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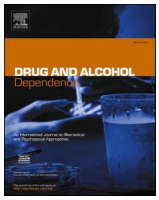

Prenatal cannabis use disorder and infant hospitalization and death in the first year of life

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ABSTRACT

Objective: To determine whether maternal cannabis use disorder is associated with infant hospitalization or death in the first year of life.

Methods: We queried an administrative birth cohort derived from the hospital discharge database maintained by the California Office of Statewide Health Planning and Development and linked with vital statistics files. We included singleton, live-birth deliveries between 2011 and 2018. Pregnancies with cannabis use disorder were classified from International Classification of Disease codes. Outcomes included infant emergency department visits and hospital admissions identified from health records, and infant deaths identified from death records. Models were adjusted for sociodemographic variables, psychiatric comorbidities and other substance use disorders.

Results: There were 34,544 births (1.0 %) with a cannabis use disorder diagnosis in pregnancy, with increasing prevalence over the study period. The incidence of infant death in the first year of life was greater among those with a maternal cannabis use disorder diagnosis than those without (1.0 % vs 0.4 %; adjusted risk ratio 1.4 95 % CI: 1.2–1.6). When examining specific causes of death, the increased risk estimates were attributable to perinatal conditions and sudden unexpected infant death. After adjustment, there was no increased risk of infant hospitalizations or emergency department visits.

Conclusions: These findings warrant further investigation into the underlying mechanisms of maternal prenatal CUD on infant outcomes, and add to a rapidly expanding body of literature supporting the need for effective treatment options for pregnant individuals with cannabis use disorders

1. Introduction

Cannabis use has become more common, including during pregnancy (Alshaarawy and Anthony, 2019; Brown et al., 2017; Volkow et al., 2019). In the 2016–2017 US National Surveys of Drug Use and Health, 12 % of pregnant individuals in their first trimester and about 4 % in their second and third trimesters reported past 30-day cannabis use (Volkow et al., 2019). From the same survey, 20% of pregnant people that reported cannabis use met criteria for cannabis dependence (now part of cannabis use disorder) (Alshaarawy and Anthony, 2019).

Tetrahydrocannabinol (THC), the main psychoactive chemical in cannabis, is a lipophilic molecule that readily crosses the placenta and can accumulate in the fetus (Gesterling and Bradford, 2021; Thompson et al., 2019). It has been hypothesized that prenatal exposure to THC causes dysregulation of the endocannabinoid system, which plays a vital role in placental implantation and fetal development (Gesterling and Bradford, 2021; Roncero et al., 2020). Findings from a rapidly growing evidence base suggest that cannabis use during pregnancy is associated with increased risk of adverse perinatal outcomes (Gesterling and Bradford, 2021; Marchand et al., 2022; Volkow et al., 2017). A 2022 meta-analysis of 16 studies reported that cannabis use during pregnancy was associated with a 61 % increased risk of small for gestational age infant, 106% increased risk of an infant with low birth weight, 28 % increased risk of preterm birth, and 38 % increased risk of neonatal intensive care unit admission (NICU) (Marchand et al., 2022). Two studies using ICD codes for cannabis use disorder (CUD) have reported

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similar findings (Bandoli et al., 2021b; Shi et al., 2021).

Only a few studies have examined infant outcomes beyond the perinatal period. One study using an administrative cohort of 2001–2012 California births reported that prenatal CUD diagnosis was associated with a slightly reduced risk of infant hospitalization and increased risk of infant death within one year of birth (Shi et al., 2021). In the ten years following this cohort, the prevalence of prenatal CUD has tripled (Bandoli et al., 2021b), and there is evidence that cannabis has become more potent (Chandra et al., 2019). Additionally, there was no disaggregation of cause of death it the previous analysis, leaving many unanswered questions. The cause of death most studied in relation to prenatal cannabis use is sudden unexpected infant death (SUID; historically termed sudden infant death syndrome (SIDS)). To date, at least 3 studies have been carried out. One study from an administrative cohort of San Diego vital records reported a strong association between prenatal CUD diagnosis and SUID (Bandoli et al., 2021a), while two older case-control studies reported a much smaller association (Scragg et al., 2001) and no association (Klonoff-Cohen and Lam-Kruglick, 2001).

To further the investigation into prenatal CUD and infant morbidity and mortality, we leveraged data from a population-based administrative cohort study of California birth records. We estimated the associations between CUD diagnosis in pregnancy and infant hospitalization and death in the first year after birth. Then, we stratified by specific causes of infant death to uncover underlying mechanisms that may contribute to these associations.

2. Materials and methods

2.1. Study design and population

We used data from 2011 to 2018 from the Study of Mothers and Infants (SOMI), an administrative birth cohort derived from a complete collection of California birth records. These records, maintained by California Vital Statistics, were linked to California Office of Statewide Health Planning and Development's (OSHPD) hospital, emergency department, and ambulatory surgery records for the mother (in the year prior to the birth through one year post-delivery) and the infant (first year of life). The OSPHD data includes diagnosis and procedure codes recorded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) and the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10). Records were additionally linked to California death files to capture maternal or infant deaths occurring within the state during the year after birth. The SOMI study was approved by the Committee for the Protection of Human Subjects within the Health and Human Services Agency of the State of California and the University of California San Diego Human Research Protections Program.

From 2011–2018, there were 3,896,792 live-births recorded in California. In these analyses, we included singleton births born between 20- and 44-weeks gestational age where linkage between vital statistics and OSHPD hospital discharge records was possible. The resulting analytic sample included 3,459,555 births (eFigure. 1).

2.2. Measurement of exposure, outcomes, and covariates

CUD was classified based on the presence or absence of a cannabis-related diagnosis code in maternal health records (ICD9 305.2 non-dependent cannabis abuse, 304.3 cannabis dependence; ICD10:F12 cannabis-related disorder). The maternal health records queried included all records (hospital or emergency department) occurring during pregnancy or during the birth admission.

