Increased risk for COVID-19 breakthrough infection in fully vaccinated patients with substance use disorders in the United States between December 2020 and August 2021

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Individuals with substance use disorders (SUDs) are at increased risk for COVID-19 infection and for adverse outcomes of the infection. Though vaccines are highly effective against COVID-19, their effectiveness in individuals with SUDs might be curtailed by compromised immune status and a greater likelihood of exposures, added to the waning vaccine immunity and the new SARS-CoV-2 variants. In a population-based cohort study, we assessed the risk, time trends, outcomes and disparities of COVID-19 breakthrough infection in fully vaccinated SUD patients starting 14 days after completion of vaccination. The study included 579,372 individuals (30,183 with a diagnosis of SUD and 549,189 without such a diagnosis) who were fully vaccinated between December 2020 and August 2021, and had not contracted COVID-19 infection prior to vaccination. We used the TriNetX Analytics network platform to access de-identified electronic health records from 63 health care organizations in the US. Among SUD patients, the risk for breakthrough infection ranged from 6.8% for tobacco use disorder to 7.8% for cannabis use disorder, all significantly higher than the 3.6% in non-SUD population (p<0.001). Breakthrough infection risk remained significantly higher after controlling for demographics (age, gender, ethnicity) and vaccine types for all SUD subtypes, except for tobacco use disorder, and was highest for cocaine and cannabis use disorders (hazard ratio, HR=2.06, 95% CI: 1.30-3.25 for cocaine; HR=1.92, 95% CI: 1.39-2.66 for cannabis). When we matched SUD and non-SUD individuals for lifetime comorbidities and adverse socioeconomic determinants of health, the risk for breakthrough infection no longer differed between these populations, except for patients with cannabis use disorder, who remained at increased risk (HR=1.55, 95% CI: 1.22-1.99). The risk for breakthrough infection was higher in SUD patients who received the Pfizer than the Moderna vaccine (HR=1.49, 95% CI: 1.31-1.69). In the vaccinated SUD population, the risk for hospitalization was 22.5% for the breakthrough cohort and 1.6% for the non-breakthrough cohort (risk ratio, RR=14.4, 95% CI: 10.19-20.42), while the risk for death was 1.7% and 0.5% respectively (RR=3.5, 95% CI: 1.74-7.05). No significant age, gender and ethnic disparities for breakthrough infection were observed in vaccinated SUD patients. These data suggest that fully vaccinated SUD individuals are at higher risk for breakthrough COVID-19 infection, and this is largely due to their higher prevalence of comorbidities and adverse socioeconomic determinants of health compared with non-SUD individuals. The high frequency of comorbidities in SUD patients is also likely to contribute to their high rates of hospitalization and death following breakthrough infection.

Key words: Substance use disorders, COVID-19 breakthrough infection, vaccination, cannabis use disorder, cocaine use disorder, comorbidities, socioeconomic determinants of health

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Substance use disorders (SUDs) are common: ~10.8% of adults in the US have had a problem with drug use[1,2]. SUDs are often associated with multiple comorbid conditions that are known risk factors for severe outcomes of COVID-19 infection, including cardiovascular, cerebrovascular, immune, hematological, pulmonary, metabolic, oncological, hepatic, renal, infectious, neurological and psychiatric diseases[3-11]. Additionally, studies from the early pandemic showed that patients with SUDs – including alcohol use disorder, cannabis use disorder, cocaine use disorder, opioid use disorder, and tobacco use disorder – were at increased risk for COVID-19 infection and associated severe outcomes, especially among African Americans[6].

In the US, three vaccines have been approved since December 2020: two mRNA vaccines developed by Pfizer-BioNTech and Moderna, and an adenovirus vaccine by Johnson & Johnson. Clinical trial data showed an efficacy of 95% for the Pfizer-BioNTech[12], 94.1% for the Moderna[13] and 66.3% for the Johnson & Johnson vaccine[14] in preventing COVID-19 infection. Clinical trials for COVID-19 vaccines did not explicitly include SUD patients, though they did include – for example, in the clinical trial for Pfizer-BioNTech vaccine – participants with a range of other diseases, including cancers, cardiovascular diseases, human immunodeficiency virus (HIV) infection, and renal diseases[12]. Currently, there are no systematic studies examining the real-world effectiveness of COVID-19 vaccines in populations with various SUDs. Vaccines are very effective, but breakthrough infections have been recorded[15-18], highlighting the need to identify populations that might be most vulnerable, as we have entered a worrisome new phase of the pandemic.

Studies have shown that individuals with compromised immune function, such as organ transplant recipients and cancer patients, have limited rates of SARS-CoV-2 IgG seroconversion[19-23]. Drugs and alcohol affect immune function, which is likely to contribute to the higher risk for infections in individuals with SUDs[3,6,24,25]. Thus, we hypothesized that individuals with SUDs could be at increased risk for vaccine breakthrough COVID-19 infection.

