Research Article

Dried Cannabis Use, Tobacco Smoking, and COVID-19 Infection: Findings from a Longitudinal Observational Cohort Study

Cannabis
2024

researchmj.org
10.26828/cannabis/2024/000248

Nadia Milad[1,2], Kyla Belisario[3,4], James MacKillop[3,4], & Jeremy A. Hirota[1,2,5,6]

[1]Firestone Institute for Respiratory Health – Division of Respirology, Department of Medicine, McMaster University
[2]McMaster Immunology Research Centre, McMaster University
[3]Peter Boris Centre for Addictions Research, McMaster University & St. Joseph's Healthcare
[4]Department of Psychiatry and Behavioural Neurosciences, McMaster University
[5]Department of Biology, University of Waterloo
[6]Department of Medicine, University of British Columbia

ABSTRACT

Objective: The potential impact of cigarette and cannabis smoking on COVID-19 infection outcomes is not well understood. We investigated the association between combustible tobacco use and dried cannabis use with COVID-19 infection in a longitudinal cohort of community adults. **Method:** The sample comprised 1,343 participants, originally enrolled in 2018, who reported their cigarette and cannabis use in 11 assessments over 44 months, until 2022. COVID-19 infection history were self-reported after the onset of the pandemic. Univariate and multivariate logistic regression analyses were performed. The potentially confounding factor of vaccination status was also considered by stratifying data by booster vaccination self-reporting. **Results:** Among 1,343 participants, 820 (61.1%) reported any COVID-19 infection. Dried cannabis use (46.3% of participants, n = 721) was associated with higher self-reporting of 2+ COVID-19 infections (13.3% vs. 7.3% in non-users, p = .0004), while tobacco use (18.5% of participants, n = 248) had no significant effect (13.3% vs. 10.0% in no use group, p = .116). When stratified into single or dual substance use groups, dried cannabis-only use was associated with increased reporting of 1 or 2+ COVID-19 infections compared to substance non-users, while tobacco-only use and dual use groups were not significantly different from non-users. To account for differences in vaccination rates between substance use groups, we found that, among individuals with a COVID-19 booster vaccine, dried cannabis use was still associated with increased reporting of 2+ COVID-19 infections (p = .008). **Conclusions:** Our study suggests that dried cannabis use is associated with a higher likelihood of reporting 2+ COVID-19 infections. Although the study was observational and relied on self-report infection status, our findings support the need for further investigation into the impact of cannabis use on COVID-19 infection, particularly studies employing controlled experimental designs.

Key words: = COVID-19; cannabis use; cigarette smoking; infection reporting; immunomodulation; prospective cohort study

Although smoke exposures have long been known to increase susceptibility and severity of respiratory tract infection (Blake et al., 1988; Cohen et al., 1993; Feldman et al., 2015; Kark et al., 1982; Noah et al., 2012; Rebuli et al., 2019; Rogot & Murray, 1980), the effects of cannabis

Corresponding Author: Jeremy Alexander Hirota, Ph.D., Firestone Institute for Respiratory Health, St. Joseph's Healthcare. 50 Charlton Avenue East, Hamilton, ON L8N 4A6, Canada. Phone: 1(905) 522-1155 ext. 33683. E-mail: hirotaja@mcmaster.ca.

smoke on respiratory tract viral infection remain poorly understood. There is some evidence that individuals who use cannabis report increased incidence of bronchitis- and pneumonia-related respiratory symptoms (Macleod et al., 2015; Tetrault et al., 2007), as well as increased hospitalization rates and length of stay associated with respiratory tract infections compared to those who do not use cannabis (Polen et al., 1993; Rosoff et al., 2021a). In preclinical models, it was shown that both direct administration of the cannabinoid tetrahydrocannabinol (THC; (Buchweitz et al., 2007; Buchweitz et al., 2008) and exposure to cannabis smoke (Milad et al., 2023) before and after influenza A infection in mice suppressed aspects of the anti-viral inflammatory response, leading to reduced immune cell recruitment and an increased pulmonary viral load. Therefore, in the wake of widespread legalization and potential for future global pandemics, it is crucial that we understand to what extent cannabis use might impact pulmonary host-defense and antiviral responses.

The SARS-CoV-2 (COVID-19) virus has dramatically affected the pulmonary health of millions of people globally, but there is ambiguity surrounding the potential additional risks among cigarette and cannabis smokers. Some early studies suggested there was a "smoker's paradox," where cigarette smokers were found to be underrepresented among patients with severe COVID-19 infection (Lippi et al., 2020; Lombardi et al., 2021; Meini et al., 2021), although data regarding the relationship between COVID-19 and smoking status are conflicting (Lippi et al., 2020; Zhou et al., 2020) (Guo, 2020; Kozak et al., 2020; Liu et al., 2020; Lowe et al., 2021; Patanavanich & Glantz, 2020, 2021; Rosoff et al., 2021b; Yu et al., 2020; Zheng et al., 2020). Similarly, the potential link between cannabis smoking and COVID-19-associated disease has also been debated. Initially, several published reviews and editorials suggested that cannabis use might dampen pulmonary inflammation associated with COVID-19 infection through the immunomodulatory effects of cannabinoids, namely THC and cannabidiol (CBD), and thus alleviate symptoms and improve outcomes (Onaivi & Sharma, 2020; Paland et al., 2021; Pascual Pastor et al., 2020; Pérez et al., 2022). When clinical data were collected, studies showed conflicting results, where some suggested a protective effect (Huang et al., 2022; Shover et al., 2022), no effect (Rosoff et al., 2021a, 2021b) or a negative effect (Hasin et al., 2022; Huang et al., 2022; Merianos et al., 2022) on COVID-19 infection rate and/or severity. Further complicating research into these topics are reports that substance use, e.g. alcohol and cannabis, may have increased early in the pandemic (Imtiaz et al., 2021; Levitt et al., 2023; Newport et al., 2023), though it subsequently decreased over the ensuing reopening and return to work.

Overall, the impact of tobacco and cannabis smoking on COVID-19 outcomes remains poorly understood, which has significantly complicated public messaging during the recent COVID-19 pandemic (Pascual Pastor et al., 2020). A common limitation of previous studies has been cross-sectional data collection. In addition, the investigation of how substance use might affect respiratory tract infections is complicated by the potentially confounding factor of vaccine hesitancy, as it is possible that significant differences in COVID-19 infections and outcomes between users and non-users may be related to reduced vaccine uptake in substance users. In the current study, a cohort of participants recruited pre-pandemic in 2018 were assessed for tobacco and cannabis use at regular intervals (3-6 months), with COVID-19 measurements added after the onset of the pandemic. This prospective observational cohort study enabled quantification of self-reported tobacco and cannabis use over 44 months spanning several COVID-19 infection waves, providing a higher resolution perspective on consumption of cannabis and tobacco in relation to COVID-19 outcomes.