Infant emergency department visits and re-hospitalization after birth were determined by OSHPD records. Infant death in the first year of life was determined from two data sources: California death records (primary) and infant hospital discharge summaries (discharge status=died; secondary). For deaths identified via California death records, we classified the underlying cause of death from the death certificate into the 21 chapters of the 2016 edition of the ICD-10 CM (listed in eTable 1) (Centers for Medicare and Medicaid Services, 2016). For infant deaths identified via infant hospital discharge summaries that could not be linked to a California death record, we classified cause of death as "within hospital- missing", as no cause of death is provided in these records. When examining individual causes of death, SUID cases were identified using three diagnostic codes (ICD-10: R95 (sudden infant death syndrome), W75 (accidental suffocation or strangulation in bed), and R99 (unknown cause)) from the cause of death field on infant death records. This group of three diagnostic codes for SUID was recognized by the National Center for Health Statistics in 2015, and for the United States Healthy People 2020 initiative (Shapiro-Mendoza et al., 2018).

Covariates were identified a priori based on literature review and data availability. Maternal sociodemographic information, collected from birth records, included self-reported race/ethnicity (Non-Hispanic White, Hispanic, Non-Hispanic Black, Non-Hispanic Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, multiple, other), maternal age (<18 years, 18–34 years, >34 years, missing), source of payment (private insurance, public insurance, other payment), and maternal education (<12 years, ≥ 12 years, missing). The presence/absence of several maternal health conditions were ascertained from maternal OSHPD records. These included anxiety disorder, major depressive disorder, bipolar disorder, preexisting or gestational diabetes, nicotine use during pregnancy, alcohol use disorder, or other substance use disorder. The data source, original functional form of each variable, and relevant ICD codes for all variables are provided in eTable 2.

2.3. Statistical analyses

To characterize the sample, we estimated the birth rate per year and, within each year, estimated the proportion of live births with a CUD diagnosis. We also summarized frequencies of maternal and infant characteristics by presence or absence of a CUD diagnosis.

We used modified Poisson regression models (Zou, 2004) to estimate crude and adjusted risk ratios (RR) of the 1-year incidence of hospital readmission, emergency room visit, and death among births with a CUD diagnosis compared to births with no CUD diagnosis. Adjusted RRs and 95 % confidence intervals were estimated from models that included pre-pregnancy BMI, race/ethnicity, payer source for delivery, anxiety diagnosis, depression diagnosis, bipolar disorder, prenatal nicotine use, alcohol use diagnosis, other substance use diagnoses, and maternal age. These analyses were repeated, maintaining the complete set of covariates but substituting maternal death as the outcome. This secondary analysis served as a negative control (Smith, 2012) based on the assumption that there is no plausible causal relationship between maternal CUD diagnosis and maternal death. Thus, we expected to estimate a null association, and any departure from the null would indicate bias due to unmeasured confounding or misclassification of study variables. Covariates were missing for 5 % or less of observations, and thus a complete case control analysis was conducted.

To disaggregate specific causes of death, we first described the proportion of deaths attributed to each cause (by ICD-10 CM chapters) for births with no CUD diagnosis and, separately, for births with a CUD diagnosis. Informed by these descriptive results, we used a Cox proportional hazards model to estimate the association between CUD diagnosis and each cause of death grouping. Individuals with causes of death other than the outcome of interest in each model were censored; days of life was the unit of time in the models. We tested the proportional hazards assumption by inclusion of an interaction term between cannabis and log (survival time). Interactions with a p value of less than 0.05 were limited into shorter durations of time, assessed again for proportional hazards, and upon no longer observing an interaction, models were repeated within the narrower time strata. Finally, as SUID

is a combination of ICD codes contained across two chapters, we created a variable for SUID and modeled the risk of SUID as a separate outcome.

Prenatal exposures may affect infant outcomes through adverse birth outcomes. We have previously published from these data that prenatal CUD was associated with preterm birth and small for gestational age (Bandoli et al., 2021b), which are risk factors for the outcomes analyzed here. Thus, for outcomes associated with prenatal CUD diagnosis, we conducted mediation analyses to quantify the excess risk of each outcome attributable to prematurity or small for gestational age. We performed these analyses using the SAS macro *%mediation*. All models had a Poisson distribution and a log link, and were adjusted for the same covariates as the total effects models. Models were assessed for exposure-mediator interaction, with evidence of interaction prompting reporting of the model with interaction.

Finally, administrative databases may inadequately capture important confounders such as nicotine, other substance use and obesity (Andrade et al., 2017; Tawfik et al., 2019). We performed a bias analysis to address unmeasured or residual confounding (R package *episensr*). We calculated the E-value, or the strength of an unmeasured confounder necessary to negate the observed exposure-outcome association. E-values were computed for adjusted effect estimates on the infant death model (any death) and separately on the SUID model. All other analyses were performed in SAS 9.4 (Cary, NC).

3. Results

Overall, 34,544 births (1.0 %) had a CUD diagnosis in pregnancy. The prevalence of CUD diagnosis in pregnancy increased from 0.7 % in 2011 to 1.4 % in 2018 (Fig. 1). Individuals with CUD diagnosis were less likely to be Hispanic or Asian and more likely to be Non-Hispanic White, America Indian/Alaska Native, or Non-Hispanic Black compared to those without a CUD diagnosis (Table 1). A greater proportion of individuals with diagnosed CUD were younger than 18 years, had public health insurance, and had less than 12 years of education. Also, those with a CUD diagnosis were much more likely to have a documented co-occurring anxiety disorder, major depressive disorder, alcohol, or other substance use disorder, and to have used nicotine during pregnancy.

