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Risk of COVID-19 reinfection and severe outcomes among people with substance use disorders

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Title

Risk of COVID-19 reinfection and severe outcomes among people with substance use disorders

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Abstract

Objective

Despite advancement in vaccines and treatments for COVID-19 over the past two years, many concerns remain about reinfection and waning immunity against COVID-19 and its variants, especially among people with substance use disorder (SUD). The study assessed the risk of COVID-19 reinfection and severe illness among adults with SUD and their vaccination status to inform management in this vulnerable population as the pandemic continues.

Design

Retrospective cohort study

Setting

Nationwide electronic health records (TriNetX database) in the United States among adults with COVID-19 infection from January 2020 to June 2022

Participants

Adults (age≥18 years) who were infected by COVID-19, excluding those who had cancer or lived in nursing homes or palliative care facilities

Outcome Measures

COVID-19 reinfection was defined as a new diagnosis after 45 days of the initial infection. Logistic regression was applied to assess the odds ratio of COVID-19 reinfection and severe outcomes within 30 day of reinfection for adults with alcohol (AUD), opioid (OUD), cocaine (CUD), stimulant (STUD), cannabis (CAUD), and other use disorders, controlled for demographic and comorbid conditions.

Results

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The SUD cohort was 13-29% more likely to be re-infected by COVID-19, and had significantly higher 30-day mortality. Adults with AUD, STUD and OUD were at greater risks (AOR=1.69-1.86) of emergency department, hospital, and intensive care admissions after 30 days of reinfection. Individuals with SUD and multiple vaccines doses were associated with decreased risks of worse COVID-19 outcomes. Lower COVID-19 reinfection rates (AOR=0.67-0.84) were only found among individuals with AUD, CAD, or CAUD who had COVID-19 vaccination.

Conclusions

Individuals with SUD had greater risks of COVID-19 reinfection and poor outcomes, especially those with OUD, STUD, and AUD. Multiple vaccinations are recommended to reduce severe illness after COVID-19 reinfection in the SUD population.

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Strengths and limitations of this study

- This study utilized large-scale electronic health record-based data which provides a wide range of medical, psychiatric, and demographic factors to assess the risk of COVID-19 reinfection and severe complications among adults with substance use disorders.
- Our findings can help elucidate substance use disorder subtypes that are at the greatest risk of COVID-19 reinfection and poor outcomes, and thus, could inform public health effort to promote the importance of multiple vaccinations in the subtypes.
- We could not control for data completed at facilities outside of the participating research network and therefore there may be uncaptured information with use of the electronic health records, potentially limiting the generalizability of the results.
- Further limitations of this study consist of inability to control for socioeconomic contexts and inability to quantify severity or stage of comorbid conditions, which may require future research to address the impact of these factors on COVID-19 reinfection.

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Introduction

The COVID-19 pandemic has led to unprecedented public health challenges in the United States, especially for individuals experiencing drug abuse and addiction problems.[1,2] Lacking access to screening and treatments during the pandemic has resulted in care disruption for people with substance use disorder (SUD) and those in recovery. Individuals with SUD are found to have increased risk of COVID-19 infection and severe complications[2] due to compromised immune systems,[3] respiratory-related functions,[4] and cardiovascular conditions.[5] With the continuation of the COVID-19 pandemic, persons previously recovered from COVID-19 can be re-infected by the disease. Despite advancement in vaccines and treatments for COVID-19 over the past two years, many concerns remain about reinfection and waning immunity against the SARS-CoV-2 virus and its variants, especially among people with SUD.

The risk of COVID-19 infection and outcomes was also found to vary by the subtype of SUD.[4,6,7] The highest risk of infection was found among individuals with opioid use disorder (OUD), followed by cocaine use disorder (CUD) and alcohol use disorder (AUD).[4] People with AUD or OUD tended to have severe complications likely to require hospital admission and intensive care compared to those with cannabis use disorder (CAUD) and CUD. Specific pharmacological effects from different drugs might contribute to this outcome variation among SUD subtypes.

The efficacy of COVID-19 vaccination also varies among individuals with multiple chronic conditions and weak immune systems.[8] Compared to people without SUD, vaccinated persons with SUD still experience significantly greater COVID-19 infection risk,[9] potentially due to higher prevalence of comorbid conditions and negative socioeconomic statuses in the SUD population. As more people with SUD receive COVID-19 vaccination, additional research

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is required to examine the vaccine effect on preventing their COVID-19 reinfection and poor outcomes.

Furthermore, individuals with SUD are more likely to have coexistent mental health conditions, including depression, anxiety, and bipolar disorder,[10–13] which can be risk factors for severe COVID-19 reinfection.[14,15] The SUD population has also been shown at increased risk of hypertension, obesity, diabetes, and cardiovascular conditions.[2] Those medical problems can negatively influence immune and respiratory system, increasing vulnerability to the SARS-CoV-2 virus infection[16] and its complications.[17,18] These co-occurring mental and physical conditions may also lead to a higher reinfection risk.

The large scale of the pandemic has raised the need for better knowledge of containing ongoing and emerging outbreaks to reduce subsequent mortality and morbidity for people with SUD. The objective of this study is to assess the risk of COVID-19 reinfection and severe illness among adults with SUD to inform clinical treatment and public policy decisions pertaining to this unique population.

METHODS

Study design and data sources

This was a retrospective cohort study utilizing electronic health records (EHRs) of 57 healthcare organizations sourced from the TriNetX research network database (Cambridge, MA). TriNetX is a large health data network that contains de-identified EHRs (demographics, diagnoses, procedures, medications, and laboratory tests) of more than 80 million patients from participating healthcare organizations predominately from the U.S. Data in the TriNetX database has undergone extensive curation and mapping to common clinical entities and terminologies to

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ensure high usability as well as consistency with the Reporting of studies Conducted using Observational Routinely collected Data (RECORD) guidelines.[19] The study used deidentified TriNetX research datasets, and was determined to be exempt from the Institutional Review Board oversight by the Pennsylvania State University's Human Research Protection Program.

Cohort description

The study population consisted of adults (age≥18 years) who were diagnosed with COVID-19 between January 1, 2020 and April 30, 2022, based on the combination of one or more disease indicators, including ICD-10 diagnosis codes and positive laboratory test results (see Supplemental Table S1 for details).[20,21] The initial COVID-19 infection episode during the study assessment period was considered the "index" infection. Individuals whose index COVID-19 infection occurred prior to the age of 18 were excluded from the study. Health data for adults with a valid index infection continued to be collect through June 30, 2022, to capture additional COVID-19 reinfection. Individuals were excluded if they had cancer or lived in nursing homes or palliative care facilities prior to COVID infection.

Substance use disorders

This analysis focused on the relationship of COVID-19 reinfection with the following SUD subtypes: alcohol (AUD), opioid (OUD), cocaine (CUD), stimulant (STUD), cannabis (CAUD), and other (other-UD). The other-UD category included sedative use disorder, hallucinogen use disorder, inhalant use disorder, and other psychoactive use disorder. A person's SUD diagnosis must have predated the index COVID-19 infection to be identified with the condition. Each subtype measure included a binary variable (yes/no) indicating whether patients had the specific subtype of SUD. This study allowed for inclusion of individuals with multiple SUD subtypes, as is common in the clinical setting. Regression modeling was able to control for

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each subtype so that interpretation of the effect of each individual SUD subtype can be observed. The list of diagnosis codes for each SUD subtype is provided in Supplemental Table S1.

COVID-19 Vaccination

COVID-19 vaccination was identified through the presence of COVID-19 vaccine codes specified by the Current Procedural Terminology (CPT) of the American Medical Association (see supplemental table S1). The total number of COVID-19 vaccine doses of individuals experiencing reinfection were computed based on the sum of vaccine doses received prior to the reinfection incident. The number of COVID-19 vaccinations of individuals without reinfection were estimated as the sum of vaccine doses received during the study period. To understand the effect of vaccine doses, this analysis categorized COVID-19 vaccine dosing to three dose levels: 0 (unvaccinated), 1 (one dose only), and 2+ (people receiving at least two doses).

Baseline demographics and comorbid characteristics

Patient demographics and health comorbidities were extracted at the time of the first COVID-19 infection. The available demographic data included sex (male/female), age group (18-39, 40-65, 65+), ethnicity (Hispanic/non-Hispanic) and race (White/Black/Other). Data on conditions known to be associated with the COVID-19 complications were also collected, including the diagnoses of medical conditions (obesity, diabetes, chronic kidney disease, cardiovascular disorders[17,20]) and mental health disorders (depression, anxiety, bipolar).[22] Because the current status of tobacco use/smoking was unavailable in the EHR data, the presence of the tobacco/nicotine use disorder diagnoses was used to serve as the proxy of smoking/tobacco use. Detailed information on the diagnostic codes for the conditions extracted in this study is provided in Supplemental Table S1.

Outcome measures

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COVID-19 reinfection was defined as a new COVID-19 diagnosis reported 45 or more days after the first infection. Reinfection analysis was completed based on the first reinfection; subsequent reinfections were not analyzed. Because a person could be infected by the virus multiple times, the reinfection analysis of the study focused on the reinfection incident after the first COVID-19 episode in the study period. The reinfection indicator was given a value of 1 for individuals re-infected by COVID-19; otherwise, a value of 0 was assigned to the reinfection indicator.

Severe COVID-19 outcomes were identified by Emergency Department (ED) visits, hospital admission, Intensive Care Unit (ICU) stay, and death within 30 days of reinfection. These outcome measures were captured as dichotomous variables, with "1" assigned if a target outcome occurred within 30 days of reinfection, and "0" assigned if a target variable did not occur in 30 days of reinfection.