In this study, we estimated the risk for breakthrough COVID-19 infection among vaccinated patients with various SUDs compared to matched vaccinated individuals without SUDs. We also examined how the rate of breakthrough cases changed between December 2020 and August 2021.

METHODS

Study population

We used the TriNetX Analytics network platform[26], which allows access to de-identified data of 84.5 million unique patients

from 63 health care organizations in the US, among whom 15 million (age ≥12 years) had medical encounter(s) with health care organizations since December 1, 2020.

The study population comprised 579,372 individuals who fulfilled the following inclusion criteria: a) they had medical encounter(s) with health care organizations since December 1, 2020; b) they had documented evidence of full vaccination in electronic health records (i.e., they had received a second dose of Pfizer-BioNTech or Moderna vaccine, or a single dose of Johnson & Johnson vaccine) between December 1, 2020 and August 14, 2021; and c) they had not contracted COVID-19 infection prior to vaccination.

The fully vaccinated study population included 30,183 patients with SUD and 549,189 patients without SUD. Among the fully vaccinated population with SUD, 7,802 patients had a diagnosis of alcohol use disorder, 2,058 of cannabis use disorder, 1,011 of cocaine use disorder, 2,379 of opioid use disorder, and 21,941 of tobacco use disorder.

TriNetX Analytics provides web-based real-time secure access to patient electronic health records from hospitals, primary care and specialty treatment providers, covering diverse geographic locations, age groups, ethnic groups, and income levels. Though the data are de-identified, end-users can use the platform built-in functions working on patient-level data for cohort selection and matching, analyzing incidence and prevalence of events in a cohort, and comparing characteristics and outcomes between matched cohorts. Multiple studies have used TriNetX to study risk, disparity, sequelae, temporal trends, clinical characteristics, and outcomes of COVID-19 infection[27-30].

The status of COVID-19 infection was based on the ICD-10 diagnosis code of "COVID-19" (U07.1) or lab-test confirmed presence of "SARS coronavirus 2 and related RNA" (TNX:LAB:9088). The status of full vaccination was based on the Current Procedural Terminology (CPT) relevant codes for Pfizer-BioNTech (0002A), Moderna (0012A) and Johnson & Johnson (0031A) vaccines.

The status of SUD was based on the ICD-10 diagnosis code of "mental and behavioural disorders due to psychoactive substance use" (F10-F19). The status of alcohol use disorder was based on the ICD-10 diagnosis code of "alcohol related disorders" (F10); that of cannabis use disorder on the code of "cannabis related disorders" (F12); that of cocaine use disorder on the code of "cocaine related disorders" (F14); that of opioid use disorder on the code of "opioid related disorders" (F11); and that of tobacco use disorder on the code of "nicotine dependence" (F17). Other subtypes of SUD, such as methamphetamine use disorder, were not examined due to their small sample sizes.

For breakthrough outcome measures, the status of hospitalization was based on the CPT code "hospital inpatient services" (013659), while the status of death was based on the vital status code "deceased" that TriNetX regularly imports from the Social Security Death index.

Procedures

We tested whether fully vaccinated SUD patients had higher risk for breakthrough infection than non-SUD patients. Separate analyses were performed for alcohol use disorder, cannabis use disorder, cocaine use disorder, opioid use disorder, and tobacco use disorder.

The cohorts of SUD and non-SUD patients were created by propensity score matching for demographics (age, gender, ethnicity); adverse socioeconomic determinants of health (including "problems related to education and literacy", "problems related to employment and unemployment", "occupational exposure to risk factors", and "problems related to housing and economic circumstances", according to the ICD-10); lifetime comorbidities (hypertension, heart diseases, cerebrovascular diseases, obesity, type 2 diabetes, cancers, chronic respiratory diseases, chronic kidney diseases, liver diseases, blood diseases and disorders involving immune mechanisms, HIV infection, dementia, depression, and psychotic disorders), and vaccine types (Pfizer, Moderna and Johnson & Johnson).

The TriNetX built-in propensity score matching function was used (1:1 matching using a nearest neighbor greedy matching algorithm with a caliper of 0.25 times the standard deviation). The outcome was COVID-19 infection at least 14 days after patients received the second dose of Pfizer-BioNTech or Moderna vaccine or a single dose of Johnson & Johnson vaccine. Kaplan-Meier analysis was performed to estimate the probability of breakthrough infection from day 14 after full vaccination to August 28, 2021. Comparisons between cohorts were made using a log-rank test (a built-in function in TriNetX). The hazard ratio (HR) was used to describe the relative risk of breakthrough infection based on comparison of time to event rates, and was calculated using a proportional hazard model (a built-in function in TriNetX). The proportional hazard assumption was tested using the generalized Schoenfeld approach.

