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RESEARCH REPORT

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Association of cannabis use during pregnancy with severe acute respiratory syndrome coronavirus 2 infection: a retrospective cohort study

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Abstract

Background and Aims: Cannabis use is increasingly common among pregnant individuals and might be a risk factor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We aimed to test whether prenatal cannabis use is associated with increased risk of SARS-CoV-2 infection during pregnancy.

Design: This is a retrospective cohort study.

Setting: The study was conducted in California, USA.

Participants: A total of 58 114 pregnancies (with outcomes from 5 March 2020 to 30 September 2021) among 57 287 unique pregnant women aged 14–54 years who were screened for prenatal substance use, enrolled in Kaiser Permanente Northern California (KPNC) (a health-care system) and had not tested positive for COVID-19 prior to pregnancy onset.

Measurements: We utilized data from the KPNC electronic health record. Cannabis use status (current, recently quit and non-user) was based on universal screenings during prenatal care (including urine toxicology testing and self-reported use on a self-administered questionnaire). SARS-CoV-2 infection [based on polymerase chain reaction (PCR) tests] was estimated in time-to-event analyses using Cox proportional hazard regression models adjusting for covariates. Secondary analyses examined differences in (a) SARS-CoV-2 testing rates and (b) SARS-CoV-2 infection rates among those tested.

Findings: We observed 348 810 person-months of follow-up time in our cohort with 41 064 SARS-CoV-2 PCR tests and 6% (n = 2414) of tests being positive. At the start of follow-up, 7% of pregnant individuals had current use, 12% had recently quit and 81% did not use cannabis. Adjusting for covariates, current use was associated with lower rates of SARS-CoV-2 infection [adjusted hazard ratio (aHR) = 0.60, 95% confidence interval (CI) = 0.49–0.74 than non-use. Those who had recently quit did not differ from non-cannabis users in infection rates (aHR = 0.96, 95% CI = 0.86–1.08). Sensitivity

analyses among patients who received a SARS-CoV-2 test also found lower odds of infection associated with current versus no cannabis use (aOR = 0.76, CI = 0.61–0.93).

Conclusions: Current cannabis use appears to be associated with a reduced risk of SARS-CoV-2 infection among pregnant individuals.

KEYWORDS
Cannabis, COVID-19, marijuana, pregnancy, prenatal, SARS-CoV-2

INTRODUCTION

Pregnant individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have an increased risk of becoming seriously ill compared to individuals not pregnant [1–3]. Further, SARS-CoV-2 infection during pregnancy is associated with increased morbidity and mortality for both mothers and fetuses [1, 2, 4–6]. Understanding factors associated with SARS-CoV-2 risk among pregnant individuals is critical for providing them with better guidance and protection.

Among pregnant and reproductive-aged women in the United States, rates of cannabis use are rising [7–10], corresponding with increases in its general acceptance and accessibility [11, 12]. Cannabis use during pregnancy is associated with health risks, including low infant birth weight and effects on offspring neurodevelopment [13–16], but its effect on risk of SARS-CoV-2 infection is unknown. Cannabis smoke has toxicity similar to that of cigarette smoke [17, 18]. Cigarette smoking substantially increases the risk of some pulmonary infectious diseases, such as tuberculosis, and might increase the risk of viral infections SARS-CoV-2 [19]. In addition, it is possible that individuals who smoke or vape cannabis are more likely to become infected because of associated risky behaviors, including increased contact between the fingers and the mouth, removal of one's mask while vaping or smoking and/or sharing cannabis products with others who are infected. Conversely, cannabis products may have pharmacological effects that might offer some protection against SARS-CoV-2 infection [20–23]. For example, some cannabinoids can bind to the SARS-CoV-2 spike protein that is critical for viral entry into cells [24]. Cannabidiol (CBD) may down-regulate angiotensin converting enzyme 2 (ACE2), which is the site of SARS-CoV-2 viral attachment on cell surfaces, and inhibits viral replication in pulmonary epithelial cells [20, 22].

Findings from general population studies are limited and equivocal. A large, retrospective case–control study of electronic health record (EHR) data found that individuals with a past-year (versus no past-year) cannabis use disorder diagnosis had significantly increased odds of SARS-CoV-2 infection, but those with a life-time (versus never) cannabis use disorder diagnosis had significantly lower odds of SARS-CoV-2 infection [25]. A population-based cohort study found that having a cannabis use disorder was associated with an increased risk for SARS-CoV-2 breakthrough infection in fully vaccinated patients [26]. Conversely, several *in-vitro* studies provide initial evidence that cannabis compounds may offer some protection against SARS-CoV-2 infection. Pre-clinical studies show that cannabis compounds bind to the spike protein of SARS-CoV-2, preventing it from entering cells and causing infection [24], decrease ACE2 protein levels to which the spike protein binds [27], prevent SARS-CoV-2 replication [20] and reduce COVID-19 related inflammation [21].

