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Prenatal cannabis use disorder and gastroschisis in California, 2007–19

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Abstract

Background: Gastroschisis is a congenital anomaly of the abdominal wall with an unknown aetiology. Recent trends in the prevalence of gastroschisis suggest that changing environmental or behavioural factors may contribute. We examined whether prenatal cannabis use disorder was associated with gastroschisis.

Methods: The Study of Outcomes of Mothers and Infants is a population-based cohort compiled of California birth records that have been linked to Department of Health Care Access and Information hospitalization, emergency department and ambulatory surgery records. We included 2007–19 singleton live births ($n = 5\,774\,656$). Cannabis use disorder was measured by diagnosis codes at any visit during pregnancy or at birth. Gastroschisis was measured by diagnosis or surgical repair procedure codes at birth or during the first year of life.

Results: The prevalence of cannabis use disorder was about 1%. The prevalence of gastroschisis was 0.14% and 0.06% among those with and without cannabis use disorder, respectively. There were positive associations between cannabis use disorder and gastroschisis when using a multivariable model [adjusted risk ratio (aRR) = 1.3, 95% confidence interval (CI) 1.0, 1.7) and a matched sample approach (aRR = 1.5, 95% CI 1.1, 2.1). The association varied by maternal age and was largest among people aged >34 years (aRR = 2.5, 95% CI 1.0, 5.8).

Conclusions: We confirm findings of a positive association between cannabis exposure and gastroschisis and add that it is strongest when maternal age is greater than 34 years. More investigation into whether the association is causal, and why the association varies by maternal age, is encouraged.

Keywords: Cannabis, gastroschisis, birth defect, sibling design.

Key Messages

- We examined associations between prenatal cannabis use disorder and gastroschisis in a population-based cohort of >5 million births.
- Prenatal cannabis use disorder was associated with a small increase in risk of gastroschisis in multivariable and matched sample models.
- The association was modified by maternal age such that it was strongest among people aged >34 years.

Introduction

Gastroschisis is an abdominal wall defect causing fetal intestines to develop outside the abdominal cavity. The defect develops during the first trimester and is identified on prenatal ultrasound scans.[1–3] Several hypotheses exist, though the pathogenesis and aetiology of gastroschisis are unknown.[4–9]

The strongest risk factor for gastroschisis is young maternal age.[9–11] Individuals with maternal age <20 years have 5- to 10-fold higher odds of gastroschisis compared with individuals aged 25 years or older.[11–13] Curiously, birth rates for females aged 15–19 in the USA dropped dramatically between 1990 and 2020, but there were no concomitant declines in gastroschisis prevalence.[14,15] Rather, the US prevalence of gastroschisis increased from 1997 (2.9 per 1000 infants) to 2008 (6.4 per 1000 infants) before declining back to pre-2000 levels by 2018

(3.3 per 1000 infants).[1,13] Considering these trends, gastroschisis risk cannot be explained only by young maternal age. Changes in environmental or behavioural exposures likely contribute.

One proposed causal exposure is prenatal cannabis use, which increased in prevalence among pregnant individuals between 2002 and 2014.[16] Reece and Hulse recently cited 2.5- to 3-fold increases in gastroschisis prevalence and similar increases in cannabis use in California, deeming these parallel trends a 'can[ary] in the Californian coal mine'.[17] Similar ecological patterns were observed in Canada and Europe.[18,19] Whereas it is plausible that cannabis use is contributing to trends in gastroschisis, causal inference is limited with ecological data.

Three cohort and three case-control studies with individual-level data estimated positive unadjusted associations between prenatal cannabis exposure and gastroschisis.[20–25] Among

these, only the case-control studies adjusted for sociodemographic characteristics and other prenatal drug exposures, reporting adjusted odds ratios of 1.2 [95% confidence interval (CI) 0.8, 1.7],[25] 3.0 (95% CI 1.3, 5.7)[24] and 2.2 (95% CI 1.0, 4.8).[21]

Future research requires prospective cohort studies with adjustment for confounding variables. Leveraging population-based birth cohort data from California, we estimated the association between prenatal cannabis use disorder diagnosis and gastroschisis. Secondarily, we evaluated whether the association varied by maternal age.