We tested whether fully vaccinated patients who received Pfizer-BioNTech vaccine had a different risk of developing breakthrough COVID-19 infection compared with a matched cohort of patients who received Moderna vaccine. Johnson & Johnson vaccine was not examined due to small sample size. The Pfizer and Moderna cohorts were propensity-score matched for demographics, adverse socioeconomic determinants of health, and comorbid medical conditions. Kaplan-Meier analysis was used to estimate the probability of breakthrough infection from day 14 after full vaccination to August 28, 2021. Separate analyses were performed for SUD, SUD subtypes, and non-SUD individuals. HR was calculated to compare the relative risk of breakthrough infection in two matched cohorts.

We explored how the rates of breakthrough infection in fully vaccinated SUD and non-SUD populations, measured by cases/person-day for each month, evolved between December 2020 and August 2021. TriNetX built-in functions were used for calculating proportion rates.

We tested whether fully vaccinated patients with break-

through infection had different risk for hospitalization and death compared with a matched cohort without breakthrough infection. Breakthrough and non-breakthrough cohorts were propensity-score matched for demographics, adverse socioeconomic determinants of health, comorbid medical conditions, and vaccine types. For the breakthrough cohort, overall risks of hospitalization and death were calculated from the day of infection to August 28, 2021. For the non-breakthrough cohort, overall risks of hospitalization and death were calculated from day 14 after full vaccination to August 28, 2021. Relative risk (RR) was used to compare matched cohorts. Separate analyses were performed for SUD and non-SUD populations.

We investigated how the risks for breakthrough infection in fully vaccinated patients differed by age, gender and ethnicity. The case cohort comprised fully vaccinated patients with one of the following demographic factors: female, older (age ≥65 years), or African American. The comparison cohort comprised matched vaccinated SUD patients with one of the following corresponding factors: male, younger (age <65 years), or Caucasian. Two cohorts were propensity-score matched on other demographics, adverse socioeconomic determinants of health, comorbid medical conditions, and vaccine types. Kaplan-Meier analysis was performed to estimate the probability of breakthrough infection from day 14 after full vaccination to August 28, 2021 in matched cohorts. HR was used to compare the relative risk of breakthrough infection between matched cohorts. Separate analyses were done for SUD, non-SUD and each SUD subtype.

We examined how the timing of recent medical encounters for SUD diagnosis was associated with the risk of breakthrough infection among fully vaccinated SUD patients. Four cohorts of SUD patients were used: a) "Ever" (all SUD patients, irrespective of when they had a medical encounter for their diagnosis, thus including both recovered patients and those with active SUD); b) "February 2019" (patients who had a medical encounter for their SUD diagnosis after February 2019); c) "February 2020" (patients who had a medical encounter for their SUD diagnosis during the pandemic, i.e. any time after February 2020); and d) "December 2020" (patients who had a medical encounter for their SUD diagnosis after the COVID-19 vaccine was approved, thus most likely having a currently active SUD). The "Ever" group was used as the reference one to which the risk of breakthrough infection in the other groups was compared. Separated analyses were conducted for each SUD subtype.

Statistical tests were conducted with significance set at $p<0.05$ (two sided) using R, version 3.6.3.

RESULTS

The demographic characteristics of the fully vaccinated patients and the sample sizes as a function of SUD subtype are shown in Table 1. Among vaccinated SUD patients, 75.6% received Pfizer-BioNTech, 21.1% Moderna, and 3.3% Johnson & Johnson vaccine. Among vaccinated non-SUD population, 88.2% received Pfizer-BioNTech, 10.6% Moderna and 1.2% Johnson & Johnson vaccine.

Patients with SUD were older (mean age: 59.3±14.4 years) than those without SUD (54.7± 19.8 years). There were more men in the SUD population (51.4% vs. 43.1%), and the percentage of African Americans was higher in the SUD (26.2%) than in the non-SUD (14.3%) sample. The prevalence of adverse socioeconomic determinants of health was also higher in the SUD population than in patients without SUD (7.9% vs. 1.2%). Vaccinated patients with SUD had a higher lifetime prevalence of all comorbidities, as well as of transplants (all $p<0.001$).

Among the vaccinated population, the risk of breakthrough infection ranged from 6.8% for tobacco use disorder to 7.8% for cannabis use disorder, all significantly higher than the 3.6% in the non-SUD population ($p<0.001$). The HRs between SUD and non-SUD cohorts after propensity score matching for demographics (age, gender, ethnicity) and vaccine types remained significantly higher for all SUD subtypes except for tobacco use disorder, being highest for cocaine use disorder and cannabis use disorder (HR=1.17, 95% CI: 1.01-1.35 for alcohol; HR=1.92, 95% CI: 1.39-2.66 for cannabis; HR=2.06, 95% CI: 1.30-3.25 for cocaine; and HR=1.31, 95% CI: 1.00-1.71 for opioids) (see Table 2).