Data analysis

Descriptive statistics were computed to summarize sample characteristics in relation to each outcome measure. Differences in continuous variables were compared using the t-test for parametric or equivalent tests for non-parametric analyses. Proportion differences in categorical variables were evaluated using the Chi-square test.

Multiple logistic regression modeling was used to assess the risk of reinfection and serious medical complications of COVID-19, including ED visit, hospitalization, ICU admission and death within 30 days of COVID-19 reinfection (binary dependent variables, Yes/No), controlled for demographics and comorbid conditions known to contribute to the COVID-19 severity risk. A subcategory analysis was also conducted by each SUD subtype to assess the impact of vaccination on the risk of reinfection and severe outcomes.

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The regression analysis was conducted using the Maximum Likelihood Estimation method, which provided regression coefficients, standard errors (SEs), Wald 95% confidence intervals (CIs) for the coefficients, and p-values for each of the model variables. The likelihood ratio test, the global test of parameters in the regression model, was assessed first; if the model's likelihood ratio test was significant ($p<0.05$), individual variables' coefficients and p values were then considered. The adjusted odds ratio (aOR) and 95% CI of each variable was also calculated to predict the risk of the outcome measure. The significance level was determined based on two-tailed p-value < 0.05. All statistical analyses were performed using PROC LOGISTIC procedure (Version 9.4 SAS Institute Inc., Carey, NC).

Patient and public involvement statement

Neither patients nor the public were involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Study population

A total of 2,682,433 adults met the study criteria between January 1, 2020 and July 31, 2022, including 872,446 (32.5%) with COVID-19 reinfection and 1,809,987 (67.5%) without reinfection. Of all people re-infected by COVID-19, about 18.7% (163,012) were admitted to ED, 5.2% (45,362) to hospital, 1.5% (12,782) to ICU, and 0.7% (5,858) died within 30 days of reinfection. Compared to those without reinfection, the reinfection group had a greater percentage of females and White individuals, was slightly younger, and had higher prevalence of chronic medical and mental health conditions, and smoking/tobacco dependency (Table 1). COVID-19 reinfection was more common in persons with SUD than those without SUD (45.6%

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vs. 32.2%, p<0.01). Reinfection prevalence was inversely proportional to the number of vaccination doses received for SUD and non-SUD persons.

<<Insert Table 1>>

Substance use disorder

Regression analysis showed increased risk of COVID-19 reinfection among individuals with SUD compared to those without SUD. The adjusted odds ratio (all significant to 95% CIs) of the reinfection rate was 1.29 for OUD, 1.28 for CUD, 1.26 for AUD, 1.18 for CAUD, 1.13 for STUD, and 1.22 for the other SUD type (see figure 1). Similarly, people with SUD diagnoses were more likely to be admitted to ED/hospital/ICU and die within 30 days of reinfection, though there was no significant association found between 30-day mortality and CUD. AUD was found to have the highest risk of hospitalization (aOR=1.77, 95% CI 1.66,1.89), ICU (aOR=1.86, 95% CI 1.67, 2.07), and 30-day mortality (aOR=1.76, 95% CI 1.46, 2.12), while STUD showed the highest risk of ED visits after reinfection (aOR=1.69, 95% CI 1.57, 1.83). Both OUD and STUD were consistently found in the top three highest risks of other severe outcome measures. The details of the regression models are provided in Supplemental Table S2.

Vaccination

Overall vaccination effect

Persons receiving COVID-19 vaccination generally showed a lower rate of COVID-19 reinfection and severe outcomes, though no significant association was found between vaccination and the 30-day mortality rate (see figure 1). Compared to unvaccinated individuals, people who received one COVID-19 vaccine dose were 11% less likely to be re-infected than those unvaccinated (aOR=0.89, 95% CI 0.79, 0.99). No significant difference was found in the reinfection rate between unvaccinated individuals and those receiving at least 2 doses. The

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analysis showed that individuals with 2 or more COVID-19 vaccinations had significantly lower 30-day admission rates to ED (aOR=0.72, 95% CI 0.64, 0.83), hospital (aOR=0.71, 95% CI 0.61, 0.83), ICU (aOR=0.50, 95% CI 0.37, 0.66), and 30-day mortality (aOR=0.50, 95% CI 0.31, 0.80), compared to those unvaccinated. There were no significant differences between these groups in ED visits, hospital admission, or ICU admission between unvaccinated individuals and those receiving only one dose.

Vaccination effect by SUD subtype

Mixed results were found in the vaccination effect on COVID-19 reinfection and severe outcomes by SUD subtype (Table 2). In the AUD and CAUD groups, lower reinfection rates were shown only among people receiving one dose (aOR=0.84, 95% CI 0.73-0.98 for AUD; aOR=0.76, 95% CI 0.59, 0.98 for CAUD) than individuals unvaccinated. Persons with CAD were 33% less likely to be re-infected when they received two vaccinations or more (aOR=0.67, 95% CI 0.50, 0.89). There was no association between vaccination and reinfection in the OUD, STUD, and other SUD groups.

<<Insert Table 2>>

The vaccination effect on ED, hospital, and ICU admissions also varied by SUD subtype. Table 2 shows that, in the AUD, OUD, STUD, CAUD, and other SUD groups, individuals with multiple vaccinations were found 25-76% less likely to utilize ED and ICU services after being re-infected by COVID-19, compared to the unvaccinated. Moreover, in the AUD and other SUD groups, people receiving two or more doses were found 28-36% less likely to require hospitalization after COVID-19 reinfection than the unvaccinated. In general, there was no significant difference in ED, ICU and hospital admissions between unvaccinated individuals and those receiving only one dose.

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Lastly, compared to the unvaccinated, two or more vaccine doses showed decreased risk of 30-day mortality among individuals with AUD (aOR=0.53, 95% CI 0.30-0.93) and the other SUD types (aOR=0.39, 95% CI 0.17-0.89). People with STUD and at least one vaccine dose were also found 40% less likely to die within 30 days of reinfection (aOR=0.60, 65% CI 0.45-0.80).

DISCUSSION

Substance use disorders and COVID-19 reinfection

The COVID-19 pandemic has presented persistent healthcare challenges, particularly among individuals with a history of substance use disorders. Literature shows that persons with SUD are at increased risk of contracting SARS-CoV-2, requiring hospitalization, and dying from the virus infection, due to compromised immune systems and comorbid conditions.[4,6,14] As the community spread of COVID-19 continues, individuals recovered from COVID-19 can be re-infected by the SARS-COV-2 virus and its variants. Despite potential protection from previous COVID-19 infections or vaccines, little is known about the frequency and severity of reinfections in this vulnerable population. The study utilized a nationwide EHR database to assess the risk for COVID-19 reinfection and severe outcome adults with SUD. The use of the nationwide database allowed researchers to capture the longitudinal clinical events of the large patient population, to generate important insights into the frequency and severity of COVID-19 reinfection among individuals with SUD at the population level.

The study reveals that people with SUD are more likely to be re-infected by COVID-19, suggesting that persons with SUD continue to experience greater risk of reinfection after

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recovering from previous COVID-19 illness. The study further shows that persons with one or more mental health conditions are more likely to contract COVID-19 again. Higher reinfection risk may stem from the same causative factors of higher initial infection risk among SUD patients with co-existing mental and behavioral problems,[23,24] whose conditions may limit their ability to adopt critical safety and preventive measures about COVID-19.[25,26] Individuals with SUD are also likely to experience poverty and other socioeconomic disadvantages.[27] They tend to live in large households without sufficient self-isolation space or work in jobs unable to provide them remote options, which put them at greater risk of re-infection by the virus.

Severity of COVID-19 reinfection

People with SUD have also been shown more likely to suffer severe complications from COVID-19 infection.[4] Our study also found that adults with SUD were at increased risk of experiencing severe illness after becoming re-infected by COVID-19, compared to those without SUD. The relatively high rate of severe outcomes could be contributed to their existing heart, lungs, and immune problems potentially caused by drug abuse. The population with SUD is also known to have poor health insurance coverage and stigma concern.[28] Those barriers can pose challenges to people with SUD seeking treatment for COVID-19 in time, leading to delay in care and worsen outcomes.

Moreover, our analysis found that the risk of severe COVID-19 outcomes varied by the subtype of SUD. Opioid, stimulant, and alcohol use disorders were consistently shown a greater likelihood to require ED visits, hospitalization, and ICD admissions, as well as die within 30 days of reinfection. COVID-19 further intensified challenges and stress on already limited

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healthcare resources and workforce for caring individuals in the midst of the alcohol, opioid, and stimulant overdose crisis.

COVID-19 Vaccination, reinfection, and severity

Despite advancement in vaccines and treatments for COVID-19 in the past two years, many concerns remain about reinfection and waning immunity against the SARS-CoV-2 virus and its variants, especially among people with SUD. While one vaccination decreased reinfection in individuals with SUD, multiple vaccinations may not increase protection against reinfection. This may be due to a multitude of viral and host factors. Recent research suggests there may be immune system fatigue with emergence of new variants over time,[29] and with increased time since pandemic onset comes increased likelihood that individuals have received more than one vaccine. In addition, there may be perceived protection from having received multiple vaccinations which may result in decreased social distancing, masking, and other preventive measures, thus increasing infection risk.[30] Individuals highly recommended to receive boosters also likely have increased immunological comorbidities that put them at higher risk of COVID-19 reinfection. Some newer studies are showing that vaccine-induced protection against infection may be short-lived.[31]

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Recent research has also suggested that the protective effect of the COVID-19 vaccination against hospitalization and death from severe COVID-19 illness may gradually reduce after multiple vaccine doses;[32] however our study shows multiple vaccinations are associated with a reduction of severe outcomes in individuals with SUD, while one vaccination was not. This suggests ≥2 vaccinations may be required for an adequate immunological response in those with SUD. Public health strategies to mitigate reinfection risk in this population may benefit from counseling on the importance of multiple vaccinations.