Methods

The Study of Outcomes in Mothers and Infants (SOMI) is a population-based cohort study compiled from 2007 to 2019 California live birth records. Individual records were probabilistically linked to Department of Health Care Access and Information (HCAI) hospitalization, emergency department and ambulatory surgery records for the person giving birth and the infant. There were 6 934 814 live births between 2007 and 2019. Of these, we included singleton births, births with gestational age between 20 and 44 weeks, and births where linkage between birth records and HCAI was possible ($n = 5\,774\,656$) (Supplementary Figure S1, available as Supplementary data at *IJE* online). 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.

HCAI hospitalization records include procedure and diagnosis 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). We used ICD codes to identify individuals with cannabis use disorder diagnosed at any visit during pregnancy or during the birth episode. We also identified gastroschisis cases from ICD codes in HCAI files, coding individuals with either a diagnosis of gastroschisis or a procedure code for gastroschisis repair as a gastroschisis case. In Supplementary Table S1, available as Supplementary data at *IJE* online, we compared the prevalence of gastroschisis when using different criteria.[26] Prior research comparing case ascertainment using diagnostic and procedure codes with second trimester ultrasound findings from the California Prenatal Screening Program reported more than 96% agreement in the identification of gastroschisis.[11]

Other variables measured in the birth record were maternal age (in years), self-reported race/ethnicity (non-Hispanic White, Hispanic Mexican, Other Hispanic, Black, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Asian, two or more races, other or unknown), payer for delivery (private insurance, public insurance, self-pay, other, unknown), maternal education ($\leq$12 years, >12 years, unknown), pre-pregnancy body mass index (underweight ($<18.5\,\text{kg/m}^2$), normal (18.5–$<25\,\text{kg/m}^2$), overweight (25–$<30\,\text{kg/m}^2$), obese (30 or more kg/m^2), unknown), and nulliparity. We assigned the National Center for Health Statistics urban-rural classification system categories (large central fringe, metro, medium metro or small metro, micropolitan or non-core, unknown) based on reported county of residence at delivery.[27] Other measured variables included pre-pregnancy diabetes, pre-pregnancy hypertension, tobacco use in pregnancy, alcohol use disorder, non-cannabis substance use disorder, major depressive disorder, anxiety disorder and bipolar disorder. We coded these variables as present if there was an indication in either the birth record or linked HCAI files (Supplementary Table S2, available as Supplementary data at *IJE* online). We used a directed acyclic graph (DAG) to inform selection of confounding variables (Supplementary Figure S2, available as Supplementary data at *IJE* online).

Statistical analysis

We described characteristics of the person giving birth according to the presence of cannabis use disorder diagnosis and, in Supplementary Table S3 (available as Supplementary data at *IJE* online), according to gastroschisis diagnosis. We plotted the prevalence of cannabis use disorder and the prevalence of gastroschisis by year. Within years, we estimated proportions of gastroschisis cases with maternal age <18 years, maternal age 18–34 years and maternal age >34 years.

We used sequentially adjusted modified Poisson regression models to estimate risk ratios (RRs) and 95% confidence intervals (CIs) for the association between cannabis use disorder and gastroschisis.[28] The first model was unadjusted, the second model adjusted for maternal age and race/ethnicity and the third model additionally adjusted for nulliparity, county urbanicity, payer for delivery, nicotine-related diagnosis, non-cannabis drug use, alcohol use disorder, maternal depression and maternal body mass index. Missingness was treated as a valid response option for confounding variables.

Next, we matched individuals with a cannabis use disorder 1:2 to people without cannabis use disorder on maternal age (exact in years), year of delivery (exact), race/ethnicity (exact) and body mass index (exact category). We used a multi-level modified Poisson regression model [strata = matched pair identification (ID)] to estimate RRs and 95% CIs. The first set of models included only the random effect for the matching ID and so should be interpreted as having adjustment for the matching variables. The second model added multivariable adjustment for all other confounding variables.