Well-designed population-based studies that compare SARS-CoV-2 infection risk among current, former and never-cannabis users could improve understanding of the mechanisms that affect susceptibility to SARS-CoV-2 and inform public health strategies to mitigate risk in future outbreaks. Further, given that rates of prenatal cannabis use are rising [7–9] and pregnancy is a unique time in which the immune system is modulated and risks associated with SARS-CoV-2 infection are heightened, research among pregnant women is of particular importance. Leveraging data from a large, diverse sample of pregnant patients with universal screening for preconception and prenatal cannabis use during standard prenatal care, we performed a retrospective cohort study to evaluate whether cannabis use status is associated with risk of SARS-CoV-2 infection during pregnancy.

METHODS

Setting and study population

Kaiser Permanente Northern California (KPNC) is an integrated health-care system with 21 hospital-based medical centers serving approximately 4.4 million racially and socio-demographically diverse patients who are representative of Northern California [28]. On 4 March 2020, following the state's first COVID-19 death, California's Governor declared a state of emergency [29].

Using EHR data, we conducted a retrospective cohort study of pregnancies that began between 1 May 2019 and 1 December 2020 and ended between 5 March 2020 and 30 September 2021. This criterion ensured that our cohort did not over-represent women with short pregnancies due to pregnancy loss. Non-KPNC members at the time of pregnancy onset, patients who discontinued membership before the pandemic began or who tested positive for SARS-CoV-2 by polymerase chain reaction (PCR) prior to pregnancy onset were excluded. To obtain measures for all pregnancies, we excluded patients who did not complete the question about self-reported cannabis use during the year before pregnancy and patients who had no urine toxicology test during pregnancy. The KPNC IRB approved the project with a waiver of informed consent.

Outcomes

The primary outcome was SARS-CoV-2 infection, defined as first positive SARS-CoV-2 PCR test recorded by KPNC during pregnancy (Supporting information). Our study included the time-period before and during the Delta variant. A secondary outcome was receiving a SARS-CoV-2 PCR test in KPNC, regardless of test outcome, to assess whether current or former cannabis users were more or less likely to be tested for SARS-CoV-2. Once a patient tested positive via PCR test, no subsequent tests were included in any analyses.

Exposure

The primary exposure of interest was cannabis use status ('current', 'recently quit' and 'non-user') during pregnancy, which we treated as time-varying. Cannabis use status was derived primarily from urine toxicology tests performed during pregnancy. All patients had initial urine toxicology tests around their first prenatal visit (~8 weeks gestation) with possible subsequent tests during pregnancy (Supporting information). Positive toxicology tests were confirmed with a laboratory test. Cannabis use status was further established using responses to a substance use screening questionnaire self-administered around the first prenatal visit, which included a question about any cannabis use during the year prior to pregnancy. A patient with a positive initial urine toxicology test was considered a 'current' cannabis user from the start of pregnancy until a subsequent negative prenatal toxicology test, if any. A negative test changed the patient's cannabis use status to 'recently quit'. A patient with a negative initial urine toxicology test was considered a 'non-user' from the start of pregnancy unless the self-report questionnaire reported use of cannabis during the year before pregnancy, which changed their cannabis status to 'recently quit'. A subsequent positive toxicology test changed their status to 'current'.

Covariates

From the EHR documentation, we extracted the following baseline information as of the pregnancy onset date: age, self-reported race/ethnicity (white, Hispanic, Asian/Pacific Islander, black and other/unknown/multi-racial), neighborhood deprivation index (NDI; categorized into quartiles) [30], insurance payor [subsidized (Medicare, Medicaid or other) versus non-subsidized], primary KPNC facility at which the patient received care (categorical, 25 facilities), parity, pre-pregnancy body mass index [BMI (kg/m^2); underweight < 18.5, normal 18.5–24.9, overweight 25.0–29.9, obese ≥ 30.0] [31], pre-existing diabetes (based on the KPNC Diabetes Registry [32–34] within 2 years prior to pregnancy onset or a recorded A1C ≥ 6.5 in the first trimester) and pre-existing hypertension classified by ICD-10 codes (Supporting information). We also assessed tobacco smoking status during pregnancy, which we treated as a time-changing variable ('current', 'former' and 'never'). Self-reported tobacco smoking status is routinely assessed and documented during KPNC primary and specialty care visits, including throughout prenatal care, and we used these assessments to create a time-changing variable.

