 (21.1)
Nicotine use	4,849 (4.2)	3,515 (3.2)	1,334 (26.2)
Stimulant use	641 (0.6)	470 (0.4)	171 (3.4)
Opioid use	3,458 (3.0)	3,041 (2.8)	417 (8.2)
Anxiolytic/Sedative use	3,089 (2.7)	2,763 (2.5)	326 (6.4)
SSRI[e] use	3,803 (3.3)	3,505 (3.2)	298 (5.9)
Non-SSRI antidepressant use	1,719 (1.5)	1,545 (1.4)	174 (3.4)
Maternal prenatal care utilization			
Gestational age at prenatal care initiation[f]			
Adequate Plus (Month 1-2)	76,616 (66.3)	73,467 (66.5)	3,149 (62.0)
Adequate (Month 3-4)	37,111 (32.1)	35,371 (32.0)	1,740 (34.2)
Intermediate (Month 5-6)	1,345 (1.2)	1,209 (1.1)	136 (2.7)
Inadequate (Month 7+)	461 (0.4)	404 (0.4)	57 (1.1)
Maternal medical comorbidities			
Pre-existing asthma	11,218 (9.7)	10,345 (9.4)	873 (17.2)
Pre-existing chronic pain	3,584 (3.1)	3,242 (2.9)	342 (6.7)
Pre-existing diabetes (Type I or II)	1,641 (1.4)	1,575 (1.4)	66 (1.3)
Pre-existing hypertensive disorder	2,879 (2.5)	2,730 (2.5)	149 (2.9)
Pre-existing thyroid disorder	6,520 (5.6)	6,351 (5.8)	169 (3.3)
Nausea/vomiting in pregnancy[g]	12,147 (10.5)	10,992 (10.0)	1,155 (22.7)
Maternal mental health comorbidities			
Pre-existing anxiety disorder	3,774 (3.3)	3,486 (3.2)	288 (5.7)
Pre-existing depressive disorder	8,943 (7.7)	8,172 (7.4)	771 (15.2)
Pre-existing substance use disorder[h]	3,541 (3.1)	2,669 (2.4)	872 (17.2)
Pre-existing other psychiatric disorder	3,317 (2.9)	2,903 (2.6)	414 (8.1)
Infant characteristics			
Sex			
Female	56,337 (48.8)	53,837 (48.7)	2,500 (49.2)
Male	59,196 (51.2)	56,614 (51.3)	2,582 (50.8)

Secondary exposure			
Frequency of prenatal cannabis use			
None	110,451 (95.6)	110,451 (100.0)	0 (0.0)
Monthly or less	1,160 (1.0)	0 (0.0)	1,160 (22.8)
Weekly	561 (0.5)	0 (0.0)	561 (11.0)
Daily	422 (0.4)	0 (0.0)	422 (8.3)
Unknown frequency[i]	2,939 (2.5)	0 (0.0)	2,939 (57.8)

[a] The cohort consisted of 115,533 unique pregnancies among 97,376 unique individuals. [b]Prenatal cannabis use was determined by self-reported use and/or urine toxicology test results. [c] Other race/ethnicity includes American Indian, Alaskan-Native, and multi-racial individuals.[d] Assessed at entrance to prenatal care by self-report or urine toxicology, or determined by prescription dispensing between the date of last menstrual period and first prenatal visit, or before pregnancy with days' supply lasting past the date of last menstrual period. [e]Selective Serotonin Reuptake Inhibitor. [f] Months gestation at first prenatal office visit. [g]Diagnosis between date of last menstrual period and first prenatal office visit. [h]Excludes cannabis-related substance use disorders. [i]Unknown frequency includes those who did not self-report cannabis use since becoming pregnant but tested positive for THC on urine toxicology.

Anxiety disorders. Prenatal cannabis use was not associated with child anxiety disorders in Model 1 (hazard ratio [HR]:1.08, 95%CI: 0.98-1.18; Table 2). However, after adjustment for covariates, there was a statistically significant inverse association in Models 3-6 (Model 6: HR:0.84, 95%CI: 0.75-0.95; Table 2, Figure 1).

For frequency of cannabis use, in Model 1 relative to no prenatal cannabis use, monthly or less use, weekly use, and daily use were associated with higher risk of child anxiety disorders (Table 2). In Model 6, after adjusting for all covariates, relative to no use, monthly or less (HR:0.91, 95%CI: 0.73-1.14), weekly (HR:1.03, 95%CI: 0.77-1.38), and daily (HR:1.07, 95%CI: 0.76-1.51) use were not associated with offspring anxiety disorders (Table 2; Figure 1). However, unknown frequency (positive toxicology but no self-reported use) was inversely associated with child anxiety disorders (HR:0.75, 95%CI: 0.63-0.88).