METHODS

Patient Recruitment, Baseline Characteristics, and COVID-19 Self-Reporting

The study population of $N = 1{,}502$ was recruited from the Population for Assessment of Tomorrow's Health (PATH) registry of 2,165 community-based adults from Hamilton, Ontario, Canada. The registry was a one-time, in-person assessment from 2016-2018 which captured biometric indices (sex, weight, height, heart rate, blood pressure, etc.). Inclusion criteria were as follows: between the ages of 18-65, minimum 9th grade education for adequate literacy to complete online assessments, willingness to receive invitations to future assessments, and no current terminal illnesses to ensure ability to participate in future assessments. The first web-administered assessment occurred in September 2018, with online follow-ups every 6 months (Supplementary Figure 1) via Research Electronic Data Capture (REDCap) software (Harris et al., 2009). Two additional follow-ups spaced at 3-month intervals were administered in the acute phase of the COVID-19 pandemic (specifically, July 2020 and January 2021). Cannabis was legalized in Canada in October 2018; therefore, data on substance use was collected pre- and post-legalization. Attrition analysis can be found in Supplementary Table 1. Quality control was administered at each wave, which consisted of asking participants to correctly answer at least 3 of 5 questions embedded throughout the assessment correctly. These questions had unambiguous correct responses, such as "For this question, choose 'Strongly Disagree.'" Retention in each wave is high, with few excluded due to low quality control (QC) where the mean average passing QC = 99.4%. The study was approved by the Hamilton Integrated Research Ethics Board (Protocol #4699), all participants underwent informed consent, and all procedures complied with the Helsinki Declaration.

To analyze COVID-19 infection self-reporting, participants were included in the final sample if they had data at either T10 (April 2022) or T11 (October 2022), as these waves captured a fulsome window of the pandemic, including the Omicron strain (Breznik et al., 2023). This saw a total of 1,343 individuals included in analysis (89% retention), in which most had data for all 11 survey waves ($M = 10.65$; median = 11). It is also in these waves that we administered a question asking about all prior COVID-19 infections. COVID-19 infections were self-reported, and thus include individuals who had confirmed COVID-19 positive tests via PCR or rapid antigen testing, as well as participants who did not test but strongly suspected they had a COVID-19 infection. The COVID-19 vaccination status of participants was also determined via self-reporting, and participants were stratified into two categories: booster vaccination (1-2 primary vaccines plus a bivalent booster dose) or no booster vaccination (includes unvaccinated and primary vaccine only without bivalent booster dose). These groups were selected in order to explore whether differences in COVID-19 infection reporting may be influenced by group differences in vaccination hesitancy, since 1 or 2 primary vaccinations were mandated by the Canadian government in September 2021, while booster vaccination was always optional (Bowdish et al., 2024; "Ontario Regulation 645/21; Rules for Areas at Step 3 and the Roadmap Exit Step," 2021), an unvaccinated group (<5% of cohort) was not included in the analyses.

Cannabis and Tobacco Use Frequency

Cannabis was legalized in Canada in October 2018, and dried cannabis use was defined as consumption of any dried flower cannabis across all waves of the study. Among dried cannabis users, dried leaf/flower could be smoked and/or vaped in a heating device that did not lead to combustion, although 92% of dried cannabis users chose combustion or combustion plus vaping as their main route of administration. Conversely, edibles were considered a separate usage group not included in our analysis. An average frequency of use across all surveys (2018-2022) in which the participant has data was used as a predictor of the COVID-19 related outcomes. In addition to frequency, typical amount of dried cannabis used per occasion in which cannabis was consumed was also collected, in which the average amount of dried cannabis product in grams consumed across waves was multiplied by frequency and used as a predictor of COVID-19 infection. To mitigate improper estimating of dried cannabis use self-reporting, a scaling image is provided within the survey comparing the size of 1 gram of dried cannabis to a bottle cap (Supplementary Figure 2).

Tobacco use was defined as smoking any cigarettes across all waves of the study. The average number of cigarettes consumed across waves for which participants have data was used as a predictor of the COVID-19 related outcomes. See Online Supplementary Materials for additional information on cannabis and tobacco cigarette use questions. Throughout the manuscript, tobacco cigarettes will simply be referred to as tobacco or cigarettes.

To attempt to establish a dose-response relationship between substance use and COVID-19 infection, we 1) compared substance use frequency between those reporting a COVID-19 infection and those not reporting a COVID-19 infection and 2) performed univariate (unadjusted) and multivariate (adjusted) logistical regression analyses of substance use frequency and COVID-19 infection reporting.

Statistical Analyses

Chi-squared tests were used to test differences in proportions, and two-sided t-tests (Welch's t-test when non-normality of variance was detected) were used when comparing the means of two groups.

Univariate and multivariate (sex, age, continuous income, and substance use as covariates) logistic regressions were performed using the entire n = 1,343 sample to predict odds ratios (OR) of having 1 or 2+ COVID-19 infections. Similarly, univariate (unadjusted) and multivariate (adjusted) logistic regressions were performed for a subset of participants with a prior COVID-19 infection who endorsed a) cigarette use or b) dried cannabis use to determine if significant predictors remain significant in a subset of substance users. Raw p values are reported throughout with a conservative significance value of $\alpha = .005$ per Benjamin et al. (2018), and effect sizes using Cohen's D are reported for statistically significant t-tests (Lakens, 2013).

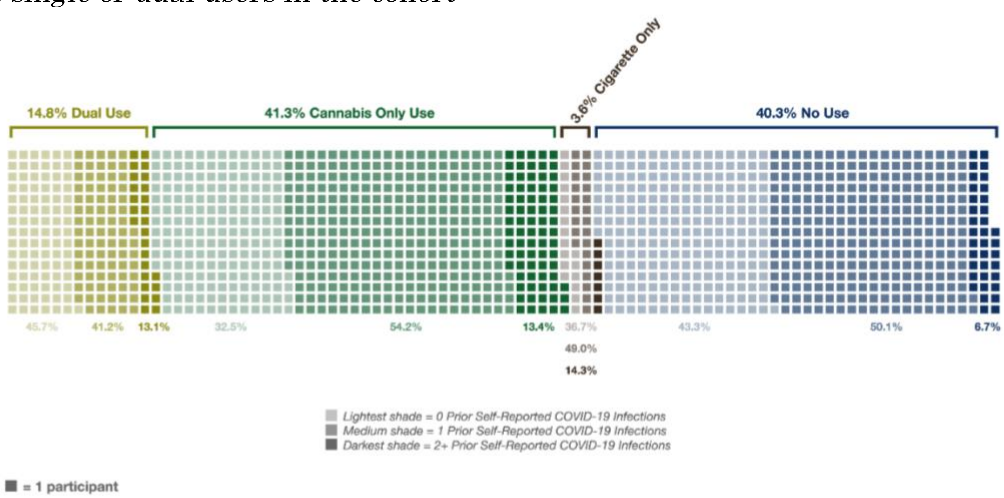
RESULTS

Baseline Characteristics and COVID-19 Outcomes

Among the 1,343 included participants, we found that 248 individuals endorsed smoking cigarettes (18.5% of cohort), and 753 individuals endorsed using dried cannabis (56.1% of cohort) during the study period. Dividing participants by cannabis use revealed that participants who endorsed dried cannabis use were significantly younger, had lower median income, and reported increased tobacco use throughout the study (Supplementary Table 2). Furthermore, when looking at vaccination status, there was a trend towards lower reporting of COVID-19 booster vaccination among dried cannabis users compared to non-users, $t(1) = 2.26$, $p = .0256$ (Supplementary Table 2). When comparing baseline characteristics, there was a trend towards White race, significantly lower median income, and significantly higher cannabis use among individuals who endorsed smoking cigarettes compared to those who did not (Supplementary Table 2). Self-reported vaccination status was also significantly different depending on cigarette use, where a smaller proportion of tobacco smokers had received a primary COVID-19 vaccination compared to non-smokers, 89.9% vs 95.5%, $X^2(1) = 11.5$, $p = .000840$, and a smaller percentage of tobacco smokers had received a COVID-19 booster vaccine, 64.1% vs 79.7%, $X^2(1) = 26.8$, $p < .0001$, Supplementary Table 2.