The incidence of infant hospital readmission and emergency department visit in the first year of life were 12.2 % and 42.2 % among those with a CUD diagnosis and 10.6 % and 32.6 % among those without a CUD diagnosis, respectively. After adjustment for confounding variables, CUD diagnosis was not associated with increased risk of either infant hospital readmission or emergency department (Table 2).

The incidence of infant death in the first year of life was 1.0% among

Table 1
Maternal and infant characteristics by cannabis use disorder diagnosis among individuals in the state of California with live-born singleton deliveries between 2011 and 2018.

	No cannabis use disorder (n = 3,425,011)		Cannabis use disorder (n = 34,544)	
	n	%	n	%
Maternal characteristics				
Race/ethnicity				
Non-Hispanic White	906,410	26.5	11,504	33.3
Hispanic	1,678,298	49.0	11,509	33.3
Non-Hispanic Black	162,409	4.7	7249	21.0
American Indian / Alaska Native	10,555	0.3	458	1.3
Hawaiian/Pacific Islander	13,075	0.4	131	0.4
Non-Hispanic Asian	505,937	14.8	406	1.2
Multiple	74,376	2.2	2234	6.5
Other	73,951	2.2	1053	3.1
Maternal age				
Less than 18 years	54,386	1.6	1024	3.0
18–34 years	2,657,323	77.6	30,627	88.7
Greater than 34 years	713,190	20.8	2891	8.4
Missing	112	0.0	2	0.0
Source of payment				
Private insurance	1,649,508	48.2	8046	23.3
Public insurance	1,608,631	47.0	25,631	74.2
Other payment	166872	4.9	867	2.5
Maternal education				
12 or more years	2,709,272	79.1	24,138	69.9
Less than 12 years	567,871	16.6	8465	24.5
Missing	147,868	4.3	1941	5.6
Pre-pregnancy BMI				
Underweight/normal weight	1,672,684	48.8	16,478	47.7
Overweight	865,278	25.3	8002	23.2
Obese	753,840	22.0	8321	24.1
Missing	133,209	3.9	1743	5.0
Anxiety disorder	81,135	2.4	4078	11.8
Major depressive disorder	68,640	2.0	3994	11.6
Bipolar disorder	21,507	0.6	2574	7.5
Preexisting or gestational diabetes	402,485	11.8	3284	9.5
Nicotine use	91,319	2.7	12,289	35.6
Other substance use disorder	30,694	0.9	8111	23.5
Alcohol use disorder	5250	0.2	1654	4.8
Infant characteristics				
Premature at birth (<37 weeks)	227,920	6.7	4621	13.4
Extremely premature (<32 weeks)	28,951	0.8	806	2.3
Small for gestational age	295,992	8.6	5411	15.7
Neonatal intensive care unit admission	206,365	6.0	4155	12.0

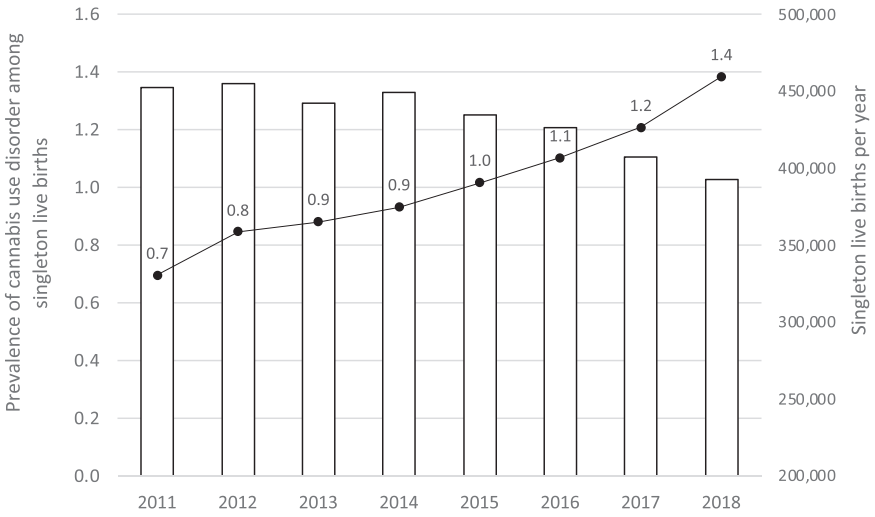

Fig. 1. Prevalence of live births with cannabis use diagnosis among singleton live births in California, 2011–2018 (primary Y axis). Secondary Y axis displays the number of singleton live births per year for the same period.

Table 2
Prenatal cannabis use disorder (CUD) diagnosis and outcomes in the first year of life among live-born singleton deliveries in California (2011–2018).

	n,% (CUD diagnosis)	n,% (no CUD diagnosis)	Unadjusted risk ratio	Adjusted[a] risk ratio
Hospital readmission	4198 (12.2)	361,772 (10.6)	1.2 (1.1, 1.2)	1.0 (0.9, 1.0)
Emergency room visit	14,579 (42.2)	1,117,141 (32.6)	1.3 (1.3, 1.3)	1.0 (1.0, 1.0)
Infant death in first year of life	350 (1.0)	13,331 (0.4)	2.6 (2.3, 2.9)	1.4 (1.2, 1.6)
Maternal death first year of life	43 (0.1)	871 (0.0)	4.9 (3.6, 6.6)	1.2 (0.8, 1.6)

[a] Models adjusted for pre-pregnancy BMI, race/ethnicity, payer source for delivery, anxiety diagnosis, depression diagnosis, bipolar disorder, prenatal nicotine use, alcohol use diagnosis, other substance use diagnoses, and maternal age

those with a maternal CUD diagnosis and 0.4 % among those without a maternal CUD diagnosis. The unadjusted risk ratio of 2.6 (95%CI: 2.3–2.9) was attenuated to 1.4 (95%CI: 1.2–1.6) after adjustment for confounding variables. When examining maternal death as a negative control, we found a strong unadjusted association between cannabis use disorder and maternal death (RR = 4.9, 95%CI 3.6–6.6) which was attenuated after adjustment for the same set of confounders used in the infant death models (RR = 1.2, 95%CI 0.8–1.6) (Table 2).