After controlling for adverse socioeconomic determinants of health and comorbid medical conditions, the risk for breakthrough infection no longer differed in SUD compared to non-SUD cohorts, except for patients with cannabis use disorder, who remained at significantly increased risk (HR=1.55, 95% CI: 1.22-1.99) (see Table 3).

Among SUD and non-SUD populations, the risk for breakthrough infection was higher in individuals who received the Pfizer than the Moderna vaccine, after matching for demographics, adverse socioeconomic determinants of health, and comorbid medical conditions (HR in SUD cohort: 1.49, 95% CI: 1.31-1.69; HR in non-SUD cohort: 1.45, 95% CI: 1.38-1.53). The same trend was observed in SUD subtypes (see Table 4).

The rate of breakthrough infection in the SUD population steadily increased from 0 cases/person-day in January 2021 to 0.001 cases/person-day in June 2021 to 0.0025 cases/person-day in August 2021 (2.5 times faster than in June 2021). A similar trend was observed in the non-SUD population: the rate of breakthrough infection steadily increased from 0 cases/person-day in January 2021 to 0.0009 cases/person-day in June 2021, and then reached 0.0049 cases/person-day in August 2021 (5.4 times faster than in June 2021) (see Figure 1).

Within the SUD population, the overall risk for hospitalization was 22.5% in the breakthrough cohort compared to 1.6% in the matched non-breakthrough cohort (RR=14.4, 95% CI: 10.19-20.42). The overall risk for death was 1.7% in the breakthrough cohort, compared to 0.5% in the matched non-breakthrough cohort (RR=3.5, 95% CI: 1.74-7.05).

Within the non-SUD population, the overall risk for hospitalization was 17.5% in the breakthrough cohort compared to 0.5% in the matched non-breakthrough cohort (RR=34.2, 95% CI: 28.05-41.67). The overall risk for death was 1.1% in the break-

Table 1 Characteristics of substance use disorder (SUD) and non-SUD vaccinated populations

	AUD	CUD	CocaineUD	OUD	TUD	SUD	Non-SUD
Total number of patients	7,802	2,058	1,011	2,379	21,941	30,184	549,189
Age (years, mean±SD)*	59.3±14.4	47.9±16.3	55.1±12.2	59.1±14.2	59.6±13.5	59.3±14.4	54.7±19.8
Gender (% male)*	61.8	60.1	61.5	45.7	50.3	51.4	43.1
Ethnicity (%)							
White	69.0	57.7	41.9	62.8	62.1	63.2	63.4
African American*	21.9	33.4	50.1	29.6	28.5	26.2	14.3
Hispanic/Latino	5.0	4.6	5.0	3.2	3.8	4.3	12.3
Asian	1.2	1.1	1.0	1.0	2.2	2.0	8.6
Unknown	7.4	7.4	6.7	6.0	6.9	7.2	12.6
Adverse socioeconomic determinants of health (%)*	10.8	18.7	22.6	14.1	7.8	7.9	1.2
Lifetime medical conditions (%)							
Hypertension*	63.3	50.8	66.8	67.2	62.9	61.6	22.8
Heart diseases*	19.6	17.0	24.2	21.0	21.5	20.1	5.3
Cerebrovascular diseases*	15.0	13.0	19.6	15.0	13.3	13.2	3.6
Obesity*	27.7	31.1	33.4	36.6	31.2	30.4	9.3
Type 2 diabetes*	21.6	19.9	28.9	30.7	25.7	24.6	8.4
Cancers*	48.8	40.9	46.6	44.5	45.2	44.9	16.2
Chronic respiratory diseases*	30.1	35.1	44.8	39.7	38.7	34.7	7.6
Chronic kidney diseases*	11.9	11.5	18.8	15.7	10.8	11.3	3.5
Liver diseases*	26.3	18.0	29.2	21.9	15.4	16.9	3.2
Blood diseases and disorders involving immune mechanisms*	41.1	40.0	50.1	49.8	34.3	35.6	10.5
HIV infection*	3.3	8.4	12.5	7.1	3.1	3.2	0.3
Dementia*	2.2	0.9	1.6	2.2	1.2	1.4	0.5
Major depression*	37.0	51.8	52.3	48.0	29.2	30.9	6.0
Psychotic disorders*	4.7	12.9	16.9	6.3	3.5	3.6	0.3
Lifetime organ transplants (%)*	3.9	3.7	3.8	3.4	1.8	2.6	0.7

*Significant difference between SUD and non-SUD populations, p<0.001. AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

through cohort compared to 0.2% in the matched non-breakthrough cohort (RR=6.0, 95% CI: 4.20-8.66).