Dual use of tobacco and dried cannabis was relatively common: 199 participants, or 14.8% of the whole cohort, endorsed using both substances, which represents 80.2% of cigarette smokers and 26.4% of dried cannabis users (Figure 1).

Figure 1. *Distribution of COVID-19 infection reporting among cigarette and dried cannabis single or dual users in the cohort*



Note. Self-reported COVID-19 infections divided by cigarette and dried cannabis use as follows: non-users (blue), cigarette only users (grayscale), dried cannabis only users (green) and dual cigarette and dried cannabis users (yellow). One square represents one participant.

Therefore, participants were divided into mutually exclusive substance use groups as follows: no use, cigarette-only use, dried cannabis-only use, and dual cigarette and cannabis use. Baseline characteristics were also compared for mutually exclusive groups, where booster vaccination was found to be lower in the dual use group compared to substance no use and dried cannabis-only use, 63.8% vs 81.1% and 78.3%, respectively, $X^2(3) = 29.0$, $p < .0001$, cannabis use throughout the study was higher in dual use group compared to cannabis-only use, and median income was significantly lower in dual use group compared to dried cannabis-only use (Table 1).

Table 1. *Baseline characteristics of cohort of mutually exclusive cigarette/cannabis use groups*

Characteristic	No Use	Cigarette Only	Dried Cannabis Only	Dual Use	Statistics
N (Overall %)	541 (40.3%)	49 (3.7%)	554 (41.3%)	199 (14.8%)	
N (%) Female	351 (64.9%)	36 (73.5%)	321 (57.9%)	114 (57.3%)	$X^2 = 9.95$ $p = 0.0190$
N (%) White Ethnicity	429 (79.3%)	47 (95.9%)	428 (77.3%)	161 (80.9%)	$X^2 = 9.97$ $p = 0.0189$
Prior Respiratory Conditions:					
COPD:	16 (3.0%)	1 (2.0%)	13 (2.3%)	8 (4.0%)	$X^2 = 1.89$ $p = 0.597$
Asthma:	92 (17.0%)	8 (16.3%)	106 (19.1%)	40 (20.1%)	$X^2 = 2.43$ $p = 0.488$
Vaccination Status:					
Primary Vaccination (1-2 vaccine)	492 (90.9%)	40 (81.6%)	509 (91.9%)	169 (84.9%)	$X^2 = 12.5$ $p = 0.00572$
Booster Vaccination (1-2 vaccines + booster)	439 (81.1%)[b]	32 (65.3%)	434 (78.3%)[a]	127 (63.8%)[a,b]	$X^2 = 29.0$ $\boldsymbol{p < 0.0001}$
Cigarette Use (mean # cigarettes throughout study +/- SD)	N/A	13,328.91 +/- 13,884.93	N/A	8,526.23 +/- 13,173.57	$t = 2.26$ $p = 0.0246$
Cannabis Use (mean grams throughout study +/- SD)	N/A	N/A	285.67 +/- 898.01	902.68 +/- 1,700.4	$t = 3.71$ $\boldsymbol{p = 0.000256}$
Alcohol Use (mean standard number of drinks throughout study +/- SD)	9,70.9 +/- 1,126.15[c]	1,601.38 +/- 1,740.71	1,618.85 +/- 1,732.23[a,c]	2,421.48 +/- 2,505.98[a]	$F = 39.2$ $\boldsymbol{p < 0.0001}$
Median Income**	\$90,000 - \$104,999	\$75,000 - \$89,999	\$75,000 - \$89,999[a]	\$45,000 - \$59,999[a]	$F = 25.0$ $\boldsymbol{p < 0.0001}$
Mean +/- SD Age at end of 2022 (median age)	43.83 +/- 14.98[c]	46.98 +/- 13[d]	35.3 +/- 12.3[c,d]	35.54 +/- 11.78	$F = 47.6$ $\boldsymbol{p < 0.0001}$

Note. [a]Post-hoc: significant difference between cannabis only use and dual use (p<0.005), [b]Post-hoc: significant difference between no substance use and dual use (p<0.005), [c]Post-hoc: significant difference between cannabis only use and no substance use (p<0.005), [d]Post-hoc: significant difference between cannabis only use and cigarette only use (p<0.005).

Dried Cannabis Use and COVID-19 Infection

In the whole cohort, 820 (61.1%) reported at least one COVID-19 infection, and 143 (10.6%) reported two or more COVID-19 infections. When comparing individuals who endorsed using dried cannabis to those who did not, dried cannabis use was associated with increased reporting of a single, trend, $X^2(1) = 6.01$, $p = .0142$, or multiple COVID-19 infections, $X^2(1) = 11.9$, $p = .000573$, Supplementary Table 3. In contrast, there was no significant difference in COVID-19 infection self-reporting associated with tobacco use (Supplementary Table 3). To ensure that any associations between multiple COVID-19 infections and cigarette/cannabis use were not the result of participants quitting or reducing their use after a COVID-19 infection, substance use before and after a participant reported their first COVID-19 infection were compared, and no significant change in substance use was observed pre- and post-infection (Supplementary Table 4).

Since dual use was common, COVID-19 infections were also assessed for the mutually exclusive groups: no use, cigarette-only use, dried cannabis-only use, and dual cigarette/cannabis use. There was a significant increase in reporting of a single COVID-19 infection among the dried cannabis-only use group (67.6%) compared to no use (56.8%; $p = .000307$) and dual use (54.3%; $p = .00115$; Figure 1 and Table 2). Similarly, a significant increase in reporting multiple COVID-19 infections was observed for dried cannabis-only use group (13.4%) compared to no use (6.7%; $p = .000267$), with trends ($p < 0.05$) towards increases for cigarette-only use and dual use groups when compared to no use (Figure 1 and Table 2).

Table 2. *COVID-19 infection self-reporting among cigarette smokers, dried cannabis users and dual users*

	Mutually Exclusive Substance Use Groups				
N (% of use group)	No Use ($N = 541$)	Dried Cannabis-only Use ($N = 554$)	Cigarette-only Use ($N = 49$)	Dual Use ($N = 199$)	Statistics
1+ COVID-19 Infection	307 (56.7%)	374 (67.5%)[a,b]	31 (63.3%)	108 (54.3%)	$X^2 = 17.9$ $p =$ **0.000466**
2+ COVID-19 Infections	36 (6.7%)	74 (13.4%)[a]	7 (14.3%)[c]	26 (13.1%)[d]	$X^2 = 15.2$ $p =$ **0.00162**

Note. [a] Post-hoc: significant difference between dried cannabis-only use vs no use, [b] Post-hoc: significant difference between dried cannabis-only use vs dual use, [c] Post-hoc: trend towards difference between cigarette-only use and no use (p < 0.05), [d] Post-hoc: trend towards difference between dual and no use (p < 0.05).

Frequency of Substance Use and COVID-19 Infection Self-Reporting

Interestingly, both cigarette use and dried cannabis use among those reporting a COVID-19 infection consumed on average fewer grams of dried cannabis (0.19 vs 0.32; trend $p = .00569$) and fewer cigarettes (3.51 vs 6.31) per day throughout the study than those not reporting a COVID-19 infection (Supplementary Table 5), initially suggesting an inverse correlation between substance use and COVID-19 infection. To assess the possible interaction between dried cannabis and tobacco use among those endorsing dual substance use, analyses were repeated using mutually exclusive substance use groups. Analysis revealed that the trend that participants endorsing dried cannabis use and reporting a COVID-19 infection consumed less dried cannabis daily on average than those not reporting an infection only remained a trend (0.63 vs 0.33 grams/day; $p = .0112$) in the dual use group, with no difference observed in the dried cannabis-only use group (0.16 vs 0.15 grams/day; Table 3). Similarly, the decrease in cigarettes consumed per day by individuals reporting a COVID-19 infection was only present in the dual use group (5.93 vs 2.9 cigarettes/day; $p = .00111$), not in the cigarette-only use group (Table 3).