Analysis

We examined patient characteristics overall and by initial cannabis use status as measured by responses to the self-administered substance use screening questionnaire and results of the first prenatal urine toxicology test. We calculated the observed rate (per 100 person-months) of SARS-CoV-2 tests and SARS-CoV-2 infections during pregnancy among all pregnancies and for each stratum of cannabis use status. One patient could have more than one SARS-CoV-2 test (until a first positive test). Cannabis use status was treated as time-varying and could change during follow-up. Therefore, when calculating rates of SARS-CoV-2 tests and infections, one patient could contribute denominator time to more than one cannabis use status level.

We used extended multivariable counting-process Cox proportional hazards [35] models that allow for time-updated covariates to examine the association between cannabis use status (at time of outcome) and risk of SARS-CoV-2 infection. In all models, we used calendar time as the time-scale to account for changes over time in SARS-CoV-2 circulation. Patients were followed from pregnancy onset (or from 5 March 2020 if onset was prior to 5 March 2020) until a positive PCR test, with censoring due to health plan disenrollment, first COVID-19 vaccine administration or pregnancy outcome. Models were fitted with varying levels of adjustment to understand the potential impact of confounding: model 1 included age (23 categories: < 19, one for each year of age up to 39, 40+), race/ethnicity, NDI, insurance payor and facility; model 2 added pre-pregnancy BMI, diabetes and hypertension, parity and tobacco smoking status. The outcome was the first positive SARS-CoV-2 test. To account for the correlation between multiple pregnancies in the same individual, we fitted marginal Cox proportional hazards models using robust sandwich covariance estimates.

We performed three sensitivity analyses where the outcome was SARS-CoV-2 infection. First, we performed a sensitivity analysis when the predictor of interest was the patient's initial cannabis use status rather than allowing cannabis use status to change. Secondly, given prior research indicating that current cigarette smoking might be related to lower risk of SARS-CoV-2 infection [36–40], we performed a sensitivity analysis where we excluded current or former tobacco smokers. In a third sensitivity analysis, we included only pregnancies in which the patient received at least one SARS-CoV-2 PCR test, and each test was a record in a logistic regression. A positive test result was the outcome and cannabis use status at the time of the test was the predictor of interest. The logistic regression was conditioned ('stratified') on the calendar date of the test so that patients testing positive on a certain day were compared to patients testing negative on that same day. This 'case-positive, control-test-negative' design has often been used in studies of vaccine effectiveness, and may

reduce bias associated with health-care-seeking behavior [41–43] and propensity to be tested.

In a secondary analysis, we examined the association between cannabis use status and receipt of SARS-CoV-2 PCR testing. In these analyses the outcome was a test, and testing was treated as a recurring event. The extended multivariable counting-process Cox proportional hazards models used for these analyses were identical in all other respects to the models used for the primary analyses where SARS-CoV-2 infection was the outcome. Analyses were conducted using SAS software, version 9.4. Statistical significance was assessed at two-sided $P \leq 0.05$.

The analysis was not pre-registered, and the results should be considered exploratory.

RESULTS

We initially identified 69 569 pregnancies during the study period. After excluding 6080 pregnancies not meeting membership criteria, 352 pregnancies testing positive for SARS-CoV-2 by PCR prior to pregnancy onset, 463 pregnancies because the patient did not complete the question about cannabis use during the year before pregnancy and 4375 pregnancies lacking ≥ 1 urine toxicology test during pregnancy, the final study sample included 58 114 pregnancies from 57 287 unique pregnant women (Supporting information).

The patient population had a mean age of 31 years at pregnancy onset and was 35% white, 27% Hispanic, 26% Asian or Pacific Islander, 6% black and 6% other/unknown/multi-racial (Table 1). At the start of follow-up, cannabis use status was 'current' for 7% of the pregnancies, 'recently quit' for 12% and 'non-user' for 81%. Patients with 'current' initial cannabis use were younger, more likely to be Hispanic or black, more likely to live in more deprived neighborhoods, have subsidized medical insurance, have hypertension and lower parity than patients classified as 'recently quit' or as 'non-user' (all *P*-values < 0.01). Among all pregnancies, 11% received ≥ 1 COVID-19 vaccine dose during pregnancy and 54% had ≥ 1 SARS-CoV-2 test recorded in the EHR. Most pregnancies (88.63%) were followed until a positive PCR test or the pregnancy outcome; 0.64% of pregnancies were censored due to membership disenrollment; 10.73% of pregnancies were censored due to vaccination.