Sensitivity analyses

We evaluated potential biases due to outcome misclassification, exposure misclassification and unmeasured confounding. In the first sensitivity analysis, we repeated multivariable regression analyses with differing definitions of gastroschisis, using only the gastroschisis repair procedure code to define the outcome. We did this because, whereas the diagnostic coding of gastroschisis and other abdominal wall abnormalities changed during the study period, the procedure code for gastroschisis repair was consistent across all years (Supplementary Table S1, available as Supplementary data at *IJE* online).[26] In the second sensitivity analysis, we used the R package 'episensr' to conduct a probabilistic misclassification analysis assuming both non-differential and differential misclassification of cannabis use disorder and assuming specificity was good (0.9).[29] For the non-differential misclassification analysis, we varied the sensitivity of cannabis use disorder from 0.2 to 0.8. For the differential misclassification analysis, we varied the sensitivity of cannabis use disorder only among those without gastroschisis, leaving sensitivity in the gastroschisis group at 0.9, until we found the combination that fully negated our findings. Our rationale was that individuals without a major structural defect like

gastroschisis may be less likely to be evaluated for cannabis use disorder, resulting in a low sensitivity in this group.

In the next analyses we calculated the e-value, which measures the magnitude of the association that an unmeasured confounder would need to have with both the exposure and the outcome to negate the findings.[29] Our final analysis to address unmeasured confounding was a sibling comparison design. We identified a subset of births where the person giving birth in two separate pregnancies was the same and where cannabis use disorder was present during one birth but not the other. We included only first (noted as nulliparous) and second live births for each birthing person. We then used a multi-level modified Poisson regression model (strata = sibling pair) to estimate RRs. These models adjusted for all confounding variables except those that did not change between pregnancies, which were adjusted by design. Finally, due to concerns that our restriction to nulliparous and second births favoured a very young distribution of maternal age, we re-ran the sibling analysis including only individuals where the first birth occurred after age 25.

Results

Approximately 1% ($n = 50\,435$) of records had a diagnosis of cannabis use disorder recorded. Compared with those without a cannabis use disorder diagnosis, those with a diagnosis were more likely to have younger maternal age and less than 12 years of education. They were more likely to be Non-Hispanic White, Black or American Indian/Alaska Native, publicly insured and living in more rural counties. Finally, those with a cannabis use disorder diagnosis were more likely to have used nicotine during pregnancy, have an alcohol use or other substance use disorder and have a diagnosis of major depressive disorder, anxiety disorder or bipolar disorder (Table 1).

The prevalence of cannabis use disorder increased from 49.3 to 145.6 per 10 000 births between 2007 and 2019. The prevalence of gastroschisis increased from 4.5 to 7.8 per 10 000 births. The proportion of gastroschisis cases born to people with young maternal age declined over time. In 2007, 9.2% of gastroschisis cases had maternal age <18 and 6.1% of cases had maternal age >34. In 2019, these percentages were 2.1% and 23.2%, respectively (Figure 1).

Among individuals with no cannabis use disorder diagnosis, the prevalence of gastroschisis was 6 per 10 000 births, or 0.06%. Among births with a cannabis use disorder diagnosis, the prevalence of gastroschisis was 14 per 10 000 births, or 2.5 (95% CI 2.0, 3.1) times higher. After adjustment for maternal age and race/ethnicity, the aRR was attenuated to 1.8 (95% CI 1.4, 2.3), and after full adjustment was 1.3 (95% CI 1.0, 1.7) (Table 2). Results were similar in the matched cohort [aRR = 1.5 (95% CI 1.1, 2.1)] (Table 2).

After stratifying by maternal age, the baseline incidence of gastroschisis was much higher at lower maternal ages. Among individuals with no cannabis use disorder, the prevalence of gastroschisis was 0.17% among individuals aged <18, 0.06% among individuals aged 18–34 and 0.03% among individuals aged >34. In fully adjusted models, there was no association between cannabis use disorder and gastroschisis in the youngest group (aRR = 0.9, 95% CI 0.3, 3.0), a small association among individuals aged 18–34 (aRR = 1.3, 95% CI 1.0, 1.7) and a larger association among individuals older than 34 years (aRR = 2.4, 95% CI 1.0, 5.8) (Table 3).