No significant age, gender and ethnic disparities of breakthrough infections were observed in SUD patients after matching for other demographics, adverse socioeconomic determinants of health, comorbid medical conditions and vaccine types, except for patients with cannabis use disorder, among whom African Americans had higher risk than matched Caucasians (HR=1.63, 95% CI: 1.06-2.51). Among vaccinated non-SUD population, older individuals (age ≥65 years) were more likely to have breakthrough infections than younger patients after matching for gender, ethnicity, adverse socioeconomic determinants of health, and comorbid medical conditions (HR=1.08, 95% CI: 1.04-1.13); women had lower risk than matched men (HR=0.87, 95% CI: 0.84-0.90); and African Americans had higher risk than matched Caucasians (HR=1.12, 95% CI: 1.07-1.18) (see Figure 2).

Within the SUD population, the risk for breakthrough infection was higher for patients who had recent medical encounters for their SUD diagnosis, ranging from 7.0% in the "Ever" group to 10.5% in the "December 2020" group (p<0.001 between these two groups). The same trends were observed for SUD subtypes (see Table 5).

DISCUSSION

In this population-based cohort study, we report that the overall risk for breakthrough infection in vaccinated SUD patients ranged from 6.8% for tobacco use disorder to 7.8% for cannabis use disorder, all significantly higher than the 3.6% in the vaccinated non-SUD population. After matching for demographics (age, gender, ethnicity) and vaccine types (Pfizer,

Table 2 Risk of breakthrough COVID-19 infection in propensity-score matched (demographics and vaccine types) substance use disorder (SUD) and non-SUD populations

Cohort	Patients in cohort	Risk in cohort	Risk in matched non-SUD cohort	Hazard ratio (95% CI)
AUD	7,802	7.2%	3.7%	1.17 (1.01-1.35)
CUD	2,055	7.8%	2.3%	1.92 (1.39-2.66)
CocaineUD	1,011	7.7%	2.4%	2.06 (1.30-3.25)
OUD	2,379	7.1%	3.2%	1.31 (1.00-1.71)
TUD	21,935	6.8%	3.9%	1.06 (0.98-1.15)

AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

Moderna, Johnson & Johnson), patients with SUD – with the exception of those with tobacco use disorder – still had higher risks for breakthrough infection compared with matched non-SUD cohorts, with the highest risks for those with cocaine use disorder (HR=2.06, 95% CI: 1.30-3.25) and cannabis use disorder (HR=1.92, 95% CI: 1.39-2.66).

Matching for adverse socioeconomic determinants of health and comorbid medical conditions removed the differences in breakthrough infection between SUD and non-SUD populations, suggesting that the increased risk in SUD patients was driven by their high prevalence of a diverse set of comorbidities. Patients with cannabis use disorder, who were younger and had less comorbidities than the other SUD subtypes, had higher risk for breakthrough infection even after they were matched for adverse socioeconomic determinants of health and comorbid medical conditions with non-SUD patients (HR=1.55, 95% CI: 1.22-1.99). This may indicate that additional variables, such as behavioral factors or adverse effects of cannabis on pulmonary and immune function[31], could contribute to the higher risk for breakthrough infection in this group.

The rate of severe COVID outcomes in vaccinated individuals with breakthrough infections is known to be much lower than in infected unvaccinated individuals[32]. However, the outcome analyses in our study showed that hospitalization and

Table 3 Risk of breakthrough COVID-19 infection in propensity-score matched (adverse socioeconomic determinants of health and comorbid medical conditions, in addition to demographics and vaccine types) substance use disorder (SUD) and non-SUD populations

Cohort	Patients in cohort	Risk in cohort	Risk in matched non-SUD cohort	Hazard ratio (95% CI)
AUD	7,754	7.2%	6.9%	1.09 (0.96-1.22)
CUD	2,032	7.8%	5.4%	1.55 (1.22-1.99)
CocaineUD	991	7.7%	7.5%	1.15 (0.83-1.58)
OUD	2,360	7.0%	7.6%	0.94 (0.76-1.16)
TUD	21,757	6.8%	6.8%	1.03 (0.96-1.11)

AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

Table 4 Risk of breakthrough COVID-19 infection in propensity-score matched (demographics, adverse socioeconomic determinants of health, and comorbid medical conditions) substance use disorder (SUD) and non-SUD populations receiving Pfizer and Moderna vaccine

Cohort	Risk in patients receiving Pfizer	Risk in patients receiving Moderna	Hazard ratio (95% CI)
SUD	8.7%	6.3%	1.49 (1.31-1.69)
AUD	8.9%	7.1%	1.41 (1.10-1.80)
CUD	8.2%	7.3%	1.16 (0.68-1.97)
CocaineUD	7.3%	4.9%	2.78 (1.08-7.16)
OUD	9.7%	6.6%	1.56 (1.01-2.42)
TUD	9.0%	5.8%	1.69 (1.46-1.97)
Non-SUD	5.4%	4.7%	1.45 (1.38-1.53)

AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

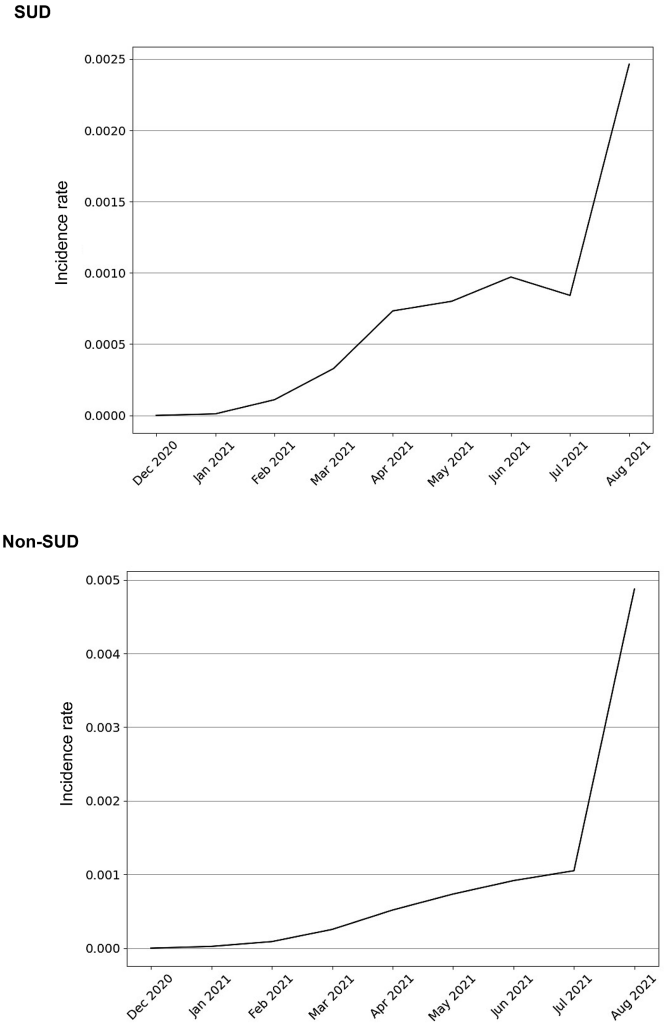

Figure 1 Time trend of incidence rates (cases/person-day) of breakthrough COVID-19 infection in patients with and without substance use disorder (SUD)