Table 3. *Dried cannabis and tobacco consumption by COVID-19 infection reporting*

Mutually Exclusive Substance Use Groups				
Mean +/- SD (Median)	No Use (N = 541)	Dried Cannabis Only Use (N = 554)	Cigarette Only Use (N = 49)	Dual Use (N = 199)
Average Cigarettes per Day				
No COVID-19 Infection	0 +/- 0 (0)	0 +/- 0	8.23 +/- 7.82 (5.59)	5.93 +/- 8.1 (1.36)
COVID-19 Infection	0 +/- 0 (0)	0 +/- 0	5.63 +/- 6.2 (3.55)	2.9 +/- 4.6 (0.48)
Significance	-	-	t = 1.29; p = 0.204	t = 3.31 **p = 0.00111**
Effect Size (Cohen's D)	-	-	-	d = 0.47
Average Daily Cannabis Grams				
No COVID-19 Infection	0 +/- 0 (0)	0.16 +/- 0.37 (0.01)	0 +/- 0	0.63 +/- 1.0 (0.1)
COVID-19 Infection	0 +/- 0 (0)	0.15 +/- 0.48 (0.01)	0 +/- 0	0.33 +/- 0.65 (0.02)
Significance	-	t = 0.115; p = 0.910	-	t = 2.56 p = 0.0112
Effect Size (Cohen's D)	-	-	-	d = 0.36

To further probe potential dose-response relationships, logistic regression analyses were performed to assess whether there was a correlation between total substance use throughout the study and COVID-19 infection self-reporting. Initially, the univariate analysis revealed a trend that each gram of dried cannabis consumed per day was associated with a 29% reduction in the odds of reporting a COVID-19 infection (OR = 0.71; p = .00745); however, dried cannabis use frequency was not a significant predictor of COVID-19 infection reporting after accounting for sex, age, household income, alcohol consumption, and tobacco cigarette smoking in the multivariate analysis (Table 4). Similarly, although cigarette smoking frequency was negatively associated with COVID-19 infection self-reporting in the univariate analysis (OR = 0.94; p = 0.0015), this relationship was no longer significant when data were adjusted for age, sex, household income, alcohol consumption, and dried cannabis use via multivariate analysis (Table 4). Overall, the dose-response pattern that increased substance use is associated with reduced COVID-19 infection self-reporting was only significant for tobacco smoking in the dual use group, and this relationship disappears for both tobacco and dried cannabis use once data were adjusted, suggesting it is related to confounding variables.

Table 4. *Univariate and multivariate odds ratios (ORs) for COVID-19 infection self-reporting among substance use groups*

	OR 1+ COVID-19 Infection	p-value
Unadjusted Analysis		
Cannabis Grams per Day Dried Cannabis Use (N = 753)	0.71 (0.55 – 0.91)	0.00745
Cigarettes per Day	**0.94 (0.90 - 0.97)**	**0.00154**

Cigarette Use (N = 248)		
Adjusted Analysis*		
Cannabis Grams per Day Dried Cannabis Use (N = 753)	0.82 (0.62 – 1.08)	0.161
Cigarettes per Day Cigarette Use (N = 248)	0.97 (0.93 – 1.01)	0.147

Note. *Adjusted for age, sex, household income, alcohol consumption and other substance use

Booster Vaccination and Self-Reported COVID-19 Infection

As previously outlined in Table 1, individuals endorsing dried cannabis and tobacco use exhibited different COVID-19 vaccination patterns. To assess the potentially confounding factor of vaccination on COVID-19 infection self-reporting, data were stratified based on COVID-19 booster vaccination status. In the whole cohort, the proportion of individuals having received a booster vaccination was not significantly different between those reporting a single COVID-19 infection versus no infection, while those reporting multiple COVID-19 infections were less likely to report receiving a booster vaccination compared to those declaring fewer than two COVID-19 infections: 67.1% vs 78.0%, respectively (Supplementary Table 6).

When we assessed the impact of dried cannabis and tobacco use on COVID-19 infection reporting only among participants with the same vaccination status, dried cannabis use among participants with a booster vaccination was associated with trends towards increased self-reporting of a single COVID-19 infection (63.3% vs 56.5%; p = .0227) or multiple COVID-19 infections (11.6% vs 6.6%; p = .00806; Supplementary Table 7). Conversely, no significant difference was observed in self-reporting of one or multiple COVID-19 infections between those endorsing cigarette use and those not endorsing cigarette use, regardless of booster vaccination status (Supplementary Table 7). When participants were divided into mutually exclusive substance use groups, we found that, among individuals with a booster vaccine, dried cannabis-only use was associated with increased reporting of at least one COVID-19 infection (66.6% vs 55.8%; p = .00338) compared to the no substance use group (Table 5). Overall, this suggests that despite differences in vaccine uptake between substance use groups, dried cannabis use among individuals with a booster vaccine is linked to a higher likelihood of reporting a COVID-19 infection.

Table 5. *Self-reported COVID-19 infection stratified by booster vaccination and substance use*

	Mutually Exclusive Substance Use Groups				
N (%)	No Use (N = 541)	Dried Cannabis-only Use (N = 554)	Cigarette-only Use (N = 49)	Dual Use (N = 199)	Statistics
	1+ COVID-19 Infection				
No booster vaccination	62 (60.8%)	85 (70.8%)	10 (58.8%)	40 (55.6%)	$X^2 = 5.22$ $p = 0.157$
Booster vaccination	245 (55.8%)	289 (66.6%)[a]	21 (65.6%)	68 (53.5%)	$X^2 = 13.7$ $p =$ **0.00338**

Note. [a]Post-hoc: significant difference between dried cannabis only use and no use ($p < 0.005$)

DISCUSSION

The impact of dried cannabis use and tobacco cigarette smoking on viral infections has been a topic of growing interest, particularly in the context of the SARS-CoV-2 (COVID-19) pandemic. In this study, we aimed to explore the association between dried cannabis use and/or cigarette smoking and COVID-19 infection. We found that dried cannabis use was associated with increased self-reporting of COVID-19 infections while, conversely, tobacco cigarette smoking led to trends towards reduced COVID-19 infection self-reporting. Even among individuals who received a booster vaccine, dried cannabis use was associated with increased reporting of one or multiple COVID-19 infections. When looking at use frequency, there were initially indications of inverse dose-response relationships between substance use and COVID-19 self-reporting: increased dried cannabis or cigarette consumption among individuals not reporting a COVID-19 infection compared to those reporting an infection and lower odds ratios. However, when multiple substance use was accounted for by dividing individuals into mutually exclusive use groups or by multivariate regression analyses, no significant associations between the frequency of dried cannabis or cigarette use and self-reported COVID-19 infections was observed. Overall, our findings suggest that dried cannabis and tobacco use impact COVID-19 self-reporting in distinct and complex ways.