Table 1. Characteristics of the birthing person stratified by presence of a cannabis use disorder diagnosis, Study of Outcomes in Mothers and Infants, 2007–19

Characteristic	Cannabis use disorder ($n = 50\,435$)		No cannabis use disorder ($n = 5\,724\,221$)	
	n	%	*n*	%
Age				
<18 years	1671	3.31	117 327	2.05
18–25 years	22 012	43.64	1 357 081	23.71
25–30 years	14 314	28.38	1 521 117	26.57
30–35 years	8271	16.40	1 585 735	27.70
>35 years	4165	8.26	1 142 785	19.96
Unknown	<5		176	<0.01
Race/ethnicity				
Non-Hispanic White	17 098	33.90	1 499 067	26.19
Hispanic-Mexican	10 662	21.14	2 139 504	37.38
Other Hispanic	5869	11.64	734 452	12.83
Black	10 725	21.26	278 235	4.86
American Indian/Alaska Native	662	1.31	18 362	0.32
Hawaiian/Pacific Islander	205	0.41	22 834	0.40
Asian	588	1.17	797 288	13.93
Two or more races	3097	6.14	116 349	2.03
Other or unknown	1529	3.03	118 130	2.06
Payer for delivery				
Private	11 397	22.60	2 724 587	47.60
Public	37 614	74.58	2 736 799	47.81
Self-pay	940	1.86	159 232	2.78
Other	479	0.95	103 373	1.81
Missing	5	0.01	230	<0.01
Urban–rural classification				
Large central	23 885	47.36	3 562 192	62.23
Fringe metropolitan	7510	14.89	712 929	12.45
Medium/small metropolitan	16 086	31.89	1 331 628	23.26
Micropolitan/non-core	2761	5.47	95 787	1.67
Unknown	193	0.38	21 685	0.38
Education				
LT or EQ to 12 years	12 989	25.75	1 105 061	19.31
>12 years	34 634	68.67	4 382 717	76.56
Unknown	2812	5.58	236 443	4.13
Pre-pregnancy health				
Diabetes	956	1.90	65 563	1.15
Hypertension	2354	4.67	116 060	2.0
Nulliparous	21 421	42.47	2 216 704	38.72
Mental health				
Major depressive disorder	6986	13.85	130 212	2.27
Anxiety disorder	7300	14.47	165 004	2.88
Bipolar disorder	3748	7.43	29 151	0.51
Substance use				
Non-cannabis drug-related diagnosis[a]	12 177	24.14	48 925	0.85
Alcohol-related diagnosis	2760	5.47	12 927	0.23
Tobacco use in pregnancy	16 950	33.61	126 513	2.21
Body mass index				
Underweight	2955	5.86	238 452	4.17
Normal	21 134	41.90	2 580 751	45.08
Overweight	11 606	23.01	1 417 615	24.77
Obese	11 923	23.64	1 203 933	21.03
Missing	2817	5.59	283 470	4.95

Data from cells with less than five births are suppressed.
LT: less than; EQ: equals.
[a] Non-cannabis drug-related diagnoses included opioid-related disorders; sedative-, hypnotic-, or anxiolytic-related disorders; cocaine-related disorders; other stimulant-related disorders; hallucinogen-related disorders; inhalant-related disorders; and other psychoactive substance-related disorders (International Classification of Disease codes presented in Supplementary Table S2, available as Supplementary data at *IJE* online).