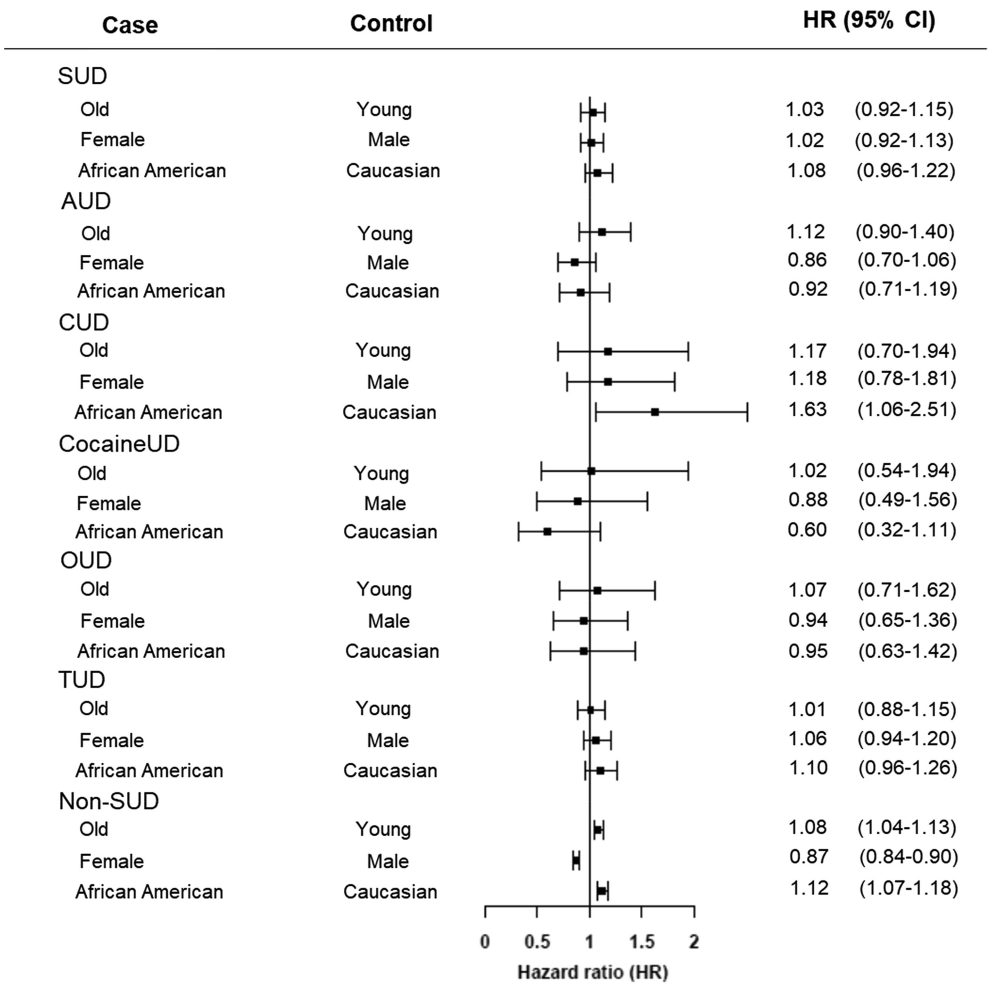

Figure 2 Hazard ratios of breakthrough COVID-19 infection in fully vaccinated substance use disorder (SUD) and non-SUD populations: female vs. male; older (age ≥65 years) vs. younger (age <65 years); African American vs. Caucasian. Two demographic-stratified cohorts were propensity-score matched based on other demographics (age, gender, ethnicity), adverse socioeconomic determinants of health, comorbid medical conditions, and vaccine types. AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

death risks were significantly different between vaccinated SUD patients with breakthroughs and those without breakthrough, after matching for demographics, adverse socioeconomic determinants of health, comorbid medical conditions, and vaccine types. The risk for hospitalization in vaccinated SUD patients with breakthrough infection was 22.5%, compared to 1.6% in matched SUD patients without breakthrough infection (RR=14.4, 95% CI: 10.19-20.42). The risk for death in vaccinated SUD patients with breakthrough infection was 1.7%, compared to 0.5% in matched SUD cohort without breakthrough infection (RR=3.5, 95% CI: 1.74-7.05). This was also the case for fully vaccinated non-SUD population. We were unable to determine whether the hospitalizations and deaths in the breakthrough cases were due to COVID-19 or were associated with other medical conditions, but the large and significant differences between breakthrough and matched non-breakthrough cases indicate that COVID-19 infection contributed.

Outcome analysis for hospitalization between breakthrough and non-breakthrough cohorts may have suffered from ascertainment bias, as patients with moderate to severe breakthrough infections are more likely to visit health care organizations than asymptomatic or mild breakthrough cases, resulting in overrepresentation of the more severe breakthrough cases in the electronic health record data. On the other hand, the analysis for death outcomes is less prone to ascertainment bias, as the death data were regularly imported from the Social Security Death index. Overall, our results suggest that vaccine breakthrough infections can result in significant adverse outcomes, including death, based on the analysis of the fully vaccinated population from a nationwide real-time electronic health record database.

Clinical trials and real-world studies have demonstrated that both Pfizer-BioNTech and Moderna vaccines are highly effective for preventing COVID-19 infection and its severe outcomes[12,13,33-35]. Two recent reports showed that Pfizer-BioNTech may be less effective than Moderna vaccine during periods of Alpha and Delta variant prevalence[36], and that elderly nurs-

Table 5 Risk of breakthrough COVID-19 infection among fully vaccinated substance use disorder (SUD) patients who had medical encounters for their diagnosis at different time cutoffs

	Medical encounter for SUD	Patients on cohort	Patients with infection	Risk of infection	p
SUD	Ever	30,183	2,113	7.0%	Ref.
	Feb. 2019	4,185	366	8.7%	0.003
	Feb. 2020	13,621	1,181	8.7%	<0.001
	Dec. 2020	9,041	946	10.5%	<0.001
AUD	Ever	7,802	563	7.2%	Ref.
	Feb. 2019	4,185	366	8.7%	0.003
	Feb. 2020	2,959	294	9.9%	<0.001
	Dec. 2020	1,858	222	11.9%	<0.001
CUD	Ever	2,058	160	7.8%	Ref.
	Feb. 2019	1,019	91	8.9%	0.270
	Feb. 2020	667	72	10.8%	0.015
	Dec. 2020	403	56	13.9%	<0.001
CocaineUD	Ever	1,011	78	7.7%	Ref.
	Feb. 2019	422	41	9.7%	0.211
	Feb. 2020	293	30	10.2%	0.168
	Dec. 2020	176	25	14.2%	0.005
OUD	Ever	2,379	170	7.1%	Ref.
	Feb. 2019	1,449	114	7.9%	0.409
	Feb. 2020	1,078	84	7.8%	0.500
	Dec. 2020	783	67	8.6%	0.193
TUD	Ever	21,941	1,490	6.8%	Ref.
	Feb. 2019	13,450	1,029	7.7%	0.002
	Feb. 2020	9,790	832	8.5%	<0.001
	Dec. 2020	6,485	678	10.5%	<0.001

Ever – all SUD patients, irrespective of when the diagnosis was made (reference group); Feb. 2019 – patients who had a medical encounter for SUD after February 2019; Feb. 2020 – patients who had a medical encounter for SUD during the pandemic, i.e. any time after February 2020; Dec. 2020 – patients who had a medical encounter for SUD after vaccines were approved. AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

ing home residents in Ontario produced stronger immune responses with the Moderna than the Pfizer BioNTech vaccine[37]. We observed a higher risk for breakthrough infection in patients who received the Pfizer-BioNTech than in those receiving the Moderna vaccine in the whole population of 579,372 vaccinated patients, with HR=1.49 (95% CI: 1.31-1.69) for the SUD population, and HR=1.45 (95% CI: 1.38-1.53) for the non-SUD population.