We observed 348 810 person-months of follow-up time in our cohort and 41 064 SARS-CoV-2 PCR tests, with 6% (n = 2414) of tests being positive (Table 2). The overall rate of testing was 11.77 per 100 person-months; the overall rate of infection was 0.692 per 100 person-months. The unadjusted rate of testing was lower among those with current cannabis use (9.33 per 100 person-months) than among those who had recently quit (13.58) or non-users (11.61). The unadjusted rate of infection was also lower among those with current cannabis use (0.647 per 100 person-months) than among those who had recently quit (0.730) or non-users (0.688).

In the fully adjusted models, patients with current cannabis use had a lower hazard of SARS-CoV-2 infection [Table 3; adjusted hazard ratio (aHR) = 0.60, 95% confidence interval (CI) = 0.49–0.74] compared to non-users. Those who had recently quit cannabis use did not differ from non-users in risk of infection (aHR = 0.96, 95% CI = 0.86–1.08).

Results of sensitivity analyses were consistent with our overall finding of a lower relative risk of SARS-CoV-2 infection among subjects with current cannabis use compared to those with non-use. In the sensitivity analysis using only the initial cannabis use status as the predictor of interest, current cannabis use was associated with a lower hazard of infection (aHR = 0.71, 95% CI = 0.60–0.83) compared to non-use (Table 4). In the sensitivity analysis that excluded those with current or former cigarette smoking status, current cannabis use was associated with a lower hazard of infection (aHR = 0.59, 95% CI = 0.46–0.76) compared to non-use (Table 4). Similarly, in the 'case-positive, control-test-negative' sensitivity analysis restricted to patients who received SARS-CoV-2 testing, current cannabis use was associated with lower odds of infection [adjusted odds ratio (aOR) = 0.76, 95% CI = 0.61–0.9] compared to non-use, as was recently quit status (aOR = 0.83, 95% CI = 0.73–0.94) compared to non-use (Table 4).

In the fully adjusted models, compared to non-users, patients with current cannabis use had a lower hazard of SARS-CoV-2 testing (Table 5; aHR = 0.80, 95% CI = 0.76–0.85), and those who had recently quit cannabis use had a higher hazard of SARS-CoV-2 testing (aHR = 1.10, CI = 1.06–1.13).

DISCUSSION

In a large multi-specialty health-care system with routine screening for prenatal cannabis use during prenatal care, pregnant patients with current cannabis use had a lower risk of SARS-CoV-2 infection relative to those not using cannabis. This finding is consistent with several studies that found a lower risk of SARS-CoV-2 infection associated with current versus never-cigarette smoking [36–40]. In our study, those with current cannabis use were more likely than recently quit or non-cannabis users to smoke cigarettes; however, results remained similar in sensitivity analyses that excluded current and former cigarette smokers, indicating that differences in cigarette smoking were not driving results. The reduced risk of SARS-CoV-2 infection among those with current cannabis use is notable as they were more likely than non-cannabis users to have other risk factors associated with increased risk of SARS-CoV-2 infection (e.g. higher neighborhood deprivation, higher percentage subsidized insurance and greater proportion of black and Hispanic patients).

Our main analysis leaves open the possibility of unmeasured confounding due to lower rates of testing among those with current cannabis use and possibly different propensity to be tested given the same symptoms and same infection status. Our 'case-positive, control-test-negative' sensitivity analysis was limited to patients who received a PCR test and may be less sensitive to biases associated with the propensity to be tested. Although potential sources of bias and confounding remain with the case–positive, control test-negative approach [42–45], the results of that sensitivity analysis were

TABLE 1 Pregnancies during the COVID-19 pandemic, Kaiser Permanente Northern California