In the first sensitivity analysis, re-running our main analyses with a different operationalization of the outcome did not change the findings (Supplementary Table S4, available as
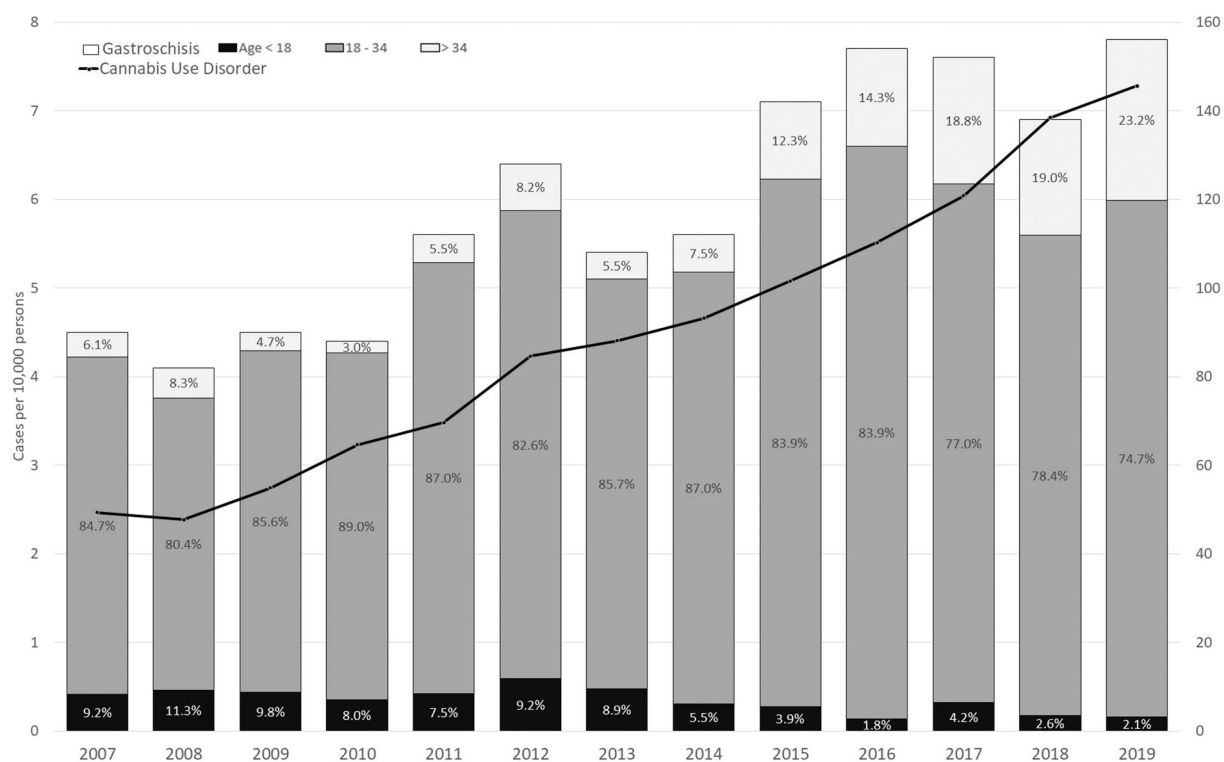
Figure 1. Trends in the prevalence of cannabis use disorder (right axis, line) and gastroschisis (left axis, bars) in California, 2007–19. The percentage inside each bar graph is the proportion of all gastroschisis cases in that year born to people with the ages highlighted. For example in 2007, 9.2% of the gastroschisis cases had maternal age <18, 84.7% of gastroschisis cases had maternal age 18–34 and 6.1% of gastroschisis cases had maternal age >34. Left axis: bar chart, prevalence of gastroschisis per 10 000 persons. Right axis: line chart, prevalence of cannabis use disorder per 10 000 persons

Table 2. Associations between cannabis use disorder and gastroschisis, Study of Outcomes in Mothers and Infants, 2007–19

Cannabis use disorder	Gastroschisis		RR (95% CI)	aRR[a] (95% CI)	aRR[b] (95% CI)
	n	%			
Full sample					
Yes (*n* = 50 435)	72	0.14	2.5 (2.0–3.1)	1.8 (1.4–2.3)	1.3 (1.0–1.7)
No (*n* = 5 724 221)	3317	0.06	1.0 (ref)	1.0 (ref)	1.0 (ref)
Matched sample[c]					
Yes (*n* = 50 358)	72	0.14	1.5 (1.1–2.0)		1.5 (1.1–2.1)
No (*n* = 100 716)	97	0.10	1.0 (ref)	n/a	1.0 (ref)

aRR, adjusted risk ratio; CI, confidence interval; RR, risk ratio; .ref, reference value; n/a, not available.
[a] Risk ratio adjusted for maternal age in years and race/ethnicity.
[b] Risk ratio adjusted for maternal age in years, nulliparity, race/ethnicity, county urbanicity, payer, tobacco use, non-cannabis drug use, alcohol use disorder, maternal depression and maternal body mass index.
[c] Matched cohort includes individual matching 1:2 (exposed to cannabis use disorder: unexposed to cannabis use disorder) on race (exact), birth year (exact to rounded year), maternal age (exact) and body mass index (exact category: underweight, normal, overweight, obese). Exposed births that were not matched to two unexposed births were excluded from the matched analyses.