The most frequently documented causes of infant death in this sample were (1) conditions originating in the perinatal period (ICD 10 P00-P96), (2) malformations, deformations and chromosomal abnormalities (Q00-Q99), and (3) symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified (R00-R99) (Fig. 2; all listed in eTable 1). There were few differences by CUD diagnosis when comparing the proportion of infant deaths attributable to each cause of death (Fig. 2), apart from a greater proportion of deaths among infants with maternal CUD diagnosis attributed to symptoms and abnormal clinical and laboratory findings (22 % vs 10 %) and external causes of morbidity and mortality (V01-Y98) (9 % vs 4 %) compared to those with no CUD diagnosis. Notably, these two categories encompass the ICD codes that collectively cover SUID.

When examining the risk for each cause of death in multivariable analyses (Table 3), there was an increase of 'certain conditions originating in the perinatal period' (aHR 1.5, 95 % CI 1.2, 1.8). There was indication that the proportionality assumption was violated, and thus we stratified models into deaths occurring on or before 7 days of life, and deaths after 7 days of life. There was heterogeneity in risk estimates; the association between cannabis and perinatal deaths was much weaker among deaths in the first week of life (aHR 1.3, 95 % CI 1.0, 1.7) than after the first week (aHR 2.1, 95 % CI 1.4, 3.0). Deaths in the two chapters that encompass SUID were also elevated among infants with maternal CUD diagnosis. When SUID was modeled as the outcome, there was an increased risk (aHR = 1.5, 95%CI 1.2–1.9) among infants with maternal CUD diagnosis after multivariable adjustment (Table 3). Although other causes of death were elevated in a similar manner, all other estimates were compatible with null findings.

We performed mediation analyses for any infant death, deaths due to 'certain conditions originating in the perinatal period', and SUID, as these were each associated with prenatal CUD diagnosis (eTable 3). Preterm birth was not a strong mediator of infant death from any cause (21 %) or SUID (2 %). However, over 40 % of the excess risk of death attributed to 'certain conditions originating in the perinatal period' associated with prenatal CUD diagnosis was mediated through prematurity. There was no evidence of mediation by infants being born small for gestational age with any of the outcomes.

In our calculation of the e-value, to fully attenuate the observed adjusted risk ratio for 'any death' (aRR 1.4, 95 % CI 1.2, 1.6), the unmeasured variable would need to have an RR of 2.1 (with a lower CI of

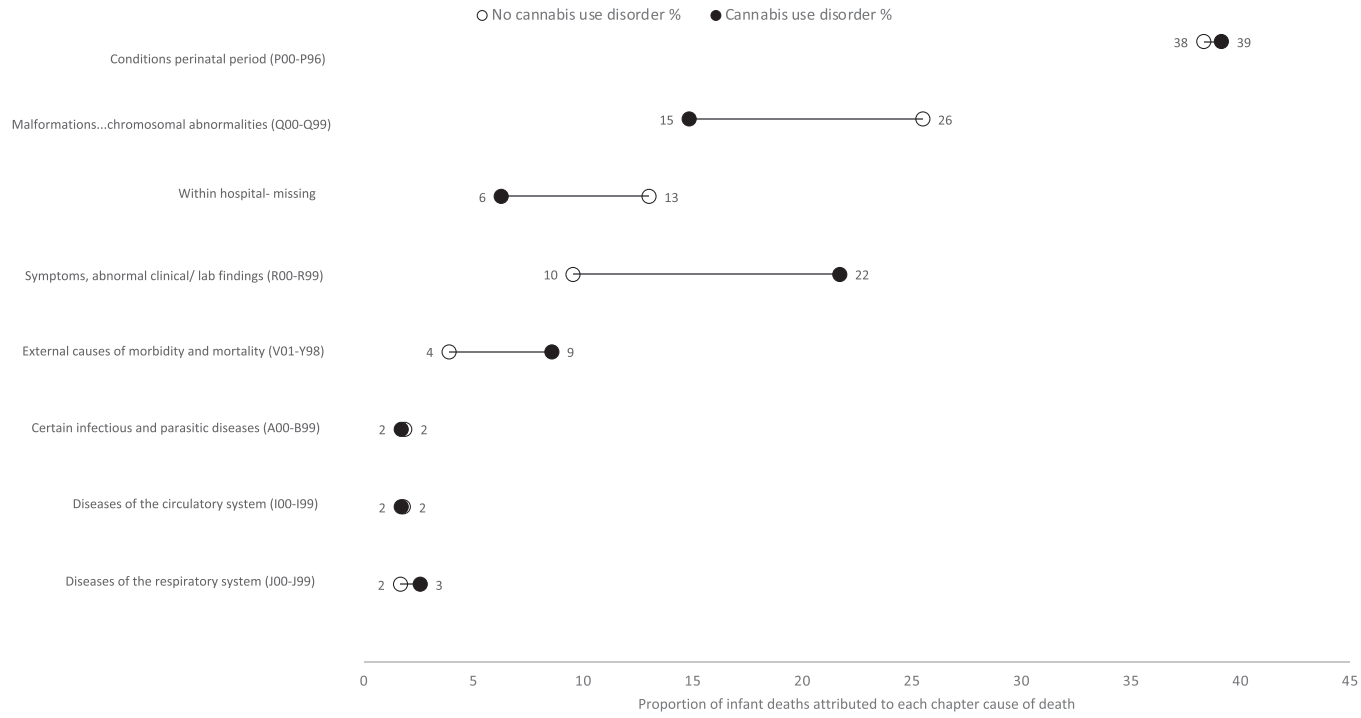

Fig. 2. Proportion of infant deaths attributable to each cause of death (according to ICD codes on death records). Only causes of death accounting for at least 2% of deaths are graphed (all causes shown in eTable 1). Example of an interpretation: 26% of infant deaths without prenatal maternal CUD exposure were attributed to 'malformations and chromosomal abnormalities', whereas only 15% of infant deaths with prenatal maternal CUD were attributed to 'malformations and chromosomal abnormalities'.