Characteristic	Cannabis use status at start of follow-up[a]			
	All (*n* = 58 114)	Current (*n* = 4053)	Recently quit (*n* = 7002)	Non-user (*n* = 47 059)
Age group, *n* (%)[b,c,d]				
< 25 years	6447 (11.09)	1347 (33.23)	1139 (16.27)	3961 (8.42)
25–< 35 years	36 742 (63.22)	2152 (53.10)	4402 (62.87)	30 188 (64.15)
35+ years	14 925 (25.68)	554 (13.67)	1461 (20.87)	12 910 (27.43)
Age, mean (median)[b,c,d]	31.08 (31.00)	27.69 (27.00)	30.18 (31.00)	31.50 (32.00)
Race/ethnicity, *n* (%)[b,c,d]				
Asian or Pacific Islander	15 317 (26.36)	233 (5.75)	1136 (16.22)	13 948 (29.64)
Black	3536 (6.08)	925 (22.82)	525 (7.50)	2086 (4.43)
Hispanic	15 528 (26.72)	1234 (30.45)	1796 (25.65)	12 498 (26.56)
Other/unknown/multi-racial	3509 (6.04)	291 (7.18)	506 (7.23)	2712 (5.76)
White	20 224 (34.80)	1370 (33.80)	3039 (43.40)	15 815 (33.61)
Neighborhood deprivation, *n* (%)[b,c]				
Quartile 1, least deprived	13 201 (22.72)	390 (9.62)	1670 (23.85)	11 141 (23.67)
Quartile 2	14 461 (24.88)	756 (18.65)	1775 (25.35)	11 930 (25.35)
Quartile 3	14 027 (24.14)	1075 (26.52)	1660 (23.71)	11 292 (24.00)
Quartile 4, most deprived	16 344 (28.12)	1820 (44.91)	1881 (26.86)	12 643 (26.87)
Missing	81 (0.14)	12 (0.30)	16 (0.23)	53 (0.11)
Subsidized insurance—Medicare, Medicaid or other, *n* (%)[b,c,d]	6016 (10.35)	1033 (25.49)	718 (10.25)	4265 (9.06)
Body mass index, *n* (%)[b,c,d]				
Underweight	1355 (2.33)	104 (2.57)	136 (1.94)	1115 (2.37)
Normal	23 070 (39.70)	1142 (28.18)	2861 (40.86)	19 067 (40.52)
Overweight	16 154 (27.80)	1035 (25.54)	1910 (27.28)	13 209 (28.07)
Obese	15 738 (27.08)	1651 (40.74)	1905 (27.21)	12 182 (25.89)
Unknown	1797 (3.09)	121 (2.99)	190 (2.71)	1486 (3.16)
Pre-existing diabetes, *n* (%)[e]	1080 (1.86)	75 (1.85)	107 (1.53)	898 (1.91)
Pre-existing hypertension, *n* (%)[b,c,e]	4061 (6.99)	412 (10.17)	513 (7.33)	3136 (6.66)
Parity, *n* (%)[b,c,d]				
0	23 027 (39.62)	1770 (43.67)	4203 (60.03)	17 054 (36.24)
1	20 803 (35.80)	1204 (29.71)	1554 (22.19)	18 045 (38.35)
2	7959 (13.70)	506 (12.48)	578 (8.25)	6875 (14.61)
3	2546 (4.38)	205 (5.06)	131 (1.87)	2210 (4.70)
4+	1247 (2.15)	75 (1.85)	48 (0.69)	1124 (2.39)
Tobacco smoking status at start of follow-up, *n* (%)[a,b,c,d]				
Current	1503 (2.59)	522 (12.88)	294 (4.20)	687 (1.46)
Former	6761 (11.63)	1094 (26.99)	1244 (17.77)	4423 (9.40)
Unknown	7 (0.01)	0 (0.00)	1 (0.01)	6 (0.01)
Never	49 843 (85.77)	2437 (60.13)	5463 (78.02)	41 943 (89.13)

The COVID-19 pandemic was considered to have begun on 5 March 2020. Pregnancies were included if they began prior to 1 December 2020 and ended between 5 March 2020 and 30 September 2021.

[a]Follow-up began at the earliest of pregnancy onset or 5 March 2020. In statistical models, cannabis use and tobacco smoking status were treated as time-changing variables during the course of the pregnancy.

[b]Differences between people whose cannabis use status at start of follow-up was 'current' and people whose cannabis use status was 'recently quit' were significant at $P < 0.01$.

[c]Differences between people whose cannabis use status at start of follow-up was 'current' and people whose cannabis use status was 'non-user' were significant at $P < 0.01$.

[d]Differences between people whose cannabis use status at start of follow-up was 'recently quit' and people whose cannabis use status was 'non-user' were significant at $P < 0.01$.