Table 3. Associations between cannabis use disorder and gastroschisis stratified by maternal age, Study of Outcomes in Mothers and Infants, 2007–19

	n	*n* (%) with gastroschisis	RR	aRR
Maternal age <18 years				
Cannabis use disorder	1671	3 (0.18)	1.0 (0.3–3.2)	0.9 (0.3–3.0)
No cannabis use disorder	117 327	203 (0.17)	ref	ref
Maternal age 18–34 years				
Cannabis use disorder	44 597	63 (0.14)	2.3 (1.8–3.0)	1.3 (1.0–1.7)
No cannabis use disorder	4 463 933	2742 (0.06)	ref	ref
Maternal age >34 years				
Cannabis use disorder	4165	6 (0.14)	4.4 (2.0–9.9)	2.4 (1.0–5.8)
No cannabis use disorder	1 142 785	372 (0.03)	ref	ref

Multivariable model includes adjustment for race/ethnicity, county urbanicity, payer, tobacco use, other drug use, alcohol use disorder, maternal depression, maternal body mass index and nulliparity.
RR, risk ratio; aRR, adjusted risk ratio; ref, reference value.

Supplementary data at *IJE* online). In the second sensitivity analysis, we found that to fully attenuate our observed RR to the null, there would need to be differential misclassification where the sensitivity in the no gastroschisis group was 0.5. Third, to assess potential unmeasured confounding, we estimated an e-value of 1.9, suggesting that an unmeasured confounder would need to have at least a 2-fold association with both the exposure and outcome to attenuate the reported adjusted estimate to the null value.[29]

Finally, in the sibling cohort, we identified 943 506 pairs of siblings, of whom 5524 had cannabis use disorder documented in the first birth only and 6501 had cannabis use disorder documented in the second birth only. Analysis of sibling pairs discrepant on exposure yielded an adjusted RR of 1.0 (95% CI 0.5, 1.9). After restricting the sibling analysis to birthing people where the first birth occurred at ages >25 years, the age-adjusted RR was 3.1 (95% CI 0.3, 29.4) (Supplementary Table S5, available as Supplementary data at *IJE* online).

Discussion

In this study, we estimated associations between cannabis use disorder and gastroschisis in a population-based cohort of births in California. The prevalence of both cannabis use disorder and gastroschisis increased between 2007 and 2019. There were small positive associations between cannabis use disorder and gastroschisis in adjusted models. These associations varied by maternal age, with stronger associations observed among individuals aged more than 34 years..

Anderson *et al.* previously reported a rise in California's prevalence of gastroschisis from 1.5 cases per 10 000 births in 1995 to 5.3 cases per 10 000 births in 2012.[10] We observed similar prevalence estimates for 2007 to 2012 and added that the estimates continued to increase through 2019. This rising prevalence of cannabis use disorder may reflect true increases in the occurrence of cannabis use disorder. It may also reflect shifting norms surrounding acceptance of cannabis use, leading to increased disclosure, screening and diagnosis in medical settings.

We reported that those with a cannabis use disorder diagnosis had a small increased risk in gastroschisis after adjustment for confounding variables and after exact matching on maternal age, race, birth year and body mass index. Our estimates were smaller than the adjusted odds ratios of 3.0 (95% CI 1.3, 6.8) reported by Torfs *et al.*[24] and 2.2 (95% CI 1.0, 4.8) reported by Lam and Torfs.[21] However, we note that the former did not adjust for maternal smoking, and neither adjusted for alcohol, which are confounding variables. Estimates without adjustment for these variables may be biased away from the null.

The magnitude of estimates from the multivariable and matched sample models were slightly larger than the estimate published by van Gelder *et al.*, who reported an adjusted odds ratio of 1.2 (95% CI 0.8, 1.7) using data from the National Birth Defects Prevention case-control study.[25] Of the prior studies, van Gelder *et al.* had the most comprehensive set of confounding variables, including sociodemographic variables, body mass index, maternal reported periconceptional smoking and drinking and folic acid supplementation.[25] Notably, our study exposure, cannabis use disorder measured by diagnosis codes, is not directly comparable to the self-reported periconceptual cannabis use

exposure examined by van Gelder *et al.*[25] Our exposed group included individuals who were identified as having life problems related to their cannabis use and likely used cannabis more frequently than other cannabis users. If there is a causal effect of cannabis on gastroschisis, it is possible that having an exposed sample using cannabis with greater frequency or consequence is contributing to a larger effect estimate than what would be observed if evaluating normative cannabis use.