We are not the first to observe features of a "smoker's paradox," where reports early in the COVID-19 pandemic showed a reduced proportion of those being admitted to hospital for COVID-19 were tobacco smokers compared to the general population (Lippi et al., 2020; Lombardi et al., 2021; Meini et al., 2021). Many mechanisms underlying the seemingly protective effect of tobacco smoking on COVID-19 self-reporting have been posited, including both behavioural and biological pathways. From the behavioural angle, cigarette smokers underestimate the negative health consequences of inhaling smoke (Krosnick et al., 2017), a perception that may also apply to COVID-19 symptoms that would contribute to reduced self-reporting of an infection. From the biological side, tobacco smoke exposure increases the expression of angiotensin converting enzyme 2 [ACE2; Lombardi et al. (2021)] and, although ACE2 is a receptor used by SARS-CoV-2 to enter cells, it also has profound anti-inflammatory effects and has been shown to exhibit protective effects in the response to lung injury (Imai et al., 2005). In our study, we observed increased mean tobacco cigarettes smoked per day in participants who did not report a COVID-19 infection compared to those reporting one or multiple COVID-19 infections only found for the dual use group, not the tobacco-only use group. Although this suggests a protective effect of tobacco smoking, no dose-response correlations persisted after correcting for age, sex, income, and other substance use. However, it is important to note that in our study, the number of participants in the cigarette-only use group was quite small (n = 49; 3.6% of cohort), since 80.2% of individuals who endorsed cigarette use also endorsed dried cannabis use, which makes specifically dissecting the impact of cigarette smoking on COVID-19 infection rate in this group of individuals particularly challenging. Taken together with previous findings, our results suggests that the "smoker's paradox" trends observed are not strong and largely disappear when other important variables are taken into account. The fact that increased tobacco use was associated with reduced COVID-19 reporting only in the dual cigarette/cannabis use group is of interest, indicating that studying individual substance use is crucial to understanding their distinct effects on respiratory infections.

There is also a lot of debate regarding the effect of cannabis smoking and COVID-19-associated disease. Although cannabinoids have long been known to exhibit anti-inflammatory effects (Klein et al., 1998), there is no consensus as to the impact of cannabis use on COVID-19 outcomes, with studies offering inconsistent results: positive effects (Shover et al., 2022), no effect (Rosoff et al., 2021a, 2021b), or negative effects (Hasin et al., 2022; Huang et al., 2022; Merianos et al., 2022). Several factors may explain these conflicting findings, including differences in study design, population characteristics, and type/frequency of cannabis use. Interpretation of these data is further limited by the fact that little is known about usage pattern, with cannabis users being identified as anyone who endorsed previously using cannabis without information on frequency, dose, potency, route of administration, or history of use. In our study, we isolated dried cannabis users only, excluding other forms of cannabis use such as edibles and tinctures. We found that dried cannabis use was associated with increased self-reporting of one or multiple COVID-19 infections. The possible confounding factor of tobacco smoking among cannabis users was also assessed, where it was shown that the dried cannabis-only use group was still significantly more likely to report one or multiple COVID-19 infections compared to the no use group. Although this seems to suggest that dried cannabis use is associated with increased risk of COVID-19 self-reporting, dried cannabis use frequency was not significantly associated with COVID-19 infection. In fact, initially there was a trend towards reduced COVID-19 infection reporting with increased daily dried cannabis use or increased daily cigarette smoking; however, this "smoker's paradox" did not persist when individuals endorsing dual substance use were excluded or when multivariate analyses were performed. The lack of any significant dose-response relationship is not surprising given the nature of the data collected, where information about potency and cannabinoid content were not gathered. Therefore, although no correlation was observed between dried cannabis use frequency and COVID-19 infection, we found that endorsing dried cannabis use is associated with increased reporting of COVID-19 infections.

The increase in self-reporting of multiple COVID-19 infections observed among those endorsing dried cannabis use may reflect physiological changes associated with dried cannabis use or other behavioral factors that may contribute to the increased infections such as lower adherence to government guidelines, scepticism towards medical interventions, increased risk of infection related to sharing of cannabis joints between individuals, and belief in the efficacy of cannabis as a natural medicine. Furthermore, there are several social factors, such as rural/urban housing, which could have affected COVID-19 infection but were not captured in this study. Though some clinical studies have found that individuals who endorse using cannabis or cigarette did not exhibit differences in vaccine hesitancy (Lum et al., 2022; Yang et al., 2021), one systematic review showed that vaccine acceptance and uptake was lowest in individuals who identify as tobacco and/or marijuana users (49.1%) compared to the general population (77.9%), as well as other hesitant groups such as pregnant women (53.8%) and religious groups (60.2%), suggesting that COVID-19 vaccination may differ significantly between users and non-users (Yasmin et al., 2021). Consequently, booster vaccination status was considered as a potential confounding factor in our study. In our cohort, there were differences in the rates of primary and booster COVID-19 vaccination between substance use groups. When analyses were stratified by vaccination status, it was shown that, even among individuals that received a booster COVID-19 vaccination, individuals endorsing dried cannabis use only still exhibited higher self-reporting of a COVID-19 infection compared to those vaccinated participants who did not endorse using either substance. Since previous animal studies have found that cannabinoids dampen the humoral response to an antigen (Karmaus et al., 2013; Karmaus et al., 2012; Milad et al., 2023), our data may also suggest that the protective effects of vaccination may be impaired by cannabis use. However, one clinical study looking at circulating spike receptor-binding domain-specific immunoglobulin G (IgG) levels 31-122 days following a COVID-19 booster vaccination in both cancer and non-cancer patients were unaffected by cannabis use, though participants in the cannabis group were significantly younger than those in the no use group (Idan et al., 2022). Therefore, the impact of substance use on the protective effects of COVID-19 vaccination and the adaptive immune response requires further investigation in larger and more controlled studies designed to address these important questions.

While our study provides valuable insights into the additional risks associated with cigarette smoking and dried cannabis use on COVID-19 infection outcomes, there are several limitations that should be acknowledged. Firstly, our study relies on self-reported data, which may be subject to several sources of error such as recall bias, underreporting of asymptomatic cases, lack of at-home testing early in the pandemic, and underlying behaviours and perceptions of health. Participants may also underreport their substance use or COVID-19 infection due to stigma or social norms, leading to potential inaccuracies in the data. Secondly, although responses related to COVID-19 infections were collected at each time-point, our infection data are not based on COVID-19 test results nor medical records and we were unable to assess COVID-19 symptom severity and could not confirm COVID-19 infection diagnoses. Furthermore, while we adjusted for age, sex, income, and other substance use in our multivariate analyses, there may be other relevant variables, such as underlying health conditions, workplace and home environment, or adherence to COVID-19 safety measures, which were not accounted for and could influence the results. The timing of data collection and participant follow-up may also have affected reporting of COVID-19 infections and of substance use. For instance, participants who experienced a COVID-19 infection during the later waves of the study may have been more or less likely to report an infection compared to those infected earlier, considering the evolving pandemic situation, new variants of the virus, differences in symptomology, and changes in public health measures.