[e]Differences between people whose cannabis use status at start of follow-up was 'recently quit' and people whose cannabis use status was 'non-user' were significant at $P < 0.05$.

TABLE 2 Unadjusted rates of SARS-CoV-2 PCR testing and infections among pregnant women

Pregnancy time classification	Pregnancies[b]	Person-months	SARS-CoV-2 PCR tests[a]		Positive SARS-CoV-2 PCR tests[a]	
			Number of tests	Tests per 100 person-months	Number of positive tests	Positive tests per 100 person-months
All pregnancy time	58 114	348 810	41 064	11.77	2414	0.692
By cannabis use status[c]						
Current	3626	18 088	1688	9.33	117	0.647
Recently quit	9256	49 745	6756	13.58	363	0.730
Non-user	47 059	280 978	32 620	11.61	1934	0.688

[a]Person-time began at the latest of pregnancy onset or 5 March 2020. Person-time was censored at the earliest of the first positive SARS-CoV-2 polymerase chain reaction (PCR) test, disenrollment from Kaiser Permanente Northern California (KPNC), any COVID-19 vaccination or pregnancy outcome.
[b]People could contribute time to more than one cannabis use category. Therefore, the sum of the number of pregnancies across the cannabis use categories totals more than the number of unique pregnancies in the study cohort.
[c]Cannabis use status was a time-changing variable. The same person can contribute time to more than one category.

TABLE 3 Relationship of cannabis use status to SARS-CoV-2 infection

Time-changing cannabis use status	Adjusted hazard ratio (95% confidence intervals)	
	Model 1[a]	Model 2[b]
Current	0.61 (0.50, 0.74)*	0.60 (0.49, 0.74)*
Recently quit	0.92 (0.82, 1.03)	0.96 (0.86, 1.08)
Non-user	1.00 (reference)	1.00 (reference)

Outcome was the first positive SARS-CoV-2 polymerase chain reaction test during pregnancy.
[a]Model 1 is adjusted for age (21 categories: < 19, one for each year of age up to 39, 40+), race/ethnicity, neighborhood deprivation index, insurance payor and primary Kaiser Permanente Northern California (KPNC) facility.
[b]Model 2 is adjusted for all covariables in model 1 one plus body mass index, pre-existing diabetes and hypertension, parity and tobacco smoking status.
*Significant at $P \leq 0.05$.

consistent with our main analysis that included all patients, indicating that current cannabis use was associated with a lower hazard of SARS-CoV-2 infection despite potential differences in testing propensity.

From a public health perspective, our findings suggest that it is unlikely that current cannabis use during pregnancy increases risk of SARS-CoV-2 infection. The protective effect is provocative, but not determinative, and worth further study. Pre-clinical research provides biological support for a protective effect of cannabis use on SARS-CoV-2 infection. The initial steps of viral infection involve attachment of the SARS-CoV-2 virus spike protein to the enzyme ACE2 in the lung, oral cavity or nose. Transmembrane serine protease 2 (TMPRSS2) on a host cell then activates the spike protein producing conformation changes that allow the virus to enter the cell. The SARS-CoV-2 M^{pro} enzyme is a viral enzyme that plays a critical role in viral replication. There is evidence that cannabinoids may have protective effects on each of the pathways.

The cannabis plant (*Cannabis sativa*) contains numerous pharmacologically active chemicals, including more than 100 phytocannabinoids [the most prevalent being delta 9-tetrahydrocannabiol (THC) and CBD]. Some cannabinoids bind to the spike protein and prevent infection of human lung epithelial cells [24]. Cannabis cultivars containing high levels of CBD were shown in three-dimensional human tissue models to down-regulate the ACE2 receptor, which is the initial binding site for SARS-CoV-2 [27]. CBD inhibits SARS-CoV infection in lung epithelial cells and in mice by inhibiting viral replication [20]. Structural-based screening of cannabinoids found that THC and CBD bind stably to SARS-CoV-2 M^{pro}, a critical enzyme in the life cycle of the virus; and these cannabinoids inhibit viral replication *in vitro* [22]. Notably, these authors found that the antiviral potencies of THC and CBD effects were similar to that of remdesivir, a Food and Drug Administration (FDA)-approved drug for treating COVID-19 infection. While a mechanism by which cannabis use might reduce the likelihood of SARS-CoV-2 infection has not been determined, the evidence to date suggests that such an effect is biologically plausible.