Limitations

Most data on the impact of SUDs on COVID-19 outcomes came from a single hospital or regional health systems, which are costly, time and effort intensive, and often based on non-representative samples. The strengths of this study include leveraging real-world EHR data from a large nationwide research network which offers access to existing longitudinal, clinically-relevant, real-life data on all health system's patients during the COVID-19 pandemic period. The use of the big dataset could also enable evaluation of rare or underdiagnosed conditions on a larger scale. This study has limitations common to all research utilizing EHR data. First, the COVID-19 diagnosis or testing could have been completed at facilities outside of the participating research network and therefore be uncaptured in the TriNetX database. The index episode of a person's COVID-19 infection in the analysis was the first known record observed in the database, but it might not be the first ever COVID-19 infection record. Second, the overall percentage of patients with any COVID-19 vaccination of the analysis was lower than the CDC

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reported national average of vaccinated individuals in the United States, suggesting that those marked as unvaccinated may have received vaccination outside of the research network. Third, we were unable to determine whether a given SUD was active versus in remission at the time of the COVID-19 infection. Fourth, the EHR data did not contain information related to patients' socioeconomic contexts (e.g., insurance, education and income levels) which would have been included as confounders in the analysis. Fifth, we were unable to quantify the severity or stage of comorbid conditions in relation to COVID-19 infection, which may limit the generalizability of comorbid outcomes. (For example, well-controlled diabetes might be expected to carry greater health risks than uncontrolled diabetes.) Lastly, there may be unobserved or unknown confounders present that we did not account for in statistical analysis. These limitations are partially mitigated by the large sample size available through the TriNetX database, which enables data analysis across a wide range of medical, psychiatric, and sociodemographic factors. Future analyses using advanced data mining techniques and advanced analytical approaches, utilizing artificial intelligence or machine learning algorithms, might better elucidate currently unidentified yet important confounders.

CONCLUSIONS

The COVID-19 pandemic has disproportionately affected people with SUD, who are at greater risk of severe COVID-19. Despite the increased availability of vaccines and treatments for COVID-19 in recent years, concerns remain about reinfection and waning immunity against the SARS-CoV-2 virus and its variants, especially among people with SUD. Our study found that adults with SUD were at greater risk of being re-infected by COVID-19, regardless of the SUD subtype. They were more likely to be admitted to ED, hospital, and ICU within 30 days of

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reinfection. Significantly higher 30-day mortality was also observed among individuals with opioid, stimulant, or alcohol use disorders. Mixed findings were shown in vaccine effects among different SUD subtypes. People with two or more vaccine doses were generally found to have lower rates of severe illness and mortality, compared to those with one or no dose. However, the vaccination effect was undetermined in the population with cocaine use disorder. The persistent pandemic has raised challenges to our healthcare practice, and the need for better knowledge of containing ongoing and emerging outbreaks to reduce subsequent mortality and morbidity for individuals with SUD. The big data analytics developed in this study offers researchers a method to routinely assess COVID-19 impacts and vaccines effectiveness, to facilitate clinical decisions and inform public health policy.

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Contributors

All authors were involved in revisions, read and approved the final manuscript. WJT contributed to the planning and design of the work, literature review, data analysis, interpretation, and writing the manuscript. HK and RL contributed to literature review, data analysis, interpretation, and writing the manuscript.

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Competing interests

None declared.

Ethic approval

All the data queries were performed in the TriNetX online portal managed by the Penn State Clinic and Translational Science Institute. Because there was no protected health information data accessed in the analysis, this research was determined to be exempt from the Institutional Review Board oversight

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination of the study.

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Data availability statement

No data are available.

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Table 1. Characteristics of the study population by COVID-19 reinfection outcome

	Reinfection, n (%)		Individuals with COVID-19 Reinfection, n (%)							
			Emergency Department (30-day)		Hospitalization (30-day)		Intensive Care (30-day)		Death (30-day)	
Characteristics	Yes (N=872,446)	No (N=1,809,987)	Yes (N=163,012)	No (N=709,434)	Yes (N=45,362)	No (N=827,084)	Yes (N=12,782)	No (N=859,664)	Yes (N=5,858)	No (N=866,588)
Age at index, mean±SD†	43.8±16.5	45.3±17.1	45.4±18.2	43.4±16	53.7±19.1	43.2±16.1	56.2±17.6	43.6±16.4	67.5±15.5	43.6±16.4
Age										
18-39	404,011 (46.3)	764,126 (42.2)	72,806 (44.7)	331,205 (46.7)	12,693(28)	391,318 (47.3)	2,584 (20.2)	401,427 (46.7)	381 (6.5)	403,630 (46.6)
40-64	353,590 (40.5)	762,587 (42.1)	61,007 (37.4)	292,583 (41.2)	17,504 (38.6)	336,086 (40.6)	5,573 (43.6)	348,017 (40.5)	1,753 (29.9)	351,837 (40.6)
65+	114,845 (13.2)	283,274 (15.7)	29,199 (17.9)	85,646 (12.1)	15,165 (33.4)	99,680 (12.1)	4,625 (36.2)	110,220 (12.8)	3,724 (63.6)	111,121 (12.8)
Female	517,916 (59.4)	966,370 (53.4)	100,293 (61.5)	417,623 (58.9)	24,690 (54.4)	493,226 (59.6)	5,997 (46.9)	511,919 (59.5)	2,699 (46.1)	515,217 (59.5)
Hispanic	53,381 (6.1)	126,502 (7)	16,168 (9.9)	37,213 (5.2)	5,009 (11)	48,372 (5.8)	1,255 (9.8)	52,126 (6.1)	373 (6.4)	53,008 (6.1)
Race										
White	410,391 (47)	809,554 (44.7)	97,110 (59.6)	313,281 (44.2)	29,984 (66.1)	380,407 (46)	8,151 (63.8)	402,240 (46.8)	3,915 (66.8)	406,476 (46.9)
Black	115,406 (13.2)	240,255 (13.3)	43,787 (26.9)	71,619 (10.1)	10,389 (22.9)	105,017 (12.7)	3,091 (24.2)	112,315 (13.1)	1,227 (20.9)	114,179 (13.2)
Other	346,649 (39.7)	760,178 (42)	22,115 (13.6)	324,534 (45.7)	4,989 (11)	341,660 (41.3)	1,540 (12)	345,109 (40.1)	716 (12.2)	345,933 (39.9)
Hypertension	152,909 (17.5)	255,440 (14.1)	51,182 (31.4)	101,727 (14.3)	20,779 (45.8)	132,130 (16)	6,699 (52.4)	146,210 (17)	3,348 (57.2)	149,561 (17.3)
Diabetes	74,105 (8.5)	128,342 (7.1)	27,554 (16.9)	46,551 (6.6)	12,533 (27.6)	61,572 (7.4)	4,377 (34.2)	69,728 (8.1)	2,195 (37.5)	71,910 (8.3)
Obesity/overweight	112,102 (12.8)	166,507 (9.2)	35,402 (21.7)	76,700 (10.8)	11,726 (25.8)	100,376 (12.1)	3,421 (26.8)	108,681 (12.6)	1,469 (25.1)	110,633 (12.8)
Chronic kidney disease	32,936 (3.8)	44,435 (2.5)	12,979 (8)	19,957 (2.8)	7,625 (16.8)	25,311 (3.1)	2,736 (21.4)	30,200 (3.5)	1,778 (30.4)	31,158 (3.6)
Heart Failure	23,458 (2.7)	30,654 (1.7)	10,966 (6.7)	12,492 (1.8)	6,745 (14.9)	16,713 (2)	2,636 (20.6)	20,822 (2.4)	1,639 (28)	21,819 (2.5)
Stroke	14,214 (1.6)	19,947 (1.1)	5,562 (3.4)	8,652 (1.2)	2,766 (6.1)	11,448 (1.4)	958 (7.5)	13,256 (1.5)	598 (10.2)	13,616 (1.6)
Ischemic Heart Disease	43,909 (5)	65,166 (3.6)	17,935 (11)	25,974 (3.7)	9,384 (20.7)	34,525 (4.2)	3,319 (26)	40,590 (4.7)	1,971 (33.6)	41,938 (4.8)
Asthma	69,883 (8)	90,818 (5)	24,551 (15.1)	45,332 (6.4)	6,512 (14.4)	63,371 (7.7)	1,895 (14.8)	67,988 (7.9)	636 (10.9)	69,247 (8)
COPD	22,857 (2.6)	31,103 (1.7)	10,541 (6.5)	12,316 (1.7)	5,484 (12.1)	17,373 (2.1)	2,061 (16.1)	20,796 (2.4)	1,148 (19.6)	21,709 (2.5)
Depression	95,776 (11)	117,360 (6.5)	33,688 (20.7)	62,088 (8.8)	11,025 (24.3)	84,751 (10.2)	3,133 (24.5)	92,643 (10.8)	1,300 (22.2)	94,476 (10.9)
Bipolar	13,976 (1.6)	15,537 (0.9)	7,096 (4.4)	6,880 (1)	2,457 (5.4)	11,519 (1.4)	672 (5.3)	13,304 (1.5)	217 (3.7)	13,759 (1.6)
Anxiety	121,345 (13.9)	154,624 (8.5)	37,970 (23.3)	83,375 (11.8)	11,359 (25)	109,986 (13.3)	3,146 (24.6)	118,199 (13.7)	1,179 (20.1)	120,166 (13.9)
Vaccine dose										
None	818,515 (93.8)	1,719,387 (95)	151,116 (92.7)	667,399 (94.1)	41,355 (91.2)	777,160 (94)	11,784 (92.2)	806,731 (93.8)	5,582 (95.3)	812,933 (93.8)