Depressive disorders. Prenatal cannabis use was positively associated with child depressive disorders in Model 1 (HR:1.62, 95%CI:1.35-1.94, Table 2). After adjustment, the association was no longer significant (Model 6: HR:1.15, 95%CI: 0.85-1.54, Table 2, Figure 1).

For frequency of cannabis use, in Model 1, relative to no prenatal cannabis use, monthly or less use and unknown frequency of use were associated with higher risk of child depressive disorders (Table 2). After adjusting for covariates, monthly or less (HR:1.54, 95%CI: 0.96-2.48), weekly (HR:0.81, 95%CI: 0.36-1.83), daily (HR:0.96, 95%CI: 0.41-2.25), and unknown frequency of use (HR:1.08, 95%CI: 0.73-1.60) were not associated with child depressive disorders relative to no use (Model 6; Table 2; Figure 1).

Sensitivity Analyses

In the fully adjusted sensitivity analyses excluding individuals who screened positive for any non-cannabis prenatal substance use, prenatal cannabis use was inversely associated with child anxiety disorders (HR:0.82, 95%CI: 0.68-0.98; eTable 1) and was not associated with child depressive disorders (HR:1.00, 95%CI: 0.62-1.60; eTable 1). There were no interactions between prenatal cannabis use and child sex ($p > .05$) for child anxiety or depressive disorders. There were no associations between the frequency of prenatal cannabis use and child outcomes.

In the fully adjusted sensitivity analyses stratified by maternal anxiety or depressive disorders, results were similar for individuals with and without anxiety or depression (eTable 2).

Prenatal cannabis use was not associated with child anxiety disorders in fully adjusted models when cannabis use was defined only by self-report (HR:1.00, 95%CI: 0.85-1.18), but there was an inverse association when use was defined only by toxicology testing (HR:0.79, 95%CI: 0.69-0.90). Prenatal cannabis use was not associated with child depressive disorders when use was defined only by self-report (HR:1.20, 95%CI: 0.83-1.78) or only by a toxicology text (HR:1.00, 95%CI: 0.71-1.39).

Table 2. *Hazard Ratios for Associations of Prenatal Cannabis Use and Self-reported Frequency of Use with Child Anxiety and Depression in Mother-Child Dyads Born 2011-2017*

		Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	Child Anxiety, *n* (%)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Prenatal Cannabis Use							
No	8,833 (8.0)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Yes	397 (7.8)	1.08 (0.98-1.18)	0.94 (0.84-1.06)	0.86 (0.76-0.97)	0.86 (0.76-0.97)	0.85 (0.75-0.95)	0.84 (0.75-0.95)
Frequency of Cannabis Use							
None	8,830 (8.0)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Monthly or less	100 (8.6)	1.19 (1.00-1.42)	1.01 (0.81-1.26)	0.90 (0.72-1.13)	0.92 (0.73-1.15)	0.91 (0.73-1.14)	0.91 (0.73-1.14)
Weekly	57 (10.2)	1.42 (1.13-1.80)	1.19 (0.89-1.59)	1.03 (0.77-1.38)	1.03 (0.77-1.39)	1.03 (0.77-1.38)	1.03 (0.77- 1.38)
Daily	42 (10.0)	1.47 (1.11-1.93)	1.27 (0.90-1.78)	1.09 (0.77-1.54)	1.12 (0.80-1.58)	1.10 (0.78-1.55)	1.07 (0.76-1.51)
Unknown frequency[a]	198 (6.7)	0.91 (0.80-1.04)	0.82 (0.70-0.96)	0.77 (0.65-0.90)	0.76 (0.65-0.90)	0.75 (0.63-0.88)	0.75 (0.63-0.88)
	Child Depression, *n* (%)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Prenatal Cannabis Use							
No	1,153 (1.0)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Yes	71 (1.4)	1.62 (1.35-1.94)	1.34 (1.02-1.77)	1.15 (0.85-1.54)	1.15 (0.86-1.54)	1.15 (0.85-1.54)	1.15 (0.85-1.54)
Frequency of Cannabis Use							
None	1,153 (1.0)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Monthly or less	23 (2.0)	2.18 (1.58-3.01)	1.86., (1.17-2.95)	1.50 (0.93-2.42)	1.53 (0.95-2.46)	1.53 (0.95-2.45)	1.54 (0.96-2.48)
Weekly	7 (1.2)	1.38 (0.78-2.43)	1.07 (0.48, 2.38)	0.80 (0.36-1.80)	0.80 (0.36-1.80)	0.81 (0.36-1.81)	0.81 (0.36-1.83)
Daily	7 (1.7)	1.77 (0.95-3.29)	1.29 (0.55, 3.02)	0.98 (0.42-2.29)	0.99 (0.42-2.32)	0.99 (0.42-2.32)	0.96 (0.41-2.25)
Unknown frequency[a]	34 (1.2)	1.42 (1.10-1.83)	1.20 (0.82, 1.75)	1.09 (0.74-1.61)	1.09 (0.74-1.61)	1.09 (0.74-1.61)	1.08 (0.73-1.60)