Our study covered months when the Delta variant appeared in the US, including July and August 2021, when it caused more than 90% of new cases[38]. Vaccine effectiveness against the Delta variant is lower than for the Alpha variant[39-42]. Evidence also suggests that vaccine efficacy against COVID-19 may wane over time[32,43]. The trend analyses in our study showed that the rate of new COVID-19 infections, measured by cases/person-day, steadily increased in vaccinated SUD patients from January to June 2021, and then accelerated and reached 0.0025 cases/person-day in August 2021 (2.5 times faster than in June 2021). A similar trend was observed for fully vaccinated non-SUD patients. As the vaccination time could be any time between December 2020 and August 2021, the increasing rates of breakthrough infections with time may reflect a possible decline in vaccine-induced immunity for those vaccinated early, especially in older persons. The rapid increase after June 2021 may be due to the emergence of the Delta and other variants and the relaxation of prevention measures.

The lack of variant sequencing information in electronic health records did not allow us to assess the contribution of the Delta variant to breakthrough infections, including differences observed between Pfizer and Moderna vaccines. Future studies are warranted to further understand how much of the breakthrough infections are contributed by waning vaccine efficacy or by the Delta variant, separately and combined. The accelerated increase in incidence rate after June 2021 highlights the impor-

tance of follow-up studies to continuously monitor incidence rates of breakthrough infections.

In our previous study during the early stage of the pandemic (February to June 2020), when vaccines were not available, we reported ethnic and gender disparities in COVID-19 risk in individuals with SUD, with African Americans at greater risk than Caucasians and women at greater risk than men[6]. In the present study, no significant age, gender and ethnic disparities of breakthrough infections were observed in vaccinated SUD patients, after matching for other demographics, adverse socioeconomic determinants of health, comorbid medical conditions, and vaccine types. This may be due to small sample sizes, as we observed age, gender and ethnic disparities in fully vaccinated non-SUD population: older individuals (age ≥65 years), African Americans and men were more likely to have breakthrough infections than matched younger patients, Caucasians or females, respectively. The age disparity might reflect age-related decline in immunity, that not only would increase susceptibility to infection but also reduce the prophylactic efficacy of vaccinations[44,45]. The reasons for gender and ethnic disparities for breakthrough infections warrant further investigation.

Among vaccinated SUD patients, the risk for breakthrough infection was higher in patients who had a recent medical encounter for their SUD diagnosis (after December 2020), who were likely patients with current SUD. These results suggest that SUD itself, apart from the contribution of comorbid medical conditions, may have increased the risk for COVID-19 infection, even among the vaccinated population. The higher rate of breakthrough infection in active SUD patients might in part be due to behaviors that place them in situations of greater infection risk, or to the effects of the drugs, such as respiratory depression with opioid consumption or the adverse impact of cannabis on immune function.

Our study has several limitations. First, although widely used and accepted for observational studies on health care utilization, drug utilization, epidemiology (incidence/prevalence), risk factors, and safety surveillance, patient electronic health record data may suffer from under-/over-/mis-diagnosis, and do not include all possible confounding factors. Second, the TriNetX database represents people who had medical encounters with health care systems, and does not necessarily represent the entire US population, for example patients from rural areas, healthy population, undocumented immigrants. Third, vaccinations made outside of health care organizations, for example at mass vaccination centers, drug stores or recreational centers, are not necessarily captured in patient electronic health records. Fourth, we were unable to determine whether the breakthrough COVID-19 cases were asymptomatic, symptomatic or severe, or whether they were caused by the Delta variant. Further studies utilizing other data resources are needed to examine these questions.

Future studies should: a) continue to evaluate the long-term effectiveness of COVID-19 vaccines, as the infection caused by the Delta variant has become dominant and the efficacy of immunization may wane after several months; b) monitor outcomes, including hospitalization and mortality, associated with breakthrough infection; c) compare outcomes of COVID-19 infection in vaccinated versus unvaccinated SUD populations, which is important as vaccine hesitancy remains high worldwide[46]. Factors independently associated with vaccine hesitancy include age, ethnicity and lower educational attainment[47], and these factors disproportionally affect SUD populations[48,49].

In our study, the overall risk of COVID-19 infection among vaccinated SUD patients was low, highlighting the effectiveness and the need for full vaccination in this population. However, our findings document that this group remains a vulnerable one even after vaccination, confirming the importance for vaccinated patients with SUD to continue to take protective preventive measures against the infection.

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