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One	12,079 (1.4)	22,997 (1.3)	2,805 (1.7)	9,274 (1.3)	922 (2)	11,157 (1.3)	240 (1.9)	11,839 (1.4)	63 (1.1)	12,016 (1.4)
Two or more	41,852 (4.8)	67,603 (3.7)	9,091 (5.6)	32,761 (4.6)	3,085 (6.8)	38,767 (4.7)	758 (5.9)	41,094 (4.9)	213 (3.6)	41,639 (4.8)
Smoking	59,674 (6.8)	89,652 (5)	26,629 (16.3)	33,045 (4.7)	8,580 (18.9)	51,094 (6.2)	2,842 (22.2)	56,832 (6.8)	898 (15.3)	58,776 (6.8)
Substance use disorder										
Alcohol	15,801 (1.8)	18,422 (1)	7,986 (4.9)	7,815 (1.1)	3,373 (7.4)	12,428 (1.5)	1,200 (9.4)	14,601 (1.7)	392 (6.7)	15,409 (1.8)
Opioid	7,642 (0.9)	7,462 (0.4)	4,461 (2.7)	3,181 (0.4)	1,844 (4.1)	5,798 (0.7)	587 (4.6)	7,055 (0.8)	186 (3.2)	7,456 (0.9)
Cocaine	4,117 (0.5)	3,367 (0.2)	2,738 (1.7)	1,379 (0.2)	1,161 (2.6)	2,956 (0.4)	414 (3.2)	3,703 (0.4)	96 (1.6)	4,021 (0.5)
Stimulant	3,922 (0.4)	3,921 (0.2)	2,593 (1.6)	1,329 (0.2)	1,094 (2.4)	2,828 (0.3)	351 (2.7)	3,571 (0.4)	84 (1.4)	3,838 (0.4)
Cannabis	6,464 (0.7)	6,683 (0.4)	3,879 (2.4)	2,585 (0.4)	1,477 (3.3)	4,987 (0.6)	461 (3.6)	6,003 (0.7)	107 (1.8)	6,357 (0.7)
Other	13,533 (1.6)	13,848 (0.8)	7,256 (4.5)	6,277 (0.9)	2,651 (5.8)	10,882 (1.3)	897 (7)	12,636 (1.5)	276 (4.7)	13,257 (1.5)

†SD: standard deviation

All the differences were statistically significant at the 0.05 level

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Table 2. Effect of vaccine dose on COVID-19 reinfection and outcomes

SUD Subtype/ Vaccine Dose (ref: none)	Reinfection, aOR (95%CI)	Individuals with COVID-19 Reinfection: Outcomes within 30 days of reinfection			
		Emergency Department, aOR (95%CI)	Hospitalization, aOR (95%CI)	Intensive Care, aOR (95%CI)	Death, aOR (95%CI)
Alcohol					
1	0.84 (0.73,0.98)	0.92 (0.73,1.16)	0.99 (0.76,1.31)	0.75 (0.48,1.18)	1.09 (0.57,2.1)
2+	1.02 (0.93,1.13)	0.68 (0.58,0.78)	0.64 (0.52,0.78)	0.49 (0.34,0.7)	0.53 (0.3,0.93)
Opioid					
1	0.90 (0.72,1.12)	0.96 (0.7,1.32)	1.28 (0.9,1.81)	0.70 (0.37,1.31)	0.39 (0.1,1.61)
2+	1.06 (0.89,1.25)	0.64 (0.5,0.81)	0.77 (0.57,1.03)	0.50 (0.29,0.87)	0.49 (0.2,1.22)
Cocaine					
1	0.88 (0.64,1.22)	1.44 (0.88,2.37)	0.89 (0.54,1.46)	0.60 (0.26,1.41)	0.22 (0.03,1.58)†
2+	0.67 (0.50,0.89)	0.75 (0.48,1.15)	1.32 (0.84,2.06)	0.43 (0.17,1.07)	
Stimulant					
1	0.84 (0.61,1.16)	1.02 (0.62,1.67)	1.57 (0.97,2.55)	0.84 (0.37,1.9)	0.60 (0.45,0.80)†
2+	0.85 (0.66,1.10)	0.46 (0.32,0.67)	0.74 (0.48,1.14)	0.24 (0.09,0.69)	
Cannabis					
1	0.76 (0.59,0.98)	0.95 (0.63,1.41)	1.04 (0.66,1.64)	0.26 (0.08,0.85)	0.25 (0.06,1.02)†
2+	1.21 (1.01,1.46)	0.67 (0.52,0.86)	0.9 (0.66,1.24)	0.26 (0.11,0.61)	
Other					
1	0.95 (0.80,1.13)	0.99 (0.77,1.29)	0.91 (0.66,1.26)	0.74 (0.43,1.26)	0.82 (0.33,2.04)
2+	1.02 (0.90,1.16)	0.75 (0.62,0.89)	0.78 (0.61,0.99)	0.35 (0.21,0.59)	0.39 (0.17,0.89)

aOR: Adjusted odds ratio; 95%CI: 95% conference intervals

† Individuals with 1 and 2+ doses were combined into one category to ensure sufficient testing power

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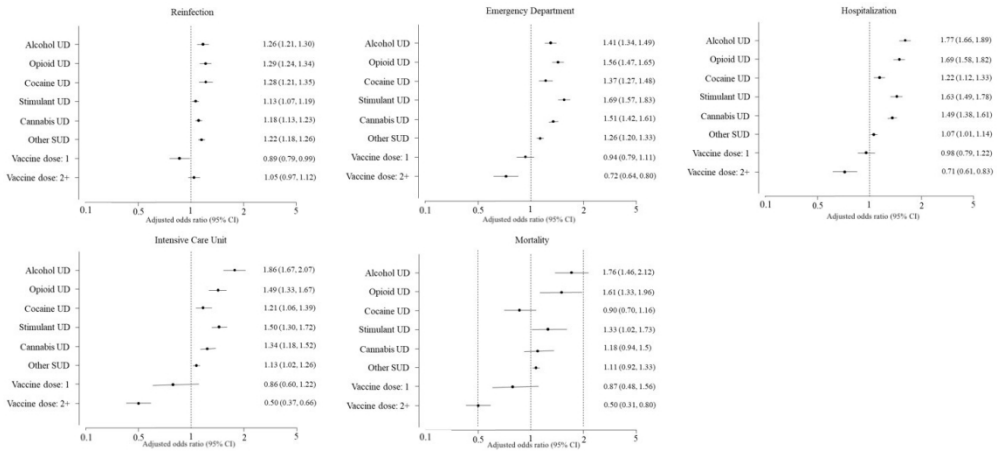

Fig 1. Risk of COVID-19 reinfection and severe outcomes by SUD subtype and vaccination

123x55mm (300 x 300 DPI)

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Appendix

Table S.1. Description of coding systems and codes

Coding System	Code	Description
COVID-19 diagnoses and lab tests		
ICD-10	U07.1, U07.2	COVID-19 (WHO)
ICD-10	B97.29	Other coronavirus as the cause of diseases classified elsewhere
ICD-10	B34.2	Coronavirus infection, unspecified
ICD-10	J12.81	Pneumonia due to SARS-associated coronavirus
LOINC	94505-5,94506-3,94558-4, 94562-6, 94762-2,94769-7,95209-3	SARS-CoV-2 (COVID19) [presence] in serum or plasma by immunoassay
COVID-19 vaccination		
CPT-4	91300,0001A,0002A,0003A,0004A, 91305,0051A,0052A,0053A,0054A 91307,0071A,0072A,0073A,0074A 91308,0081A,0082A,0083A,0084A	Pfizer-BioNTech
CPT-4	91301,0011A,0012A,0013A,91306, 0064A,91311,0111A,0112A,0113A, 91309,0091A,0092A,0093A,0094A	Moderna
CPT-4	91302,0021A,0022A	AstraZeneca
CPT-4	91303,0031A,0034A	Janssen
CPT-4	91304,0041A,0042A	Novavax
CPT-4	91310,0104A	Sanofi Pasteur
Baseline characteristics		
ICD-10	I10	Essential hypertension
ICD-10	E10-E11	Diabetes (type I and II)
ICD-10	E66	Overweight, obesity
ICD-10	N18	Chronic kidney diseases
ICD-10	I50	Heart failure
ICD-10	I63	Stroke
ICD-10	I20-I25	Ischemic heart disease
ICD-10	J45	Asthma
ICD-10	J44	Chronic obstructive pulmonary disease
ICD-10	F33	Depression
ICD-10	F41	Anxiety
ICD-10	F31	Bipolar disorder
ICD-10	F17	Tobacco/nicotine dependence

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Substance use disorder		
ICD-10	F10.1, F10.2	Alcohol use disorder
ICD-10	F11.1, F11.2	Opioid use disorder
ICD-10	F12.1, F12.2	Cannabis use disorder
ICD-10	F14.1, F14.2	Cocaine use disorder
ICD-10	F15.1, F15.2	Stimulant use disorder
ICD-10	F13.1, F13.2, F16.1, F16.2, F18.1, F18.2, F19.1, F19.2	Other substance use disorder

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Table S2. Risk of COVID-19 reinfection and outcomes