Another complicating factor in our study is that many features of cannabis consumption could not be incorporated (e.g., strain, cannabinoid content, etc.). Although we observed a trend towards reduced self-reporting of COVID-19 infections with increased daily dried cannabis use, this trend was no longer present when data were adjusted in the multivariate analyses and, furthermore, the dose-response relationship between substance use and COVID-19 outcomes is difficult to elucidate without details of cannabis potency and route of administration. Firstly, we considered any participant who endorsed using dried cannabis at any point during the study period as a dried cannabis user, meaning there were many participants who reported using less than 1 gram over the 4-year period. Therefore, our substance use groups are likely diluted with participants who only tried cannabis once or twice and would not be considered cannabis users in a clinically relevant way; nevertheless, we still see important differences between non-users and dried cannabis users indicating the strength of the association. It would be prudent for future studies of cannabis use to establish use cutoffs to differentiate between "regular users" and "non-regular users," as has been done by the Centre for Disease Control (CDC) for tobacco smoking, where individuals are considered current or former smokers if they have consumed more than 100 cigarettes in their lifetime (*Adult Tobacco Use Glossary*). Secondly, dried cannabis flower can differ dramatically in cannabinoid content and, although both CBD and THC exhibit significant anti-inflammatory effects (Klein et al., 1998), it is unclear to what extent the individual cannabinoids may contribute to COVID-19 infection risk. Finally, dried cannabis can be consumed in many ways, including but not limited to dry-herb vaping (non-combustion) and smoking dried cannabis alone or mixed with tobacco (Russell et al., 2018). How these routes of administration differ in their impact on the immune response to infection has yet to be explored. Preclinical studies comparing cannabis strains of differing cannabinoid contents as well as comparing cannabis smoke and cannabis vapour exposures are required to mechanistically determine the impact of THC/CBD ratios and route of administration on respiratory tract infection outcomes. In subsequent clinical studies, thorough examination of cannabinoid content and specific routes of administration will allow us to better elucidate the contribution of each cannabinoid and truly assess dose-response relationships.

In conclusion, our study suggests that cigarette smoking and dried cannabis use have distinct, and in some ways unexpected, effects on COVID-19 infection reporting. While those endorsing cigarette use exhibited trends towards reduced self-reporting of COVID-19 infection, especially among the dual cigarette/cannabis use group, these effects were greatly mitigated by corrections for age, sex, income, and other substance use. On the other hand, dried cannabis use was associated with increased COVID-19 infection reporting, even among those that received a COVID-19 booster vaccine. Although this study relies on infection and substance use self-reporting, our findings support further study into the impact of cigarette smoking and cannabis use on COVID-19 outcomes and overall adaptive immune competency. Understanding the consequences of inhaled psychoactive substances on respiratory tract infections is critical to develop effective, evidence-based public health strategies and to adequately inform the public. As the COVID-19 pandemic continues to evolve and future pandemics are inevitable (The Lancet Respiratory, 2022), ongoing observational and experimental investigations will be essential to shed light on these complex relationships.

REFERENCES

Centers for Disease Controls. (2017, August 29). *Adult Tobacco Use Glossary.* https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm#print

Benjamin, D. J., Berger, J. O., Johannesson, M., Nosek, B. A., Wagenmakers, E. J., Berk, R., Bollen, K. A., Brembs, B., Brown, L., Camerer, C., Cesarini, D., Chambers, C. D., Clyde, M., Cook, T. D., De Boeck, P., Dienes, Z., Dreber, A., Easwaran, K., Efferson, C., Fehr, E., Fidler, F., Field, A. P., Forster, M., George, E. I., Gonzalez, R., Goodman, S., Green, E., Green, D. P., Greenwald, A. G., Hadfield, J. D., Hedges, L. V., Held, L., Hua Ho, T., Hoijtink, H., Hruschka, D. J., Imai, K., Imbens, G., Ioannidis, J. P. A., Jeon, M., Jones, J. H., Kirchler, M., Laibson, D., List, J., Little, R., Lupia, A., Machery, E., Maxwell, S. E., McCarthy, M., Moore, D. A., Morgan, S. L., Munafó, M., Nakagawa, S., Nyhan, B., Parker, T. H., Pericchi, L., Perugini, M., Rouder, J., Rousseau, J., Savalei, V., Schönbrodt, F. D., Sellke, T., Sinclair, B., Tingley, D., Van Zandt, T., Vazire, S., Watts, D. J., Winship, C., Wolpert, R. L., Xie, Y., Young, C., Zinman, J., & Johnson, V. E. (2018, Jan). Redefine statistical significance. *Nature Human Behavior, 2*(1), 6-10. https://doi.org/10.1038/s41562-017-0189-z

Blake, G. H., Abell, T. D., & Stanley, W. G. (1988). Cigarette smoking and upper respiratory infection among recruits in basic combat training. *Annals of Internal Medicine, 109*(3), 198-202. https://doi.org/10.7326/0003-4819-109-3-198

Bowdish, D. M. E., Chandran, V., Hitchon, C. A., Kaplan, G. G., Avina-Zubieta, J. A., Fortin, P. R., Larché, M. J., Boire, G., Gingras, A.-C., Dayam, R. M., Colmegna, I., Lukusa, L., Lee, J. L. F., Richards, D. P., Pereira, D., Watts, T. H., Silverberg, M. S., Bernstein, C. N., Lacaille, D., Benoit, J., Kim, J., Lalonde, N., Gunderson, J., Allard-Chamard, H., Roux, S., Quan, J., Hracs, L., Turnbull, E., Valerio, V., & Bernatsky, S. (2024). When should I get my next COVID-19 vaccine? Data from the surveillance of responses to COVID-19 vaccines in Systemic Immune-Mediated Inflammatory Diseases (SUCCEED) study. *The Journal of Rheumatology, 51*(7), 721-727. https://doi.org/10.3899/jrheum.2023-1214

Breznik, J. A., Rahim, A., Zhang, A., Ang, J., Stacey, H. D., Bhakta, H., Clare, R., Liu, L. M., Kennedy, A., Hagerman, M., Kajaks, T., Miller, M. S., Nazy, I., Bramson, J. L., Costa, A. P., & Bowdish, D. M. E. (2023). Early Omicron infection is associated with increased reinfection risk in older adults in long-term care and retirement facilities. *EClinicalMedicine, 63*, 102148. https://doi.org/10.1016/j.eclinm.2023.102148

Buchweitz, J. P., Karmaus, P. W., Harkema, J. R., Williams, K. J., & Kaminski, N. E. (2007). Modulation of airway responses to influenza A/PR/8/34 by Delta9-tetrahydrocannabinol in C57BL/6 mice. *Journal of Pharmacology and Experimental Therapeutics, 323*(2), 675-683. https://doi.org/10.1124/jpet.107.124719

Buchweitz, J. P., Karmaus, P. W., Williams, K. J., Harkema, J. R., & Kaminski, N. E. (2008, Mar). Targeted deletion of cannabinoid receptors CB1 and CB2 produced enhanced inflammatory responses to influenza A/PR/8/34 in the absence and presence of Delta9-tetrahydrocannabinol. *Journal of Leukocyte Biology, 83*(3), 785-796. https://doi.org/10.1189/jlb.0907618

Cohen, S., Tyrrell, D. A., Russell, M. A., Jarvis, M. J., & Smith, A. P. (1993). Smoking, alcohol consumption, and susceptibility to the common cold. *American Journal of Public Health, 83*(9), 1277-1283. https://doi.org/10.2105/ajph.83.9.1277

Feldman, A. S., He, Y., Moore, M. L., Hershenson, M. B., & Hartert, T. V. (2015). Toward primary prevention of asthma. Reviewing the evidence for early-life respiratory viral infections as modifiable risk factors to prevent childhood asthma. *American Journal Respiratory and Critical Care Medicine, 191*(1), 34-44. https://doi.org/10.1164/rccm.201405-0901PP

Guo, F. R. (2020). Active smoking is associated with severity of coronavirus disease 2019 (COVID-19): An update of a meta-analysis. *Tobacco Induced Diseases, 18*, 37. https://doi.org/10.18332/tid/121915