Conversely, compared to non-cannabis users, those who had recently quit using cannabis were significantly more likely to be tested for SARS-CoV-2, but they did not differ in their risk of infection. This is consistent with active but not recent cannabis use having a potentially protective effect. In our case-positive, control-test-negative sensitivity analysis that was limited to patients who were tested for SARS-CoV-2 infection, those who had recently quit had a lower risk of infection relative to non-cannabis users. This sensitivity analysis provides some evidence that pregnant patients who had recently quit using cannabis may also have a lower risk of infection. If this is confirmed, it could mean that a less strong protective effect of cannabis use persists for a period of time after patients stop using cannabis, and the higher rates of SARS-CoV-2 testing among patients who had recently quit use in the primary analysis may have masked this effect. It is also possible that SARS-CoV-2 infection rates do not truly differ among those who recently quit cannabis use versus non-users. The higher rates of testing among the recently quit group may have created the appearance of a lower risk because the sensitivity analysis

TABLE 4 Sensitivity analyses, relationship of cannabis use status to SARS-CoV-2 infection

Cannabis use status	Sensitivity analysis 1: using initial cannabis use status rather than time-varying status		Sensitivity analysis 2: excluding time when people were current or former smokers		Sensitivity analysis 3: case-positive, control-test-negative approach[a]	
	Adjusted hazard ratio (95% confidence intervals)				Adjusted odds ratio (95% confidence intervals)	
	Model 1[b]	Model 2[c]	Model 1[b]	Model 2[c]	Model 1[b]	Model 2[c]
Current	0.71 (0.60, 0.83)*	0.71 (0.60, 0.83)*	0.59 (0.46, 0.76)*	0.59 (0.46, 0.77)*	0.73 (0.60, 0.90)*	0.76 (0.61, 0.93)*
Recently quit	0.92 (0.81, 1.04)	0.97 (0.85, 1.10)	0.92 (0.81, 1.05)	0.96 (0.84, 1.09)	0.77 (0.68, 0.87)*	0.83 (0.73, 0.94)*
Non-user	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)

[a]Logistic regression model that includes all COVID tests during follow-up, stratified by (conditioned on) calendar date of the test. This analysis only includes people who received at least one test. The cannabis status of people who tested positive on a given day is compared to the cannabis status of people who tested negative on the same day.
[b]Model 1 is adjusted for age (21 categories: < 19, one for each year of age up to 39, 40+), race/ethnicity, neighborhood deprivation index, insurance payor and primary Kaiser Permanente Northern California (KPNC) facility.
[c]Model 2 is adjusted for all covariables in model 1 plus body mass index, pre-existing diabetes and hypertension, parity and tobacco smoking status.
*Significant at $P \leq 0.05$.

TABLE 5 Relationship of cannabis use status to SARS-CoV-2 testing

Time-changing cannabis use status	Adjusted hazard ratio (95% confidence intervals)	
	Model 1[a]	Model 2[b]
Current	0.83 (0.79, 0.88)*	0.80 (0.76, 0.85)*
Recently quit	1.11 (1.08, 1.15)*	1.10 (1.06, 1.13)*
Non-user	1.00 (reference)	1.00 (reference)

Outcome was receipt of SARS-CoV-2 polymerase chain reaction (PCR) tests during pregnancy. Testing was treated as a recurring event outcome. All SARS-CoV-2 PCR tests prior to a patient's first positive test were included.
[a]Model 1 is adjusted for age (21 categories: < 19, one for each year of age up to 39, 40+), race/ethnicity, neighborhood deprivation index, insurance payor and primary Kaiser Permanente Northern California (KPNC) facility.
[b]Model 2 is adjusted for all covariables in model 1 plus body mass index, pre-existing diabetes and hypertension, parity and tobacco smoking status.
*Significant at $P \leq 0.05$.

includes more negative tests in the denominator. Notably, those who had recently quit using cannabis (versus current users) tended to be more similar to non-cannabis users in socio-demographics and clinical characteristics. Additional research is needed to replicate these findings and to more clearly understand the factors that might be related to differences in risk of SARS-CoV-2 infection during pregnancy among current versus recently quit cannabis users.