[a] Unknown frequency includes those who did not self-report cannabis use since becoming pregnant but tested positive for THC on urine toxicology.

Model 1: Cox proportional hazards model with child age (in months) as time scales, with inverse-probability of censoring weights (IPCW) applied and maternal-level cluster term, and no additional covariates.

Model 2: Adjusted for maternal demographics (age at pregnancy onset, race/ethnicity, education, neighborhood deprivation index, parity, Medicaid insurance, delivery year).

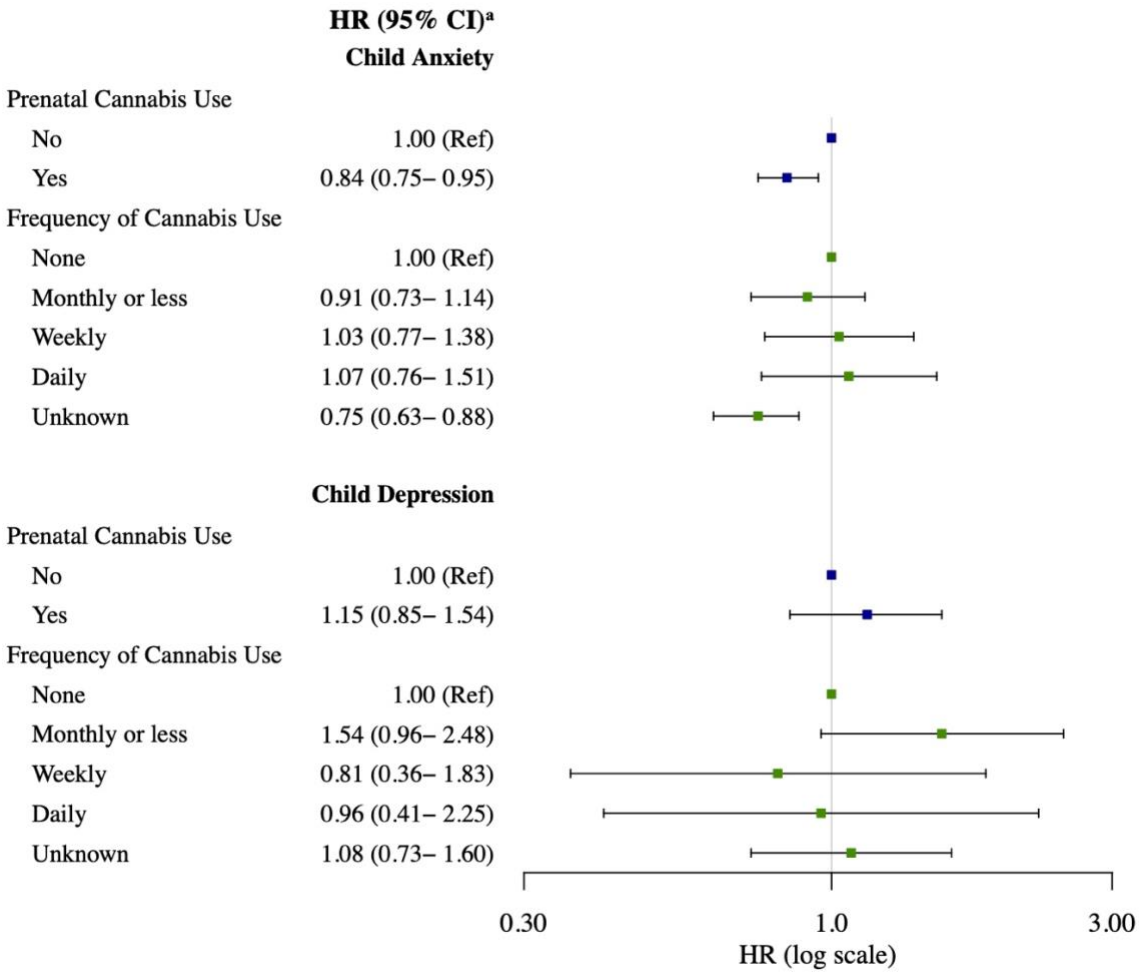
Model 3: Additionally adjusted for other non-cannabis substance exposure (alcohol, nicotine, opioids, stimulants, anxiolytics/sedatives, SSRIs, non-SSRI antidepressants).