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics, 42*(2), 377-381. https://doi.org/10.1016/j.jbi.2008.08.010

Hasin, D. S., Fink, D. S., Olfson, M., Saxon, A. J., Malte, C., Keyes, K. M., Gradus, J. L., Cerdá, M., Maynard, C. C., Keyhani, S., Martins, S. S., Livne, O., Mannes, Z. L., Sherman, S. E., & Wall, M. M. (2022). Substance use disorders and COVID-19: An analysis of nation-wide Veterans Health Administration electronic health records. *Drug and Alcohol Dependence, 234*, 109383. https://doi.org/10.1016/j.drugalcdep.2022.109383

Huang, D., Xu, R., & Na, R. (2022). Cannabis Use is associated with lower COVID-19 susceptibility but poorer survival. *Frontiers in Public Health, 10*, 829715. https://doi.org/10.3389/fpubh.2022.829715

Idan, C., Salvatore, C. P., Orit, R., Ariel, A., Marah, K., Dana, A., Harel, E., Raul, C., Mona, K., Hassan, S., Yousef, S., Camel, M., Mahmoud, A. A., & Gil, B. S. (2022). Evaluation of immune response to anti-COVID-19 booster in cancer patients and chronic medical cannabis users and its association with circulating Eosinophils levels. *Cancer Communications, 42*(12), 1417-1420. https://doi.org/10.1002/cac2.12353

Imai, Y., Kuba, K., Rao, S., Huan, Y., Guo, F., Guan, B., Yang, P., Sarao, R., Wada, T., Leong-Poi, H., Crackower, M. A., Fukamizu, A., Hui, C. C., Hein, L., Uhlig, S., Slutsky, A. S., Jiang, C., & Penninger, J. M. (2005). Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature, 436*(7047), 112-116. https://doi.org/10.1038/natur e03712

Imtiaz, S., Wells, S., Rehm, J., Hamilton, H. A., Nigatu, Y. T., Wickens, C. M., Jankowicz, D., & Elton-Marshall, T. (2021). Cannabis use during the COVID-19 pandemic in Canada: A repeated cross-sectional study. *Journal of Addiction Medicine, 15*(6), 484-490. https://doi.org/10.1097/ADM.0000000000000798

Kark, J. D., Lebiush, M., & Rannon, L. (1982). Cigarette smoking as a risk factor for epidemic a(h1n1) influenza in young men. *New England Journal of Medicine, 307*(17), 1042-1046. https://doi.org/10.1056/NEJM198210213071702

Karmaus, P. W., Chen, W., Crawford, R., Kaplan, B. L., & Kaminski, N. E. (2013). Δ9-Tetrahydrocannabinol impairs the inflammatory response to influenza infection: role of antigen-presenting cells and the cannabinoid receptors 1 and 2. *Toxicological Sciences, 131*(2), 419-433. https://doi.org/10.1093/toxsci/kfs315

Karmaus, P. W., Chen, W., Kaplan, B. L., & Kaminski, N. E. (2012). Δ9-tetrahydrocannabinol suppresses cytotoxic T lymphocyte function independent of CB1 and CB 2, disrupting early activation events. *Journal of Neuroimmune Pharmacology, 7*(4), 843-855. https://doi.org/10.1007/s11481-011-9293-4

Klein, T. W., Friedman, H., & Specter, S. (1998). Marijuana, immunity and infection. *Journal of Neuroimmunology, 83*(1-2), 102-115. https://doi.org/10.1016/s0165-5728(97)00226-9

Kozak, R., Prost, K., Yip, L., Williams, V., Leis, J. A., & Mubareka, S. (2020). Severity of coronavirus respiratory tract infections in adults admitted to acute care in Toronto, Ontario. *Journal of Clinical Virology, 126*, 104338. https://doi.org/10.1016/j.jcv.2020.104338

Krosnick, J. A., Malhotra, N., Mo, C. H., Bruera, E. F., Chang, L., Pasek, J., & Thomas, R. K. (2017). Perceptions of health risks of cigarette smoking: A new measure reveals widespread misunderstanding. *PLoS One, 12*(8), e0182063. https://doi.org/10.1371/journal.pone.0182063

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in Psychology, 4*, 863. https://doi.org/10.3389/fpsyg.2013.00863

Levitt, E. E., Belisario, K., Gillard, J., DeJesus, J., Gohari, M. R., Leatherdale, S. T., Syan, S. K., Scarfe, M., & MacKillop, J. (2023). High-resolution examination of changes in drinking during the COVID-19 pandemic: Nine-wave findings from a longitudinal observational cohort study of community adults. *Journal of Psychiatric Research, 168*, 249-255. https://doi.org/10.1016/j.jpsychires.2023.10.027

Lippi, G., Sanchis-Gomar, F., & Henry, B. M. (2020). Active smoking and COVID-19: a double-edged sword. *European Journal of Internal Medicine, 77*, 123-124. https://doi.org/10.1016/j.ejim.2020.04.060

Liu, W., Tao, Z. W., Wang, L., Yuan, M. L., Liu, K., Zhou, L., Wei, S., Deng, Y., Liu, J., Liu, H. G., Yang, M., & Hu, Y. (2020, May 5). Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chinese Medical Journal, 133*(9), 1032-1038. https://doi.org/10.1097/cm9.0000000000000775

Lombardi, C., Roca, E., Ventura, L., & Cottini, M. (2021). Smoking and COVID-19, the paradox to discover: An Italian retrospective, observational study in hospitalized and non-hospitalized patients. *Medical Hypotheses, 146*, 110391. https://doi.org/10.1016/j.mehy.2020.110391

Lowe, K. E., Zein, J., Hatipoglu, U., & Attaway, A. (2021). Association of smoking and cumulative pack-year exposure with COVID-19 outcomes in the cleveland clinic COVID-19 registry. *JAMA Internal Medicine, 181*(5), 709-711. https://doi.org/10.1001/jamainternmed.2020.8360

Lum, E., Tummalapalli, S. L., Khare, M., & Keyhani, S. (2022). Receipt of preventive health services and current cannabis users. *Journal of Addictive Diseases, 40*(2), 192-196. https://doi.org/10.1080/10550887.2021.1967688

Macleod, J., Robertson, R., Copeland, L., McKenzie, J., Elton, R., & Reid, P. (2015). Cannabis, tobacco smoking, and lung function: a cross-sectional observational study in a general practice population. *British Journal of General Practice, 65*(631), e89-95. https://doi.org/10.3399/bjgp15X683521

Meini, S., Fortini, A., Andreini, R., Sechi, L. A., & Tascini, C. (2021). The paradox of the low prevalence of current smokers among COVID-19 patients hospitalized in nonintensive care wards: results from an Italian multicenter case-control study. *Nicotine & Tobacco Research, 23*(8), 1436-1440. https://doi.org/10.1093/ntr/ntaa188

Merianos, A. L., Russell, A. M., Mahabee-Gittens, E. M., Barry, A. E., Yang, M., & Lin, H. C. (2022, Mar). Concurrent use of e-cigarettes and cannabis and associated COVID-19 symptoms, testing, and diagnosis among student e-cigarette users at four U.S. universities. *Addictive Behaviors, 126*, 107170. https://doi.org/10.1016/j.addbeh.2021.107170