Table 3
Prenatal cannabis use disorder and cause of death[a] in the first year of life among singleton live-births in California (2011–2018).

	Prenatal cannabis use disorder diagnosis (n = 34,544)		No prenatal cannabis use disorder diagnosis (n = 3425,011)			
	n	Prevalence per 1000 births	n	Prevalence per 1000 births	Unadjusted hazard ratio	Adjusted[b] hazard ratio
Certain conditions originating in the perinatal period (P00-P96)	137	4.0	5109	1.5	2.7 (2.2, 3.2)	1.5 (1.2, 1.8)[5]
Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	52	1.5	3400	1.0	1.5 (1.2, 2.0)	1.2 (0.8, 1.6)
Within hospital- missing[c]	22	0.6	1735	0.5	1.3 (0.8, 1.9)	0.9 (0.6, 1.5)
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)[d]	76	2.2	1275	0.4	5.9 (4.7, 7.5)	1.5 (1.1, 1.9)
External causes of morbidity and mortality (V01-Y98)[d]	30	0.9	518	0.2	5.8 (4.0, 8.3)	1.7 (1.1, 2.7)
Certain infectious and parasitic diseases (A00-B99)	6	0.2	251	0.1	2.4 (1.1, 5.3)	1.0 (0.4, 2.5)
Diseases of the circulatory system (I00-I99)	6	0.2	242	0.1	2.5 (1.1, 5.6)	1.6 (0.7, 3.9)
Diseases of the respiratory system (J00-J99)	9	0.3	223	0.1	4.0 (2.1, 7.8)	1.9 (0.9, 4.0)
Sudden unexpected infant death (R95, R99, W75)[d]	88	2.5	1461	0.4	6.0 (4.8, 7.4)	1.5 (1.2, 1.9)

[5] Proportional hazards assumption met when stratified by timing of death; death in first 7 days of life: aHR 1.3, 95% CI 1.0, 1.7; death after first 7 days of life: aHR 2.1, 95 % CI 1.4, 3.0

[a] Models only performed where count of deaths > 5

[b] Models adjusted for pre-pregnancy BMI, race/ethnicity, payer source for delivery, anxiety diagnosis, depression diagnosis, bipolar disorder, prenatal nicotine use, alcohol use diagnosis, other substance use diagnoses, and maternal age

[c] Cause of death was unknown for deaths occurring in the hospital

[d] R95 (sudden infant death syndrome), W75 (accidental suffocation or strangulation in bed), and R99 (unknown cause) make up the diagnosis of sudden unexpected infant death

1.7) with both the exposure (CUD) and outcome (any death). For the SUID model, the unmeasured variable would need an RR of 2.4 (with a lower bound of 1.7) to render our findings null.

4. Discussion

In this study, we analyzed data from an administrative population-based cohort of over 3 million live-births in California. Prenatal CUD diagnosis was associated with increased risk of infant death in the year after birth after multivariable adjustment. When disaggregated into specific cause of death, these findings appeared attributable to 'conditions originating in the perinatal period' and SUID deaths. Maternal CUD diagnosis was not associated with increased risks of either infant hospital readmission or emergency room department visits in the first year.

Despite a few differences in the covariate adjustment set and statistical approach between our study and the earlier California administrative cohort study, we estimated an association between CUD in pregnancy and infant death that was nearly identical to the one reported in the prior California study (OR = 1.4, 95%CI 1.1, 1.6) (Shi et al., 2021). The stability in the magnitude of effect estimates across time may be informative in understanding the potential mechanisms linking prenatal exposure to cannabis and adverse outcomes.

Our examination of prenatal CUD as it relates to specific causes of infant death is an important extension of the existing literature. We reported a 50% increased risk of death from conditions originating in the perinatal period after adjusting for covariates. This chapter classification includes 'newborns affected by pregnancy complications' and 'disorders related to length of gestation and fetal growth'. We previously reported an increased risk for preterm birth and the infant being small for gestational age associated with maternal CUD in this cohort (Bandoli et al., 2021b). Through a mediation analysis, we found that 40% of the excess risk associated with prenatal CUD diagnosis was mediated by prematurity. There was no evidence of mediation through small for gestational age. The only other cause of death in this study associated with prenatal CUD diagnosis was SUID. These findings were not without precedence. A previous study conducted within the San Diego subset of this cohort with data from 2005 to 2017 identified a 2.5-fold increased risk between prenatal CUD diagnosis and SUID (Bandoli et al., 2021a). A case control study of births between 1987 and 1990 in New Zealand reported a much smaller association between maternal-reported cannabis use and SIDS (OR = 1.55, 95%CI: 0.87–2.75) (Scragg et al., 2001) and a case control study of births between 1989 and 1992 in Southern California reported no association (OR = 0.6, 95%CI: 0.3–1.6) (Klonoff-Cohen and Lam-Kruglick, 2001). Although prematurity is a risk factor for SUID (Getahun et al., 2004; Hakeem et al., 2015), we found no evidence that prematurity accounted for the excess risk of SUID associated with maternal CUD diagnosis in this cohort. One analytical challenge in studying prenatal maternal CUD and SUID is the well-documented associations between prenatal tobacco and alcohol use and the risk of SUID (Anderson et al., 2019; Elliott et al., 2020; Getahun et al., 2004; Hakeem et al., 2015; King-Hele et al., 2007). Although we adjusted for both in models, they can be poorly captured on birth records and through ICD codes, which could have resulted in residual confounding. However, there is emerging evidence that cannabis may directly contribute to SUID, as prenatal cannabis exposure affects the health and vascularization of the placenta (Lee and Hardy, 2021; Natale et al., 2020), resulting in placental insufficiency and intrauterine hypoxia, which have been associated with SUID (Donnelly et al., 2020; Widdows et al., 2012). Future studies should attempt to replicate these findings in new settings and identify mediating variables on the causal pathway from CUD to cause-specific infant mortality.