		Individuals with COVID-19 Reinfection: Outcomes within 30 days of reinfection			
Factors	Reinfection, aOR (95% CI)	Emergency Department, aOR (95% CI)	Hospitalization, aOR (95% CI)	Intensive Care, aOR (95% CI)	Death, aOR (95% CI)
Intercept					
Female	1.11** (1.08,1.15)	0.96 (0.91,1.01)	0.85** (0.8,0.91)	0.80** (0.72,0.89)	0.99 (0.83,1.19)
Age (ref: 18-39 yrs)					
40-64 yrs	0.97 (0.94,1.01)	0.91** (0.86,0.97)	1.20** (1.12,1.30)	1.36** (1.20,1.54)	2.41** (1.87,3.13)
65+ yrs	0.88** (0.83,0.94)	0.89* (0.82,0.98)	1.43** (1.27,1.60)	1.38** (1.16,1.66)	4.49** (3.31,6.09)
Hispanic	1.46** (1.38,1.56)	1.07 (0.98,1.17)	1.21** (1.08,1.36)	0.99 (0.83,1.21)	0.65* (0.45,0.95)
Race (ref: White)					
Black	1.09** (1.05,1.14)	1.52** (1.43,1.61)	1.11** (1.03,1.20)	1.08 (0.95,1.22)	0.86 (0.69,1.06)
Other	0.71** (0.67,0.74)	1.42** (1.31,1.54)	0.93 (0.84,1.04)	1.37** (1.17,1.61)	1.45** (1.12,1.89)
Hypertension	1.10** (1.06,1.15)	1.14** (1.07,1.20)	1.34** (1.24,1.45)	1.44** (1.27,1.62)	0.97 (0.78,1.20)
Diabetes	1.07** (1.02,1.12)	1.17** (1.09,1.24)	1.30** (1.20,1.41)	1.64** (1.46,1.85)	1.30** (1.07,1.58)
Obesity/overweight	1.10** (1.05,1.14)	0.94* (0.89,0.99)	0.87** (0.81,0.94)	0.76** (0.68,0.86)	0.85 (0.70,1.03)
Chronic kidney disease	1.11** (1.05,1.17)	0.93 (0.86,1.01)	1.29** (1.17,1.42)	1.34** (1.17,1.54)	2.15** (1.72,2.58)
Heart failure	1.18 (1.10,1.26)	1.25** (1.14,1.38)	1.39** (1.25,1.54)	1.53** (1.32,1.77)	1.84** (1.48,2.29)
Stroke	0.99 (0.93,1.06)	0.86** (0.78,0.94)	0.98 (0.87,1.10)	1.01 (0.85,1.19)	1.47** (1.13,1.81)
Ischemic heart disease	1.02 (0.96,1.07)	1.27** (1.18,1.38)	1.20** (1.10,1.31)	1.18* (1.03,1.35)	1.28* (1.04,1.58)
Asthma	1.28** (1.23,1.34)	1.20** (1.13,1.27)	0.98 (0.90,1.06)	0.99 (0.88,1.12)	0.86 (0.69,1.07)
COPD	1.20** (1.13,1.27)	1.16** (1.06,1.26)	1.45** (1.32,1.59)	1.63** (1.43,1.87)	1.58** (1.29,1.94)
Depression	1.20 (1.16,1.24)	1.00 (0.95,1.05)	1.04 (0.97,1.12)	0.93 (0.83,1.03)	0.93 (0.78,1.12)
Anxiety	1.11** (1.07,1.15)	0.95 (0.90,1.00)	1.06 (0.99,1.13)	1.10 (0.98,1.23)	0.88 (0.73,1.06)
Bipolar	1.13** (1.07,1.18)	1.46** (1.36,1.56)	1.25** (1.15,1.36)	0.93 (0.80,1.07)	0.95 (0.73,1.23)
Smoking	0.96* (0.93,0.99)	1.42 (1.35,1.49)	1.29** (1.21,1.38)	1.29** (1.16,1.44)	1.15 (0.96,1.37)
Vaccine dose (ref: none)					
1	0.89* (0.79,0.99)	0.94 (0.79,1.11)	0.98 (0.79,1.22)	0.86 (0.60,1.22)	0.87 (0.48,1.56)
2+	1.05 (0.97,1.12)	0.72** (0.64,0.80)	0.71** (0.61,0.83)	0.50** (0.37,0.66)	0.50** (0.31,0.80)

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Alcohol use disorder	1.26** (1.21,1.30)	1.41** (1.34,1.49)	1.77** (1.66,1.89)	1.86** (1.67,2.07)	1.76** (1.46,2.12)
Opioid use disorder	1.29** (1.24,1.34)	1.56** (1.47,1.65)	1.69** (1.58,1.82)	1.49** (1.33,1.67)	1.62** (1.33,1.96)
Cocaine use disorder	1.28** (1.21,1.35)	1.37** (1.27,1.48)	1.22** (1.12,1.33)	1.21** (1.06,1.39)	0.90 (0.70,1.16)
Stimulant use disorder	1.13** (1.07,1.19)	1.69** (1.57,1.83)	1.63** (1.49,1.78)	1.50** (1.30,1.72)	1.33* (1.02,1.73)
Cannabis use disorder	1.18** (1.13,1.23)	1.51** (1.42,1.61)	1.49** (1.38,1.61)	1.34** (1.18,1.52)	1.08 (0.94,1.50)
Other use disorder	1.22** (1.18,1.26)	1.26** (1.20,1.33)	1.07 (1.00,1.14)	1.13* (1.02,1.26)	1.11 (0.92,1.33)

*p<0.05; **p<0.01

aOR: Adjusted odds ratio; 95% CI: 95% conference intervals

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The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title and abstract PP:1, 2 Geographic region: title and abstract Timeframe: abstract PP: 1, 2 Not applicable
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction PP: 5, 6

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Objectives	3	State specific objectives, including any pre-specified hypotheses			P: 6
Methods					
Study Design	4	Present key elements of study design early in the paper			PP: 6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			P: 7
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published	Methods, Cohort Description PP: 7-8 P: 7

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		Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	PP: 7-8
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of			PP: 7-8

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		assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias			P: 9 (Regression analysis controlled for baseline characters to address bias from observable covariate differences)
Study size	10	Explain how the study size was arrived at			P: 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			PP: 9-10 Appendix
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed			PP: 9-10

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		Case-control study - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	P: 6 P: 7
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases.	N/A

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				The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Cohort Description PP: 10-11, and Table 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for			PP: 10-11

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		each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			Outcome indicators PP: 10-11, Table 1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included			Results PP: 11-13 Figure 1 Table 2

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		(b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			N/A
Discussion					
Key results	18	Summarise key results with reference to study objectives			P: 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Strength and Limitations of this study P: 3 Limitation PP: 16-17

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Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			PP: 13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results			P: 16
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			P: 16
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	P: 18

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Assessing the risk of COVID-19 reinfection and severe outcomes among individuals with substance disorders: A retrospective study using real-world electronic health records

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Title

Assessing the risk of COVID-19 reinfection and severe outcomes among individuals with substance disorders: A retrospective study using real-world electronic health records

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Abstract

Objective

Despite advancement in vaccines and treatments for COVID-19 over the past two years, many concerns remain about reinfection and waning immunity against COVID-19 and its variants, especially among people with substance use disorder (SUD). The study assessed the risk of COVID-19 reinfection and severe illness among adults with SUD and their vaccination status to inform management in this vulnerable population as the pandemic continues.

Design

Retrospective cohort study

Setting

Nationwide electronic health records (TriNetX database) in the United States among adults with COVID-19 infection from January 2020 to June 2022

Participants

Adults (age≥18 years) who were infected by COVID-19, excluding those who had cancer or lived in nursing homes or palliative care facilities

Outcome Measures

COVID-19 reinfection was defined as a new diagnosis after 45 days of the initial infection. Logistic regression was applied to assess the odds ratio of COVID-19 reinfection and severe outcomes within 30 day of reinfection for adults with alcohol (AUD), opioid (OUD), cocaine (CUD), stimulant (STUD), cannabis (CAUD), and other use disorders, controlled for demographic and comorbid conditions.

Results

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The SUD cohort was 13-29% more likely to be re-infected by COVID-19, and had significantly higher 30-day mortality. Adults with AUD, STUD and OUD were at greater risks (AOR=1.69-1.86) of emergency department, hospital, and intensive care admissions after 30 days of reinfection. Individuals with SUD and multiple vaccines doses were associated with decreased risks of worse COVID-19 outcomes. Lower COVID-19 reinfection rates (AOR=0.67-0.84) were only found among individuals with AUD, CUD, or CAUD who had COVID-19 vaccination.

Conclusions

Individuals with SUD had greater risks of COVID-19 reinfection and poor outcomes, especially those with OUD, STUD, and AUD. Multiple vaccinations are recommended to reduce severe illness after COVID-19 reinfection in the SUD population.

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Strengths and limitations of this study

- This study utilized large-scale electronic health record-based data which provides a wide range of medical, psychiatric, and demographic factors to assess the risk of COVID-19 reinfection and severe complications among adults with substance use disorders.
- Our findings can help elucidate substance use disorder subtypes that are at the greatest risk of COVID-19 reinfection and poor outcomes, and thus, could inform public health effort to promote the importance of multiple vaccinations in the subtypes.
- We could not control for data completed at facilities outside of the participating research network and therefore there may be uncaptured information with use of the electronic health records, potentially limiting the generalizability of the results.
- Further limitations of this study consist of inability to control for socioeconomic contexts and inability to quantify severity or stage of comorbid conditions, which may require future research to address the impact of these factors on COVID-19 reinfection.