Milad, N., Fantauzzi, M. F., McGrath, J. J. C., Cass, S. P., Thayaparan, D., Wang, P., Afkhami, S., Aguiar, J. A., Ask, K., Doxey, A. C., Stampfli, M. R., & Hirota, J. A. (2023). Cannabis smoke suppresses antiviral immune responses to influenza A in mice. *ERJ Open Research, 9*(6). https://doi.org/10.1183/23120541.00219-2023

Newport, K., Bishop, L., Donnan, J., Pal, S., & Najafizada, M. (2023). The COVID-19 pandemic and cannabis use in Canada-a scoping review. *Journal of Cannabis Research, 5*(31). https://doi.org/10.1186/s42238-023-00196-7

Noah, T. L., Zhou, H., Zhang, H., Horvath, K., Robinette, C., Kesic, M., Meyer, M., Diaz-Sanchez, D., & Jaspers, I. (2012). Diesel exhaust exposure and nasal response to attenuated influenza in normal and allergic volunteers. *American Journal of Respiratory and Critical Care Medicine, 185*(2), 179-185. https://doi.org/10.1164/rccm.201103-0465OC

Onaivi, E. S., & Sharma, V. (2020). Cannabis for COVID-19: can cannabinoids quell the cytokine storm? *Future Science OA, 6*(8), Fso625. https://doi.org/10.2144/fsoa-2020-0124

Ontario Government (2021, September 14). *Ontario Regulation 645/21; Rules for Areas at Step 3 and the Roadmap Exit Step*. https://www.ontario.ca/laws/regulation/r21645

Paland, N., Pechkovsky, A., Aswad, M., Hamza, H., Popov, T., Shahar, E., & Louria-Hayon, I. (2021). The immunopathology of COVID-19 and the Cannabis Paradigm. *Frontiers in Immunology, 12*, 631233. https://doi.org/10.3389/fimmu.2021.631233

Pascual Pastor, F., Isorna Folgar, M., Carvalho, N., Carvalho, F., & Arias Horcajadas, F. (2020). Therapeutic cannabis and COVID-19: Between opportunism and infoxication. *Adicciones, 32*(3), 167-172. https://doi.org/10.20882/adicciones.1603

Patanavanich, R., & Glantz, S. A. (2020). Smoking is associated with COVID-19 progression: A meta-analysis. *Nicotine & Tobacco Research, 22*(9), 1653-1656. https://doi.org/10.1093/ntr/ntaa082

Patanavanich, R., & Glantz, S. A. (2021). Smoking is associated with worse outcomes of COVID-19 particularly among younger adults: a systematic review and meta-analysis. *BMC Public Health, 21*(1), 1554. https://doi.org/10.1186/s12889-021-11579-x

Pérez, R., Glaser, T., Villegas, C., Burgos, V., Ulrich, H., & Paz, C. (2022). Therapeutic effects of cannabinoids and their applications in COVID-19 treatment. *Life, 12*(12), 2117. https://doi.org/10.3390/life12122117

Polen, M. R., Sidney, S., Tekawa, I. S., Sadler, M., & Friedman, G. D. (1993). Health care use by frequent marijuana smokers who do not smoke tobacco. *Western Journal of Medicine, 158*(6), 596-601. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1311782/

Rebuli, M. E., Speen, A. M., Martin, E. M., Addo, K. A., Pawlak, E. A., Glista-Baker, E., Robinette, C., Zhou, H., Noah, T. L., & Jaspers, I. (2019, Apr 15). Wood Smoke Exposure Alters Human Inflammatory Responses to Viral Infection in a Sex-Specific Manner. A Randomized, Placebo-controlled Study. *American Journal of Respiratory and Critical Care Medicine, 199*(8), 996-1007. https://doi.org/10.1164/rccm.201807-1287OC

Rogot, E., & Murray, J. L. (1980). Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Reports, 95*(3), 213-222. http://www.ncbi.nlm.nih.gov/pubmed/7384406

Rosoff, D. B., Yoo, J., & Lohoff, F. W. (2021a). A genetically-informed study disentangling the relationships between tobacco smoking, cannabis use, alcohol consumption, substance use disorders and respiratory infections, including COVID-19. *medRxiv*. https://doi.org/10.1101/2021.02.11.21251581

Rosoff, D. B., Yoo, J., & Lohoff, F. W. (2021b). Smoking is significantly associated with increased risk of COVID-19 and other respiratory infections. *Communications Biology, 4*(1). https://doi.org/10.1038/s42003-021-02685-y

Russell, C., Rueda, S., Room, R., Tyndall, M., & Fischer, B. (2018). Routes of administration for cannabis use - basic prevalence and related health outcomes: A scoping review and synthesis. *International Journal of Drug Policy, 52*, 87-96. https://doi.org/10.1016/j.drugpo.2017.11.008

Shover, C. M., Yan, P., Jackson, N. J., Buhr, R. G., Fulcher, J. A., Tashkin, D. P., & Barjaktarevic, I. (2022). Cannabis consumption is associated with lower COVID-19 severity among hospitalized patients: a retrospective cohort analysis. *Journal of Cannabis Research, 4*(1), 46. https://doi.org/10.1186/s42238-022-00152-x

Tetrault, J. M., Crothers, K., Moore, B. A., Mehra, R., Concato, J., & Fiellin, D. A. (2007). Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. *JAMA Internal Medicine, 167*(3), 221-228. https://doi.org/10.1001/archinte.167.3.221

The Lancet Respiratory, M. (2022). Future pandemics: failing to prepare means preparing to fail. *The Lancet Respiratory Medicine, 10*(3), 221-222. https://doi.org/10.1016/s2213-2600(22)00056-x

Yang, Y., Dobalian, A., & Ward, K. D. (2021). COVID-19 vaccine hesitancy and its determinants among adults with a history of tobacco or marijuana use. *Journal of Community Health, 46*(6), 1090-1098. https://doi.org/10.1007/s10900-021-00993-2

Yasmin, F., Najeeb, H., Moeed, A., Naeem, U., Asghar, M. S., Chughtai, N. U., Yousaf, Z., Seboka, B. T., Ullah, I., Lin, C. Y., & Pakpour, A. H. (2021). COVID-19 vaccine hesitancy in the United States: A systematic review. *Frontiers in Public Health, 9*, 770985. https://doi.org/10.3389/fpubh.2021.770985

Yu, T., Cai, S., Zheng, Z., Cai, X., Liu, Y., Yin, S., Peng, J., & Xu, X. (2020). Association Between Clinical Manifestations and Prognosis in Patients with COVID-19. *Clinical Therapeutics, 42*(6), 964-972. https://doi.org/10.1016/j.clinthera.2020.04.009

Zheng, Z., Peng, F., Xu, B., Zhao, J., Liu, H., Peng, J., Li, Q., Jiang, C., Zhou, Y., Liu, S., Ye, C., Zhang, P., Xing, Y., Guo, H., & Tang, W. (2020). Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *Journal of Infection, 81*(2), e16-e25. https://doi.org/10.1016/j.jinf.2020.04.021

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet, 395*(10229), 1054-1062. https://doi.org/10.1016/s0140-6736(20)30566-3

Funding and Acknowledgements: This work was supported by funding from Canadian Institutes for Health Research (CIHR, #437075), Canada Research Chair in Translational Addiction Research (CRC-2020-00170) and Peter Boris

Chair in Addictions Research. JM is a principal and senior scientist in Beam Diagnostics, Inc and has consulted to Clairvoyant Therapeutics, Inc. The other authors have no conflicts of interest to disclose. Thank you to Jane De Jesus, Jessica Gillard, Emily Vandehei, and Laura Lee for helping to collect data and give invaluable feedback throughout the manuscript writing process.