Model 4: Additionally adjusted for month of prenatal care initiation.

Model 5: Additionally adjusted for maternal medical comorbidities (asthma, diabetes mellitus, nausea/vomiting during pregnancy, chronic pain, thyroid disorders, hypertensive disorders).

Model 6: Additionally adjusted for maternal mental health comorbidities (anxiety disorders, depression, substance use disorders, other psychiatric disorders)

Figure 1. *Adjusted Hazard Ratios for Associations of Maternal Prenatal Cannabis Use with Child Anxiety and Depression*



DISCUSSION

In this large, retrospective cohort study of maternal-child dyads in a diverse, integrated healthcare delivery system, prenatal cannabis use was not associated with increased risk of child early-onset anxiety or depressive disorders after adjusting for key covariates, including maternal use of other non-cannabis substances during early pregnancy and maternal pre-pregnancy anxiety and depressive disorders.

In unadjusted analyses, prenatal cannabis use was associated with increased risk of early-onset depressive disorders and was not associated with early-onset anxiety disorders; however, the association with depressive disorders was attenuated after sequential adjustment for maternal sociodemographic characteristics, other prenatal substance use, and maternal comorbidities. These findings suggest that the initial unadjusted associations may reflect common underlying risk factors rather than an independent effect of prenatal cannabis use on offspring depressive disorders.

Several small studies have evaluated the relationship between prenatal cannabis use and child anxiety outcomes from ages 2-9, using parent-reported screening measures or structured interviews (Moore et al., 2023; Nomura et al., 2023; O'Connell & Fried, 1991; Rompala et al., 2021; Sullivan et al., 2024). The number of pregnancies with cannabis use ranged from 6 to 68, and findings were mixed, with only one study reporting an increased risk of child anxiety associated with prenatal cannabis use (Rompala et al., 2021), while the remaining four found no

association (Moore et al., 2023; Nomura et al., 2023; O'Connell & Fried, 1991; Sullivan et al., 2024). There are several potential explanations for the lower risk of offspring anxiety disorders associated with prenatal cannabis use in our study. For example, individuals who use cannabis during pregnancy may be different in other key ways that could contribute to lower risk of offspring anxiety disorders (e.g., different lifestyle behaviors, support networks, or parenting approaches). A supportive postnatal environment can potentially impact offspring brain development, including cognitive ability, cell proliferation, and synaptic protein expression, induced by adverse environmental exposures in utero (Koo et al., 2003; Soeda et al., 2010). Further, those who use cannabis could be less likely to recognize symptoms of anxiety in their children or less likely to seek medical care for anxiety symptoms. Importantly, having a positive toxicology test for prenatal cannabis use but not disclosing use by self-report was associated with lower risk of a child anxiety disorder diagnosis, and those who do not report their cannabis use may also underreport anxiety symptoms in their children.

Maternal stress and depression during pregnancy and postpartum have also been shown to play a large role in offspring development and mental health (Rogers et al., 2020). Pregnant individuals report using cannabis for stress and anxiety relief (Skelton et al., 2020; Vanstone et al., 2021), and there is emerging evidence suggesting the potential therapeutic benefit of cannabis on depression symptoms, as an anxiolytic, for stress relief, and improved sleep quality (Ayisire et al., 2022). However, meta-analyses suggest that long-term cannabis use is associated with worse mental health outcomes, particularly in vulnerable populations (Lacasse et al., 2023; Xue et al., 2021). Maternal cannabis use might have a protective effect on offspring anxiety disorders by mitigating maternal stress and other psychosocial factors impacting offspring development, highlighting the importance of early interventions to support those transitioning into parenthood with mental health resources.