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Introduction

The COVID-19 pandemic has led to unprecedented public health challenges in the United States, especially for individuals experiencing drug abuse and addiction problems.[1,2] Lacking access to screening and treatments during the pandemic has resulted in care disruption for people with substance use disorder (SUD) and those in recovery. Individuals with SUD are found to have increased risk of COVID-19 infection and severe complications[2] due to compromised immune systems,[3] respiratory-related functions,[4] and cardiovascular conditions.[5] With the continuation of the COVID-19 pandemic, persons previously recovered from COVID-19 can be re-infected by the disease. Despite advancement in vaccines and treatments for COVID-19 over the past two years, many concerns remain about reinfection and waning immunity against the SARS-CoV-2 virus and its variants, especially among people with SUD.

The risk of COVID-19 infection and outcomes was also found to vary by the subtype of SUD.[4,6,7] The highest risk of infection was found among individuals with opioid use disorder (OUD), followed by cocaine use disorder (CUD) and alcohol use disorder (AUD).[4] People with AUD or OUD tended to have severe complications likely to require hospital admission and intensive care compared to those with cannabis use disorder (CAUD) and CUD. Specific pharmacological effects from different drugs might contribute to this outcome variation among SUD subtypes.

The efficacy of COVID-19 vaccination also varies among individuals with multiple chronic conditions and weak immune systems.[8] Compared to vaccinated persons without SUD, vaccinated persons with SUD still experience significantly greater COVID-19 infection risk,[9] potentially due to higher prevalence of comorbid conditions and negative socioeconomic statuses in the SUD population. As more people with SUD receive COVID-19 vaccination, additional

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research is required to examine the vaccine effect on preventing COVID-19 reinfection and poor outcomes.

Furthermore, individuals with SUD are more likely to have coexistent mental health conditions, including depression, anxiety, and bipolar disorder,[10–13] which can be risk factors for severe COVID-19 reinfection.[14,15] The SUD population has also been shown at increased risk of hypertension, obesity, diabetes, and cardiovascular conditions.[2] These conditions can negatively influence immune and respiratory systems, increasing vulnerability to the SARS-CoV-2 virus infection[16] and its complications.[17,18] These co-occurring mental and physical conditions may also lead to a higher reinfection risk.

The large scale of the pandemic has raised the need for better knowledge of containing ongoing and emerging outbreaks to reduce subsequent mortality and morbidity for people with SUD. While prior research has found higher COVID-19 infection rates among persons with SUD, little is known about how reinfection and outcomes vary by vaccination status and SUD subtype. The objective of this study is to assess the risk of COVID-19 reinfection and severe illness among adults with SUD to inform clinical treatment and public policy decisions pertaining to this unique population.

METHODS

Study design and data sources

This was a retrospective cohort study utilizing electronic health records (EHRs) of 57 healthcare organizations sourced from the TriNetX research network database (Cambridge, MA). TriNetX is a large health data network that contains de-identified EHRs (demographics, diagnoses, procedures, medications, and laboratory tests) of more than 80 million patients from

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participating healthcare organizations predominately from the U.S. Data in the TriNetX database has undergone extensive curation and mapping to common clinical entities and terminologies to ensure high usability as well as consistency with the Reporting of studies Conducted using Observational Routinely collected Data (RECORD) guidelines.[19] The study used deidentified TriNetX research datasets, and was determined to be exempt from the Institutional Review Board oversight by the Pennsylvania State University's Human Research Protection Program.

Cohort description

The study population consisted of adults (age≥18 years) who were diagnosed with COVID-19 between January 1, 2020 and April 30, 2022, based on the combination of one or more disease indicators, including ICD-10 diagnosis codes and positive laboratory test results (see supplemental table S1 for details).[20,21] The initial COVID-19 infection episode during the study assessment period was considered the "index" infection. Individuals whose index COVID-19 infection occurred prior to the age of 18 were excluded from the study. Health data for adults with a valid index infection continued to be collect through June 30, 2022, to capture additional COVID-19 reinfection. Individuals were excluded if they had cancer or lived in nursing homes or palliative care facilities prior to COVID infection.

Substance use disorders

This analysis focused on the relationship of COVID-19 reinfection with the following SUD subtypes: alcohol (AUD), opioid (OUD), cocaine (CUD), stimulant (STUD), cannabis (CAUD), and other (other-UD). The other-UD category included sedative use disorder, hallucinogen use disorder, inhalant use disorder, and other psychoactive use disorder. A person's SUD diagnosis must have predated the index COVID-19 infection to be identified with the condition. Each subtype measure included a binary variable (yes/no) indicating whether patients

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had the specific subtype of SUD. This study allowed for inclusion of individuals with multiple SUD subtypes, as is common in the clinical setting. Regression modeling was able to control for each subtype so that interpretation of the effect of each individual SUD subtype can be observed. The list of diagnosis codes for each SUD subtype is provided in online supplemental table S1.

COVID-19 Vaccination

COVID-19 vaccination was identified through the presence of COVID-19 vaccine codes specified by the Current Procedural Terminology (CPT) of the American Medical Association (see supplemental table S1). The total number of COVID-19 vaccine doses of individuals experiencing reinfection were computed based on the sum of vaccine doses received prior to the reinfection incident. The number of COVID-19 vaccinations of individuals without reinfection were estimated as the sum of vaccine doses received during the study period. To understand the effect of vaccine doses, this analysis categorized COVID-19 vaccine dosing to three dose levels: 0 (unvaccinated), 1 (one dose only), and 2+ (people receiving at least two doses).

Baseline demographics and comorbid characteristics

Patient demographics and health comorbidities were extracted at the time of the first COVID-19 infection. The available demographic data included sex (male/female), age group (18-39, 40-65, 65+), ethnicity (Hispanic/non-Hispanic) and race (White/Black/Other). Data on conditions known to be associated with the COVID-19 complications were also collected, including the diagnoses of medical conditions (obesity, diabetes, chronic kidney disease, cardiovascular disorders[17,20]) and mental health disorders (depression, anxiety, bipolar).[22] Because the current status of tobacco use/smoking was unavailable in the EHR data, the presence of the tobacco/nicotine use disorder diagnoses was used to serve as the proxy of

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smoking/tobacco use. Detailed information on the diagnostic codes for the conditions extracted in this study is provided in online supplemental table S1.

Outcome measures

COVID-19 reinfection was defined as a new COVID-19 diagnosis reported 45 or more days after the first infection. Reinfection analysis was completed based on the first reinfection; subsequent reinfections were not analyzed. Because a person could be infected by the virus multiple times, the reinfection analysis of the study focused on the reinfection incident after the first COVID-19 episode in the study period. The reinfection indicator was given a value of 1 for individuals re-infected by COVID-19; otherwise, a value of 0 was assigned to the reinfection indicator.

Severe COVID-19 outcomes were identified by Emergency Department (ED) visits, hospital admission, Intensive Care Unit (ICU) stay, and death within 30 days of reinfection. These outcome measures were captured as dichotomous variables, with "1" assigned if a target outcome occurred within 30 days of reinfection, and "0" assigned if a target variable did not occur in 30 days of reinfection.

Data analysis

Descriptive statistics were computed to summarize sample characteristics in relation to each outcome measure. Differences in continuous variables were compared using the t-test for parametric or equivalent tests for non-parametric analyses. Proportion differences in categorical variables were evaluated using the Chi-square test.

Multiple logistic regression modeling was used to assess the risk of reinfection and serious medical complications of COVID-19, including ED visit, hospitalization, ICU admission and death within 30 days of COVID-19 reinfection (binary dependent variables, Yes/No),

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controlled for demographics and both medical and mental health comorbidities known to contribute to the COVID-19 severity risk. A subcategory analysis was also conducted by each SUD subtype to assess the impact of vaccination on the risk of reinfection and severe outcomes.

The regression analysis was conducted using the Maximum Likelihood Estimation method, which provided regression coefficients, standard errors (SEs), Wald 95% confidence intervals (CIs) for the coefficients, and p-values for each of the model variables. The likelihood ratio test, the global test of parameters in the regression model, was assessed first; if the model's likelihood ratio test was significant ($p<0.05$), individual variables' coefficients and p values were then considered. The adjusted odds ratio (aOR) and 95% CI of each variable was also calculated to predict the risk of the outcome measure. The significance level was determined based on two-tailed p-value < 0.05. All statistical analyses were performed using PROC LOGISTIC procedure (Version 9.4 SAS Institute Inc., Carey, NC).

Patient and public involvement statement

Neither patients nor the public were involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Study population

A total of 2,682,433 adults met the study criteria between January 1, 2020 and July 31, 2022, including 872,446 (32.5%) with COVID-19 reinfection and 1,809,987 (67.5%) without reinfection. The time between the initial infection and reinfection for persons with SUD (mean=211 days, median=164 days) was shorter than the time for individuals without SUD (mean=229 days, median=187 days). Of all people re-infected by COVID-19, about 18.7%

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(163,012) were admitted to ED, 5.2% (45,362) to hospital, 1.5% (12,782) to ICU, and 0.7% (5,858) died within 30 days of reinfection. Compared to those without reinfection, the reinfection group had a greater percentage of females and White individuals, was slightly younger, and had higher prevalence of chronic medical and mental health conditions, and smoking/tobacco dependency. COVID-19 reinfection was more common in persons with SUD than those without SUD (45.6% vs. 32.2%, $p<0.01$). Reinfection prevalence was inversely proportional to the number of vaccination doses received for SUD and non-SUD persons. The details of the summary statistics are provided in online supplemental table S2.