The stratification by maternal age was motivated by prior studies showing that the effects of cigarette smoking on gastroschisis were much larger at older maternal ages.[12,30] Our results show the same phenomenon for cannabis use disorder. We reported no associations between cannabis use disorder and gastroschisis among births with maternal age <18 years and a doubling of gastroschisis risk with cannabis use disorder among births with maternal age >34 years. It is also noteworthy that when examining trends in gastroschisis prevalence over time, the proportion of cases born to people >34 years increased over the study period. It is possible that older birthing persons are more likely to have pre-pregnancy vascular diseases which leave them more vulnerable to the effects of vasoconstrictive exposures, one of the proposed risk factors for gastroschisis.[30] This hypothesis could be investigated further by examining effect modification by vasoconstrictive exposures such as hypertension, cocaine use, or some therapeutic drugs. It is also possible that older maternal age is a marker for longer duration of cannabis exposure. More investigation of mechanisms explaining potentially different aetiological factors at different maternal ages is needed.

Last, we extended our interrogation of the association between cannabis use and gastroschisis with use of a sibling comparison design, by leveraging data from a subset of people with nulliparous and second births that were discrepant on exposure to cannabis use disorder. Estimates from this approach should be interpreted as adjusted for any shared confounders that are specific to the birthing person (e.g. genetic factors, common household factors) in addition to the measured confounders included in regression models. The RR estimated from the sibling comparison sample was 1.0, suggesting that the positive associations observed using previous approaches may have been inflated due to unmeasured confounding. However, this estimate should be viewed considering limitations. First, limiting the sibling sample to birthing persons' nulliparous and second births shifted the age distribution of the sample to younger individuals. In post hoc analyses, we restricted our sibling sample to individuals where maternal age was older than 25 and observed a much larger RR (3.0), paralleling findings from the effect modification analyses. Another limitation is that discrepancies in cannabis use disorder across two pregnancies may have reflected differences in recording of the diagnosis and not differences in exposure to cannabis. Also, change of paternity between pregnancies, which has been linked to gastroschisis risk, was not considered.[8]

Other limitations should be considered. First, administrative data may have poor measurement of confounding variables, leaving unmeasured and residual confounding likely. Second, use of diagnosis codes in hospitalization records to identify cannabis use disorder most likely resulted in underascertainment of the exposure. Third, our sample was restricted to live births. If cannabis exposure in pregnancy

caused either spontaneous abortion or stillbirth, our restriction to live births would have induced selection bias towards the null. Similarly, we lacked data on elective termination. Gastroschisis is readily prenatally diagnosed, and likelihood of termination may vary by socioeconomic and demographic factors. Our estimates may be biased by this non-random selection. The trend data could also be influenced by trends in termination of gastroschisis cases.

Despite limitations, we provide the most comprehensive investigation of the association between disordered cannabis use and gastroschisis to date. We used data from a large population-based sample, considered multiple approaches to adjust for confounding bias and conducted sensitivity analyses to account for confounding and information biases. Considering all analyses together, we conclude that cannabis use disorder and gastroschisis are correlated at the ecological and individual levels. The question of whether these associations are causal remains. We found that after adjustment for measured confounding variables, a small positive association remained which was strongest in individuals over age 34. These findings were reinforced by the sibling design. We encourage replication to see whether these findings persist across different settings.

Ethics approval

The Study of Outcomes in Mothers and Infants 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.

Data availability

The data underlying this article cannot be shared under the current Institutional Review Board agreement. We direct researchers to the California Department of Public Health Center for Health Statistics and Information, and the California Department of Health Care Access and Information for information on requesting and accessing California state data.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

E.D. and G.B. conceived the study methods and design. R.J. B. and C.C. were responsible for data access and advised on the data analytical plan. C.C. and A.E.K. provided subject matter and clinical expertise. All authors were involved in the interpretation of the data. E.D. drafted the initial manuscript, which was reviewed and revised by all authors. All authors read and approved the final manuscript.

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Conflict of interest

None declared.

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