We were motivated to study maternal CUD and infant outcomes by the increasing prevalence of CUD both in pregnant and non-pregnant people (Alshaarawy and Anthony, 2019). From 2001–2012 in California birth records, the prevalence of CUD diagnosis during pregnancy increased from 0.3 % to 0.7 % (Shi et al., 2021). Prevalence estimates have continued to rise in California, where 1.4% of births had a CUD diagnosis in 2018 – a doubling of the prevalence within a decade. This upward trend mirrors what has been observed among pregnant people nationally, where CUD was diagnosed in 0.9 % of pregnancies in 2014, a 5-fold increase from 1993 (Shi and Zhong, 2018). It is difficult to determine how much of the change reflects real increases in the occurrence of disordered cannabis use in pregnancy versus increases in screening, reporting, and documentation of the diagnosis. Further, this estimate may underestimate the prevalence of CUD among pregnant people, and greatly underestimates the prevalence of any cannabis use during pregnancy.

These findings add to a growing literature on the adverse outcomes associated with prenatal cannabis exposure to the developing fetus (El

Marroun et al., 2018; Gunn et al., 2016). The medical model of addiction views substance use disorders as chronic, relapsing diseases, and promotes treatment and education to reduce consumption of substances during pregnancy. However, women with a CUD likely require additional support beyond education. To date, there are few treatments aimed at prenatal CUD, although motivational interviewing, cognitive behavioral therapy and contingency management therapies have been used in non-pregnant women (Forray, 2016). Access to specialized health care services, providing comprehensive care that is responsive to comorbid mental and medical conditions, and safeguarding against criminalization, discrimination and stigmatization (World Health Organization, 2014) should be priorities. Additionally, given the findings on SUID, postpartum individuals with CUD may benefit from increased education regarding SUID prevention, including reinforcing the importance of safe sleeping behaviors and environments free of secondhand tobacco smoke.

4.1. Limitations and strengths

Study findings should be interpreted with methodological limitations in mind. First, we were limited by reliance on ICD codes for CUD. Different providers and health systems likely employ different criteria for screening and detection of CUD during pregnancy. Further, there is likely bias in who receives a CUD diagnosis during pregnancy (Winchester et al., 2022), which may favor individuals with other risk factors (public insurance, comorbid mental health diagnoses and other substance use diagnoses) which would bias our findings away from the null. However, there are very likely individuals who use similar or greater amounts of cannabis who don't receive a CUD, which could bias our estimates towards the null. Due to these competing forces, the ultimate effect of CUD misclassification on our reported effect estimates are unknown, and likely vary by the screening and coding policies at individual health systems. Methodologic studies that validate cannabis use disorder ICD codes would inform misclassification bias analyses in future work. Additionally, CUD diagnosis, which may reflect frequency of use, provides no information on potency of the product, amount in each use, or mode of use. These factors may influence risk estimates for SUID and infant death, and their omission limits these findings. Second, administrative data sources may provide inadequate capture of important confounders, including nicotine and alcohol use. To address this concern, we calculated the E-value to demonstrate the extent to which residual confounding would need to be present to negate our results. Associations between confounders and both cannabis and the outcomes would need to be greater than 2.0 to negate findings. Although prenatal alcohol has observed effect estimates of that magnitude (O'Leary et al., 2013) with SUID, most other risk factors, including prenatal tobacco (Adgent, 2006), are lower. Thus, while residual confounding in administrative data should be assumed, the likelihood that it is fully explaining our findings is low. Further, we pre-specified a negative control with maternal death, and saw strong unadjusted risk estimates attenuate greatly when adjusting for the same set of covariates as the infant mortality models. Third, we have no information on the postnatal environment. Particularly with outcomes like SUID, factors like secondhand marijuana or tobacco smoke, bed sharing, and the potential for postnatal cannabis exposure via breastmilk are important and cannot be accounted for in our findings. Finally, although this dataset represents almost a complete capture of births in California from 2011 to 2018, the description of the sample and distribution of covariates are not meant to represent any other sample, and should not be interpreted outside of the population from which they arose.

Despite these limitations, a key strength of this study is use of a population-based cohort of California births. This resulted in a study sample that was diverse with respect to race/ethnicity, socioeconomic status, and geographic region. The sample included 34,544 births with maternal CUD, allowing for precise estimates of rare outcomes like infant death and for stratification of data by specific causes of death, which is a critical step towards understanding the underlying pathways through with cannabis may affect the offspring.

5. Conclusions

In this administrative birth cohort, infant deaths attributed to conditions originating in the perinatal period and SUID were associated with maternal prenatal CUD. These findings contribute to a rapidly expanding body of literature about the potential effects of prenatal CUD on the developing offspring and amplifies the prioritization of education and treatment options for individuals with a CUD diagnosis who become pregnant.