Substance use disorder

Regression analysis controlled for medical and mental health comorbidities showed increased risk of COVID-19 reinfection among individuals with SUD compared to those without SUD. The adjusted odds ratio (all significant to 95% CIs) of the reinfection rate was 1.29 for OUD, 1.28 for CUD, 1.26 for AUD, 1.18 for CAUD, 1.13 for STUD, and 1.22 for the other SUD type (see figure 1). Similarly, people with SUD diagnoses were more likely to be admitted to ED/hospital/ICU and die within 30 days of reinfection, though there was no significant association found between 30-day mortality and CUD. AUD was found to have the highest risk of hospitalization (aOR=1.77, 95% CI 1.66,1.89), ICU (aOR=1.86, 95% CI 1.67, 2.07), and 30-day mortality (aOR=1.76, 95% CI 1.46, 2.12), while STUD showed the highest risk of ED visits after reinfection (aOR=1.69, 95% CI 1.57, 1.83). Both OUD and STUD were consistently found in the top three highest risks of other severe outcome measures. The details of the regression models are provided in online supplemental table S3.

Vaccination

Overall vaccination effect

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Persons receiving COVID-19 vaccination generally showed a lower rate of COVID-19 reinfection and severe outcomes, though no significant association was found between vaccination and the 30-day mortality rate (see figure 1). Compared to unvaccinated individuals, people who received one COVID-19 vaccine dose were 11% less likely to be re-infected than those unvaccinated (aOR=0.89, 95% CI 0.79, 0.99). No significant difference was found in the reinfection rate between unvaccinated individuals and those receiving at least 2 doses. The analysis showed that individuals with 2 or more COVID-19 vaccinations had significantly lower 30-day admission rates to ED (aOR=0.72, 95% CI 0.64, 0.83), hospital (aOR=0.71, 95% CI 0.61, 0.83), ICU (aOR=0.50, 95% CI 0.37, 0.66), and 30-day mortality (aOR=0.50, 95% CI 0.31, 0.80), compared to those unvaccinated. There were no significant differences between these groups in ED visits, hospital admission, or ICU admission between unvaccinated individuals and those receiving only one dose.

Vaccination effect by SUD subtype

Mixed results were found in the vaccination effect on COVID-19 reinfection and severe outcomes by SUD subtype (see table 1). In the AUD and CAUD groups, lower reinfection rates were shown only among people receiving one dose (aOR=0.84, 95% CI 0.73-0.98 for AUD; aOR=0.76, 95% CI 0.59, 0.98 for CAUD) than individuals unvaccinated. Persons with CUD were 33% less likely to be re-infected when they received two vaccinations or more (aOR=0.67, 95% CI 0.50, 0.89). There was no association between vaccination and reinfection in the OUD, STUD, and other SUD groups.

<<Insert Table 1>>

The vaccination effect on ED, hospital, and ICU admissions also varied by SUD subtype. Table 1 shows that, in the AUD, OUD, STUD, CAUD, and other SUD groups, individuals with

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multiple vaccinations were found 25-76% less likely to utilize ED and ICU services after being re-infected by COVID-19, compared to the unvaccinated. Moreover, in the AUD and other SUD groups, people receiving two or more doses were found 28-36% less likely to require hospitalization after COVID-19 reinfection than the unvaccinated. In general, there was no significant difference in ED, ICU and hospital admissions between unvaccinated individuals and those receiving only one dose.

Lastly, compared to the unvaccinated, two or more vaccine doses showed decreased risk of 30-day mortality among individuals with AUD (aOR=0.53, 95% CI 0.30-0.93) and the other SUD types (aOR=0.39, 95% CI 0.17-0.89). People with STUD and at least one vaccine dose were also found 40% less likely to die within 30 days of reinfection (aOR=0.60, 65% CI 0.45-0.80).

DISCUSSION

Substance use disorders and COVID-19 reinfection

The COVID-19 pandemic has presented persistent healthcare challenges, particularly among individuals with a history of substance use disorders. Literature shows that persons with SUD are at increased risk of contracting SARS-CoV-2, requiring hospitalization, and dying from the virus infection, due to compromised immune systems and comorbid conditions.[4,6,14] As the community spread of COVID-19 continues, individuals recovered from COVID-19 can be re-infected by the SARS-COV-2 virus and its variants. Despite potential protection from previous COVID-19 infections or vaccines, little is known about the frequency and severity of reinfections in this vulnerable population. The study utilized a nationwide EHR database to assess the risk for COVID-19 reinfection and severe outcome adults with SUD. The use of the

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nationwide database allowed researchers to capture the longitudinal clinical events of the large patient population, to generate important insights into the frequency and severity of COVID-19 reinfection among individuals with SUD at the population level.

Our study shows that, in general, persons with medical/mental health comorbidities are more likely than those without medical/mental comorbidities to be re-infected by COVID-19, regardless of the presence of SUD diagnoses. Controlled for medical and mental health comorbidities, the study reveals that people with SUD are more likely to be re-infected by COVID-19, suggesting that persons with SUD continue to experience greater risk of reinfection after recovering from previous COVID-19 illness. Higher reinfection risk may stem from the same causative factors of higher initial infection risk among SUD patients with co-existing mental and behavioral problems,[23,24] whose conditions may limit their ability to adopt critical safety and preventive measures about COVID-19.[25,26] Individuals with SUD are also likely to experience poverty and other socioeconomic disadvantages.[27] They tend to live in large households without sufficient self-isolation space or work in jobs unable to provide them remote options, which put them at greater risk of re-infection by the virus.

Severity of COVID-19 reinfection

People with SUD have also been shown more likely to suffer severe complications from COVID-19 infection.[4] Our study also found that adults with SUD were at increased risk of experiencing severe illness after becoming re-infected by COVID-19, compared to those without SUD. The relatively high rate of severe outcomes could be contributed to their existing cardiac, respiratory, and immune problems potentially caused by drug abuse. The population with SUD is also known to have poor health insurance coverage and stigma concern.[28] These barriers can

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pose challenges to people with SUD seeking treatment for COVID-19 in time, leading to delay in care and worsened outcomes.

Moreover, our analysis found that the risk of severe COVID-19 outcomes varied by the subtype of SUD. Opioid, stimulant, and alcohol use disorders were consistently shown a greater likelihood to require ED visits, hospitalization, and ICU admissions, as well as die within 30 days of reinfection. COVID-19 further intensified challenges and stress on already limited healthcare resources and workforce required to care for individuals in the midst of the alcohol, opioid, and stimulant overdose crisis.

COVID-19 Vaccination, reinfection, and severity

Despite advancement in vaccines and treatments for COVID-19 in the past two years, many concerns remain about reinfection and waning immunity against the SARS-CoV-2 virus and its variants, especially among people with SUD. While one vaccination decreased reinfection in individuals with SUD, multiple vaccinations may not increase protection against reinfection. This may be due to a multitude of viral and host factors. Recent research suggests there may be immune system fatigue with emergence of new variants over time,[29] and with increased time since pandemic onset comes increased likelihood that individuals have received more than one vaccine. In addition, there may be perceived protection from having received multiple vaccinations which may result in decreased social distancing, masking, and other preventive measures, thus increasing infection risk.[30] Individuals highly recommended to receive boosters

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also likely have increased immunological comorbidities that put them at higher risk of COVID-19 reinfection. Some newer studies are showing that vaccine-induced protection against infection may be short-lived.[31]

Recent research has also suggested that the protective effect of the COVID-19 vaccination against hospitalization and death from severe COVID-19 illness may gradually reduce after multiple vaccine doses;[32] however our study shows multiple vaccinations are associated with a reduction of severe outcomes in individuals with SUD, while one vaccination was not. This suggests ≥2 vaccinations may be required for an adequate immunological response in those with SUD. Public health strategies to mitigate reinfection risk in this population may benefit from counseling on the importance of multiple vaccinations.

Limitations

Most data on the impact of SUDs on COVID-19 outcomes came from a single hospital or regional health systems, which are costly, time and effort intensive, and often based on non-representative samples. The strengths of this study include leveraging real-world EHR data from a large nationwide research network which offers access to existing longitudinal, clinically-relevant, real-life data on all health system's patients during the COVID-19 pandemic period. The use of the big dataset could also enable evaluation of rare or underdiagnosed conditions on a larger scale. This study has limitations common to all research utilizing EHR data. First, the COVID-19 diagnosis or testing could have been completed at facilities outside of the

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participating research network and therefore be uncaptured in the TriNetX database. The index episode of a person's COVID-19 infection in the analysis was the first known record observed in the database, but it might not be the first ever COVID-19 infection record. Second, the overall percentage of patients with any COVID-19 vaccination of the analysis was lower than the CDC reported national average of vaccinated individuals in the United States, suggesting that those marked as unvaccinated may have received vaccination outside of the research network. Third, we were unable to determine whether a given SUD was active versus in remission at the time of the COVID-19 infection. Fourth, our study sample showed that, in the population with SUD, 66% were diagnosed with one SUD type, 19% diagnosed with two SUD types, and 15% diagnosed with three or more SUD types. While the study applied multiple regression modeling to assess the main effect of each SUD type, the regression analysis did not include interaction terms to assess the effect of polysubstance use disorders. We were unable to directly estimate the risk of reinfection for people with multiple SUD types. Nonetheless, all SUD types had an odds ratio greater than one, suggesting that persons with multiple SUD types would be more likely to be re-infected or experience poor outcomes after reinfection. Fifth, the EHR data did not contain information related to patients' socioeconomic contexts (e.g., insurance, education and income levels) which would have been included as confounders in the analysis. Sixth, we were unable to quantify the severity or stage of comorbid conditions in relation to COVID-19 infection, which may limit the generalizability of comorbid outcomes. (For example, well-controlled diabetes might be expected to carry greater health risks than uncontrolled diabetes.) Lastly, there may be unobserved or unknown confounders present that we did not account for in statistical analysis. These limitations are partially mitigated by the large sample size available through the TriNetX database, which enables data analysis across a wide range of medical, psychiatric, and

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sociodemographic factors. Future analyses using advanced data mining techniques and advanced analytical approaches, utilizing artificial intelligence or machine learning algorithms, might better elucidate currently unidentified yet important confounders.