It is critical to note that cannabis use during pregnancy is associated with adverse perinatal outcomes, including low offspring birth weight and pre-term delivery [46, 47], and may increase risk for offspring psychopathology in childhood, including externalizing, attention, thought and social problems [48]. Because of concerns regarding these health risks, national organizations recommend that pregnant women abstain from prenatal cannabis use [49]. While cannabis use may not be a risk factor for SARS-CoV-2 infection, having a past-year cannabis use disorder is associated with elevated risk for SARS-CoV-2 [25] and having a current or in-remission cannabis use disorder is associated with elevated risk for a breakthrough infection among fully vaccinated individuals [26]. Given documented health risks associated with prenatal cannabis use, clinicians should continue to encourage pregnant patients to avoid prenatal cannabis use and offer support and resources to assist with quitting.

Limitations and strengths

This study has several limitations and results should be considered preliminary. Our sample is limited to KPNC pregnant patients screened for prenatal substance use and results may not generalize to all pregnant women or other populations. Our measure of prenatal cannabis use does not account for frequency, potency or mode of cannabis use. Although population-based surveillance data indicate that most (91%) women who use cannabis during pregnancy report smoking it [50], the individuals in our study may have differed in their patterns of use (e.g. frequency, mode of administration and potency of products used). We were also unable to determine whether there is a dose–response relation between prenatal cannabis use and SARS-CoV-2 infection. Additional studies are needed that examine how these important aspects of cannabis use relate to SARS-CoV-2 infection during pregnancy. Further, because we only assessed cannabis use during the year before and during pregnancy, individuals who quit using cannabis more than a year prior to pregnancy cannot be differentiated from those who never used cannabis and are combined in our 'non-cannabis' use group. Self-reported data on cannabis use during the year before pregnancy may be under-reported, and some women with former cannabis use may have been classified as never-users. Although a study strength was accounting for changes in

cannabis use status during pregnancy, not all patients had subsequent toxicology tests, so some misclassification of exposure is possible. However, we conducted a sensitivity analysis that limited the exposure to cannabis use status at baseline, and results were very similar to results from our models where cannabis use was time-varying. PCR tests were limited to those conducted in KPNC; positive cases tested elsewhere or not tested at all were not included. Our study was limited to first SARS-CoV-2 infection, and additional studies are needed to examine the relation between prenatal cannabis use and risk of recurrent infection. The Cox proportional hazards model assumes non-informative censoring, and bias may occur if patients have a censoring time that is dependent upon their failure time. While no study can unequivocally rule out this potential for bias, we do not expect that our censoring events (vaccination and health plan disenrollment) would have a strong dependency on the unobserved outcomes of those patients. Finally, while we adjusted for many confounders, some possible confounders were missed, such as exposure to the virus, number and frequency of social contacts and gatherings, occupation and essential worker designation and mask-wearing. The study is observational and has a potential bias related to PCR testing behaviors. To address potential differences between cannabis users and non-users in the propensity to be tested, we performed a sensitivity analysis using only people who were tested and found similar results to our main analysis. Further, while we adjusted for several important covariates, unmeasured biases related to who is tested or potential differences in behaviors or risk (e.g. willingness to wear a mask or socially distance from others and essential worker designation) may remain. Finally, causal interpretations should not be based on one observational study.

This study also has important strengths. We included a large sample of pregnant patients at-risk for COVID-19 and followed them from testing to infection. Our study design allows us to estimate risk properly over time using semi-parametric Cox proportional hazards models and is more rigorous than studies using convenience samples. Our models account for changes in underlying baseline risks and variations in risks and exposures during the course of the pandemic.

CONCLUSIONS

In this retrospective cohort study, prenatal cannabis use was associated with a reduced risk for SARS-CoV-2 infection during pregnancy. Additional research is needed to replicate this finding and to understand possible factors driving lower infection risk during pregnancy among individuals with prenatal cannabis use. Regardless of its association with COVID-19, because of other health risks associated with prenatal cannabis use, clinicians should continue to advise pregnant patients to abstain from using cannabis.

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DECLARATION OF INTERESTS

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Kelly Young-Wolff: Conceptualization; funding acquisition; investigation; methodology; supervision. **G. Thomas Ray:** Data curation; formal analysis; methodology. **Stacey Alexeeff:** Conceptualization; formal analysis; investigation; methodology; supervision. **Neal Benowitz:** Investigation; methodology. **Sara Adams:** Data curation; investigation; methodology. **Monique Does:** Investigation; methodology; project administration. **Nancy Goler:** Investigation; methodology. **Deborah Ansley:** Investigation; methodology. **Amy Conway:** Investigation; methodology. **Lyndsay Avalos:** Conceptualization; funding acquisition; investigation; methodology; supervision.

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SUPPORTING INFORMATION

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

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