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Contributors

Dr. Bandoli conceptualized and designed the study, performed statistical analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Chambers acquired the data, and reviewed and revised the manuscript. Ms. Baer cleaned and performed linkages for the dataset, and maintains the database. She also reviewed and revised the manuscript. Drs. Delker and Schumacher and Ms. Kelly critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest

The authors report no conflicts to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109728.

References

Adgent, M.A., 2006. Environmental tobacco smoke and sudden infant death syndrome: a review. Birth Defects Res. Part B Dev. Reprod. Toxicol. 77, 69–85. https://doi.org/10.1002/bdrb.20068.

Alshaarawy, O., Anthony, J.C., 2019. Cannabis use among women of reproductive age in the United States: 2002–2017. Addict. Behav. 99, 106082 https://doi.org/10.1016/j.addbeh.2019.106082.

Anderson, T.M., Lavista Ferres, J.M., Ren, S.Y., Moon, R.Y., Goldstein, R.D., Ramirez, J.-M., Mitchell, E.A., 2019. Maternal smoking before and during pregnancy and the risk of sudden unexpected infant death. Pediatrics 143, e20183325. https://doi.org/10.1542/peds.2018-3325.

Andrade, S.E., Bérard, A., Nordeng, H.M.E., Wood, M.E., van Gelder, M.M.H.J., Toh, S., 2017. Administrative claims data versus augmented pregnancy data for the study of pharmaceutical treatments in pregnancy. Curr. Epidemiol. Rep. 4, 106–116. https://doi.org/10.1007/s40471-017-0104-1.

Bandoli, G., Baer, R.J., Owen, M., Kiernan, E., Jelliffe-Pawlowski, L., Kingsmore, S., Chambers, C.D., 2021a. Maternal, infant, and environmental risk factors for sudden unexpected infant deaths: results from a large, administrative cohort. J. Matern. Fetal Neonatal Med. 1–8. https://doi.org/10.1080/14767058.2021.2008899.

Bandoli, G., Jelliffe-Pawlowski, L., Schumacher, B., Baer, R.J., Felder, J.N., Fuchs, J.D., Oltman, S.P., Steurer, M.A., Marienfeld, C., 2021b. Cannabis-related diagnosis in pregnancy and adverse maternal and infant outcomes. Drug Alcohol Depend. 225, 108757 https://doi.org/10.1016/j.drugalcdep.2021.108757.

Brown, Q.L., Sarvet, A.L., Shmulewitz, D., Martins, S.S., Wall, M.M., Hasin, D.S., 2017. Trends in Marijuana use among pregnant and nonpregnant reproductive-aged women, 2002-2014. JAMA 317, 207. https://doi.org/10.1001/jama.2016.17383.

Centers for Medicare and Medicaid Services, 2016. ICD-10-CM Official Guidelines for Coding and Reporting; FY 2016 [WWW Document]. URL ⟨https://www.cms.gov/medicare/coding/icd10/downloads/2016-icd-10-cm-guidelines.pdf⟩ (accessed 4.11.22).

Chandra, S., Radwan, M.M., Majumdar, C.G., Church, J.C., Freeman, T.P., ElSohly, M.A., 2019. New trends in cannabis potency in USA and Europe during the last decade