Our finding of no association between prenatal cannabis use and early onset of offspring depressive disorders is consistent with two of three smaller studies investigating the association between prenatal cannabis use, assessed by self-report (Gray et al., 2005; Rompala et al., 2021) or urine toxicology testing (Moore et al., 2023), and child depression symptoms from ages 3-10, with the number of pregnancies with prenatal cannabis use ranging from 6 to 268. Notably, an older study of pregnancies from 1982-1985, reported a positive association between self-reported prenatal cannabis use and child depression (Gray et al., 2005). However, a more recent study of pregnancies from 2010-2014, relying on urine toxicology testing in the second trimester, found no association with depressive or anxiety problems based on the DSM-oriented Child Behavior Checklist (CBCL) and an inverse association with mean internalizing behaviors (Moore et al., 2023). Additionally, a study of pregnancies from 2010-2015 (Rompala et al., 2021) found that self-reported prenatal cannabis use was not associated with child depression on the Behavior Assessment System for Children, Second Edition (BASC-2).

Strengths and Limitations

This study has several strengths, including the large and diverse sample of pregnant individuals who were universally screened for prenatal cannabis use by self-report and urine toxicology testing during standard prenatal care. KPNC has universal screening for parent-reported child depression symptoms as part of standard well child visits, increasing the likelihood that children with symptoms were identified, assessed, and given a diagnosis when needed. Further, the cohort included children born between 2011 and 2017, allowing us to examine outcomes in the context of higher strength cannabis products that have become prevalent in recent years. We also adjusted for a range of potential confounders assessed prior to or concurrent with prenatal cannabis screening and conducted sensitivity analyses that excluded individuals with any non-cannabis prenatal substance use. We did not adjust for post-exposure or downstream variables that could be on the causal pathway from cannabis to offspring mental health outcomes, and consistent findings across sensitivity analyses support the interpretation that attenuation in adjusted results reflects confounding rather than over-adjustment.

Finally, the number of pregnancies with prenatal cannabis use in our sample was nearly twenty times larger than the largest study to date examining prenatal cannabis use and child depression or anxiety.

Our study also has limitations. The sample was limited to insured pregnant individuals in California, where cannabis has been legal for medical use since 1996 and for adult recreational use since 2016, and results may not generalize to uninsured individuals or to those in other states. Further, our cohort was limited to pregnant individuals who were enrolled with KPNC in the year prior to pregnancy through delivery, and to children who were enrolled with KPNC at age 6. These exclusions contributed to selection bias, as pregnant individuals who entered prenatal care later were more likely to use cannabis, and children who left KPNC may be at a greater risk for adverse outcomes. Additionally, while prenatal cannabis use was universally assessed by self-report and toxicology testing as part of standard care, we cannot distinguish between use in pregnancy that stopped after recognition of pregnancy versus use that continued throughout pregnancy. We did not have data on paternal cannabis use, mode of use, or secondhand cannabis exposure, which may impact offspring outcomes. Although we adjusted for a range of covariates in the EHR, unmeasured confounding cannot be ruled out. However, we applied inverse probability of censoring weights calculated using maternal sociodemographic characteristics, prenatal substance use, pre-existing medical comorbidities, and prenatal care utilization to account for differential healthcare utilization patterns, reducing the impact of informative censoring on model results. Still, applying the IPCW may have not fully eliminated informative censoring bias due to unmeasured factors not included in the weights. In addition, the IPCW did not address potential selection bias introduced by child loss to follow-up before age 6 (Avalos et al., 2023). While we followed children up to a maximum age of 13 years, our results reflect early onset of depressive and anxiety disorders, and future research with longer follow-up is needed as some may go on to develop these disorders. Finally, given the importance of social determinants of health in shaping the risk for and development of mental health problems among children and adolescents, it is crucial that future studies examine whether associations between prenatal cannabis use and offspring mental health vary by key social determinants of health.

Conclusions

In a large, diverse cohort of pregnant individuals and their children, maternal cannabis use during early pregnancy was not associated with an increased risk of child anxiety or depressive disorders. Additional research is needed to test whether the association between prenatal cannabis use and child anxiety and depressive disorders varies depending on the timing, duration, mode and strength of cannabis. Despite the findings of no increased risk for these mental health outcomes in this study, prenatal cannabis use remains associated with adverse neonatal and maternal outcomes and national guidelines recommend discontinuation of cannabis use during pregnancy (Committee on Obstetric Practice, 2017).

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Dr. Kelly Young-Wolff received funding, conceptualized the study, assisted with interpretation of data, drafted the manuscript, and provided critical revisions to the manuscript.
Mahlet Shenkute and Nina Oberman extracted and analyzed the data from the electronic health record, assisted with interpretation of data, drafted the manuscript, and provided critical revisions to the manuscript.
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