(2008–2017. Eur. Arch. Psychiatry Clin. Neurosci. 269, 5–15. https://doi.org/10.1007/s00406-019-00983-5.
Donnelly, W.T., Haynes, R.L., Commons, K.G., Erickson, D.J., Panzini, C.M., Xia, L., Han, Q.J., Leiter, J.C., 2020. Prenatal intermittent hypoxia sensitizes the laryngeal chemoreflex, blocks serotoninergic shortening of the reflex, and reduces 5-HT(3) receptor binding in the NTS in anesthetized rat pups. Exp. Neurol. 326, 113166 https://doi.org/10.1016/j.expneurol.2019.113166.
El Marroun, H., Brown, Q.L., Lund, I.O., Coleman-Cowger, V.H., Loree, A.M., Chawla, D., Washio, Y., 2018. An epidemiological, developmental and clinical overview of cannabis use during pregnancy. Prev. Med. 116, 1–5. https://doi.org/10.1016/j.ypmed.2018.08.036.
Elliott, A.J., Kinney, H.C., Haynes, R.L., Dempers, J.D., Wright, C., Fifer, W.P., Angal, J., Boyd, T.K., Burd, L., Burger, E., Folkerth, R.D., Groenewald, C., Hankins, G., Hereld, D., Hoffman, H.J., Holm, I.A., Myers, M.M., Nelsen, L.L., Odendaal, H.J., Petersen, J., Randall, B.B., Roberts, D.J., Robinson, F., Schubert, P., Sens, M.A., Sullivan, L.M., Tripp, T., Van Eerden, P., Wadee, S., Willinger, M., Zaharie, D., Dukes, K.A., 2020. Concurrent prenatal drinking and smoking increases risk for SIDS: safe passage study report. EClinicalMedicine 19, 100247. https://doi.org/10.1016/j.eclinm.2019.100247.
Forray, A., 2016. Substance use during pregnancy. F1000Research 5, F1000 Faculty Rev-887. ⟨https://doi.org/10.12688/f1000research.7645.1⟩.
Gesterling, L., Bradford, H., 2021. Cannabis use in pregnancy: a state of the science review. J. Midwifery Women's. Health. https://doi.org/10.1111/jmwh.13293.
Getahun, D., Amre, D., Rhoads, G.G., Demissie, K., 2004. Maternal and obstetric risk factors for sudden infant death syndrome in the United States. Obstet. Gynecol. 103, 646–652. https://doi.org/10.1097/01.AOG.0000117081.50852.04.
Gunn, J.K.L., Rosales, C.B., Center, K.E., Nuñez, A., Gibson, S.J., Christ, C., Ehiri, J.E., 2016. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. BMJ Open 6. https://doi.org/10.1136/bmjopen-2015-009986.
Hakeem, G.F., Oddy, L., Holcroft, C.A., Abenhaim, H.A., 2015. Incidence and determinants of sudden infant death syndrome: a population-based study on 37 million births. World J. Pediatr. 11, 41–47. https://doi.org/10.1007/s12519-014-0530-9.
King-Hele, S.A., Abel, K.M., Webb, R.T., Mortensen, P.B., Appleby, L., Pickles, A.R., 2007. Risk of sudden infant death syndrome with parental mental illness. Arch. Gen. Psychiatry 64, 1323–1330. https://doi.org/10.1001/archpsyc.64.11.1323.
Klonoff-Cohen, H., Lam-Kruglick, P., 2001. Maternal and paternal recreational drug use and sudden infant death syndrome. Arch. Pediatr. Adolesc. Med. 155, 765. https://doi.org/10.1001/archpedi.155.7.765.
Lee, K., Hardy, D.B., 2021. Metabolic consequences of gestational cannabinoid exposure. Int. J. Mol. Sci. https://doi.org/10.3390/ijms22179528.
Marchand, G., Masoud, A.T., Govindan, M., Ware, K., King, A., Ruther, S., Brazil, G., Ulibarri, H., Parise, J., Arroyo, A., Coriell, C., Goetz, S., Karrys, A., Sainz, K., 2022. Birth outcomes of neonates exposed to marijuana in utero: a systematic review and meta-analysis. JAMA Netw. Open 5, e2145653. https://doi.org/10.1001/jamanetworkopen.2021.45653.
Natale, B.V., Gustin, K.N., Lee, K., Holloway, A.C., Laviolette, S.R., Natale, D.R.C., Hardy, D.B., 2020. Δ9-tetrahydrocannabinol exposure during rat pregnancy leads to symmetrical fetal growth restriction and labyrinth-specific vascular defects in the placenta. Sci. Rep. 10, 544. https://doi.org/10.1038/s41598-019-57318-6.
O'Leary, C.M., Jacoby, P.J., Bartu, A., D'Antoine, H., Bower, C., 2013. Maternal alcohol use and sudden infant death syndrome and infant mortality excluding SIDS. Pediatrics 131, e770–e778. https://doi.org/10.1542/peds.2012-1907.
Roncero, C., Valriberas-Herrero, I., Mezzatesta-Gava, M., Villegas, J.L., Aguilar, L., Grau-López, L., 2020. Cannabis use during pregnancy and its relationship with fetal developmental outcomes and psychiatric disorders. A systematic review. Reprod. Health 17, 25. https://doi.org/10.1186/s12978-020-0880-9.
Scragg, R.K., Mitchell, E.A., Ford, R.P., Thompson, J.M., Taylor, B.J., Stewart, A.W., 2001. Maternal cannabis use in the sudden death syndrome. Acta Paediatr. 90, 57–60. https://doi.org/10.1080/080352501750064888.
Shapiro-Mendoza, C.K., Parks, S., Lambert, A.E., Camperlengo, L., Cottengim, C., Olson, C., 2018. The epidemiology of sudden infant death syndrome and sudden unexpected infant deaths: diagnostic shift and other temporal changes. In: Duncan, J.R., Byard, R.W. (Eds.), Adelaide (AU).
Shi, Y., Zhong, S., 2018. Trends in cannabis use disorder among pregnant women in the U.S.,1993-2014. J. Gen. Intern. Med. 33, 245–246. https://doi.org/10.1007/s11606-017-4201-0.
Shi, Y., Zhu, B., Liang, D., 2021. The associations between prenatal cannabis use disorder and neonatal outcomes. Addiction 116, 3069–3079. https://doi.org/10.1111/add.15467.
Smith, G.D., 2012. Negative control exposures in epidemiologic studies. Epidemiology 23, 350–351. https://doi.org/10.1097/EDE.0b013e318245912c.
Tawfik, D.S., Gould, J.B., Profit, J., 2019. Perinatal risk factors and outcome coding in clinical and administrative databases. Pediatrics 143, e20181487. https://doi.org/10.1542/peds.2018-1487.
Thompson, R., DeJong, K., Lo, J., 2019. Marijuana use in pregnancy: a review. Obstet. Gynecol. Surv. 74, 415–428. https://doi.org/10.1097/OGX.0000000000000685.
Volkow, N.D., Compton, W.M., Wargo, E.M., 2017. The risks of marijuana use during pregnancy. JAMA 317, 129. https://doi.org/10.1001/jama.2016.18612.
Volkow, N.D., Han, B., Compton, W.M., McCance-Katz, E.F., 2019. Self-reported medical and nonmedical cannabis use among pregnant women in the United States. JAMA 322, 167–169. https://doi.org/10.1001/jama.2019.7982.
Widdows, K., O'Malley, A., O'Neill, B., Kingdom, J., Gillan, J., Ansari, T., 2012. Altered placental development in pregnancies resulting in sudden infant death syndrome (SIDS). Early Hum. Dev. 88, 805–811. https://doi.org/10.1016/j.earlhumdev.2012.05.006.
Winchester, M.-L., Shahiri, P., Boevers-Solverson, E., Hartmann, A., Ross, M., Fitzgerald, S., Parrish, M., 2022. Racial and ethnic differences in urine drug screening on labor and delivery. Matern. Child Health J. 26, 124–130. https://doi.org/10.1007/s10995-021-03258-5.
World Health Organization, 2014. Guidelines for the identification and management of substance use and substance use disorders in pregnancy. Geneva, Switzerland.
Zou, G., 2004. A modified poisson regression approach to prospective studies with binary data. Am. J. Epidemiol. 159, 702–706. https://doi.org/10.1093/aje/kwh090.