CONCLUSIONS

The COVID-19 pandemic has disproportionately affected people with SUD, who are at greater risk of severe COVID-19. Despite the increased availability of vaccines and treatments for COVID-19 in recent years, concerns remain about reinfection and waning immunity against the SARS-CoV-2 virus and its variants, especially among people with SUD. Our study found that adults with SUD were at greater risk of being re-infected by COVID-19, regardless of the SUD subtype. They were more likely to be admitted to the ED, hospital, and ICU within 30 days of reinfection. Significantly higher 30-day mortality was also observed among individuals with opioid, stimulant, or alcohol use disorders. Mixed findings were shown in vaccine effects among different SUD subtypes. People with two or more vaccine doses were generally found to have lower rates of severe illness and mortality, compared to those with one or no dose. However, the vaccination effect was undetermined in the population with cocaine use disorder. The persistent pandemic has raised challenges to our healthcare practice, and there remains a need for better knowledge of containing ongoing and emerging outbreaks to reduce subsequent mortality and morbidity for individuals with SUD. The big data analytics developed in this study offers researchers a method to routinely assess COVID-19 impacts and vaccines effectiveness, to facilitate clinical decisions and inform public health policy.

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Contributors

All authors were involved in revisions, read and approved the final manuscript. WJT contributed to the planning and design of the work, literature review, data analysis, interpretation, and writing the manuscript. HK and RL contributed to literature review, data analysis, interpretation, and writing the manuscript.

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Competing interests

None declared.

Ethic approval

All the data queries were performed in the TriNetX online portal managed by the Penn State Clinic and Translational Science Institute. Because there was no protected health information data accessed in the analysis, this research was determined to be exempt from the Institutional Review Board oversight by the Pennsylvania State University's Human Research Protection Program.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

No data are available.

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Table 1. Effect of vaccine dose on COVID-19 reinfection and outcomes

SUD Subtype/ Vaccine Dose (ref: none)	Reinfection, aOR (95%CI)	Individuals with COVID-19 Reinfection: Outcomes within 30 days of reinfection			
		Emergency Department, aOR (95%CI)	Hospitalization, aOR (95%CI)	Intensive Care, aOR (95%CI)	Death, aOR (95%CI)
Alcohol					
1	0.84 (0.73,0.98)	0.92 (0.73,1.16)	0.99 (0.76,1.31)	0.75 (0.48,1.18)	1.09 (0.57,2.1)
2+	1.02 (0.93,1.13)	0.68 (0.58,0.78)	0.64 (0.52,0.78)	0.49 (0.34,0.7)	0.53 (0.3,0.93)
Opioid					
1	0.90 (0.72,1.12)	0.96 (0.7,1.32)	1.28 (0.9,1.81)	0.70 (0.37,1.31)	0.39 (0.1,1.61)
2+	1.06 (0.89,1.25)	0.64 (0.5,0.81)	0.77 (0.57,1.03)	0.50 (0.29,0.87)	0.49 (0.2,1.22)
Cocaine					
1	0.88 (0.64,1.22)	1.44 (0.88,2.37)	0.89 (0.54,1.46)	0.60 (0.26,1.41)	0.22 (0.03,1.58)†
2+	0.67 (0.50,0.89)	0.75 (0.48,1.15)	1.32 (0.84,2.06)	0.43 (0.17,1.07)	
Stimulant					
1	0.84 (0.61,1.16)	1.02 (0.62,1.67)	1.57 (0.97,2.55)	0.84 (0.37,1.9)	0.60 (0.45,0.80)†
2+	0.85 (0.66,1.10)	0.46 (0.32,0.67)	0.74 (0.48,1.14)	0.24 (0.09,0.69)	
Cannabis					
1	0.76 (0.59,0.98)	0.95 (0.63,1.41)	1.04 (0.66,1.64)	0.26 (0.08,0.85)	0.25 (0.06,1.02)†
2+	1.21 (1.01,1.46)	0.67 (0.52,0.86)	0.9 (0.66,1.24)	0.26 (0.11,0.61)	
Other					
1	0.95 (0.80,1.13)	0.99 (0.77,1.29)	0.91 (0.66,1.26)	0.74 (0.43,1.26)	0.82 (0.33,2.04)
2+	1.02 (0.90,1.16)	0.75 (0.62,0.89)	0.78 (0.61,0.99)	0.35 (0.21,0.59)	0.39 (0.17,0.89)

aOR: Adjusted odds ratio; 95%CI: 95% conference intervals

† Individuals with 1 and 2+ doses were combined into one category to ensure sufficient testing power

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Figure Legend:

Figure 1 - Risk of Covid-19 reinfection and severe outcomes by SUD subtype and vaccination

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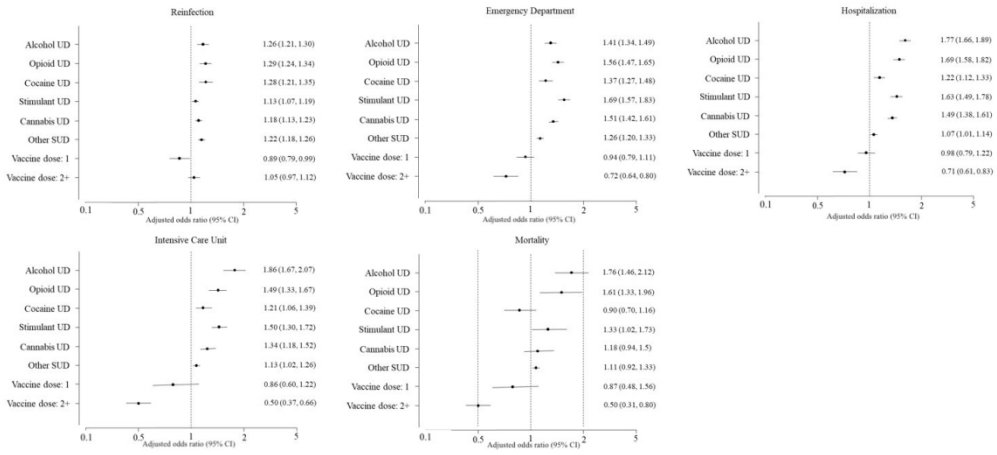

Fig 1. Risk of COVID-19 reinfection and severe outcomes by SUD subtype and vaccination

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Supplemental Material

Table S1. Description of coding systems and codes

Coding System	Code	Description
COVID-19 diagnoses and lab tests		
ICD-10	U07.1, U07.2	COVID-19 (WHO)
ICD-10	B97.29	Other coronavirus as the cause of diseases classified elsewhere
ICD-10	B34.2	Coronavirus infection, unspecified
ICD-10	J12.81	Pneumonia due to SARS-associated coronavirus
LOINC	94505-5,94506-3,94558-4, 94562-6, 94762-2,94769-7,95209-3	SARS-CoV-2 (COVID19) [presence] in serum or plasma by immunoassay
COVID-19 vaccination		
CPT-4	91300,0001A,0002A,0003A,0004A, 91305,0051A,0052A,0053A,0054A 91307,0071A,0072A,0073A,0074A 91308,0081A,0082A,0083A,0084A	Pfizer-BioNTech
CPT-4	91301,0011A,0012A,0013A,91306, 0064A,91311,0111A,0112A,0113A, 91309,0091A,0092A,0093A,0094A	Moderna
CPT-4	91302,0021A,0022A	AstraZeneca
CPT-4	91303,0031A,0034A	Janssen
CPT-4	91304,0041A,0042A	Novavax
CPT-4	91310,0104A	Sanofi Pasteur
Baseline characteristics		
ICD-10	I10	Essential hypertension
ICD-10	E10-E11	Diabetes (type I and II)
ICD-10	E66	Overweight, obesity
ICD-10	N18	Chronic kidney diseases
ICD-10	I50	Heart failure
ICD-10	I63	Stroke
ICD-10	I20-I25	Ischemic heart disease
ICD-10	J45	Asthma
ICD-10	J44	Chronic obstructive pulmonary disease
ICD-10	F33	Depression
ICD-10	F41	Anxiety
ICD-10	F31	Bipolar disorder
ICD-10	F17	Tobacco/nicotine dependence

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Substance use disorder		
ICD-10	F10.1, F10.2	Alcohol use disorder
ICD-10	F11.1, F11.2	Opioid use disorder
ICD-10	F12.1, F12.2	Cannabis use disorder
ICD-10	F14.1, F14.2	Cocaine use disorder
ICD-10	F15.1, F15.2	Stimulant use disorder
ICD-10	F13.1, F13.2, F16.1, F16.2, F18.1, F18.2, F19.1, F19.2	Other substance use disorder

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Table S2. Characteristics of the study population by COVID-19 reinfection outcome

	Reinfection, n (%)		Individuals with COVID-19 Reinfection, n (%)							
			Emergency Department (30-day)		Hospitalization (30-day)		Intensive Care (30-day)		Death (30-day)	
Characteristics	Yes (N=872,446)	No (N=1,809,987)	Yes (N=163,012)	No (N=709,434)	Yes (N=45,362)	No (N=827,084)	Yes (N=12,782)	No (N=859,664)	Yes (N=5,858)	No (N=866,588)
Age at index, mean±SD†	43.8±16.5	45.3±17.1	45.4±18.2	43.4±16	53.7±19.1	43.2±16.1	56.2±17.6	43.6±16.4	67.5±15.5	43.6±16.4
Age										
18-39	404,011 (46.3)	764,126 (42.2)	72,806 (44.7)	331,205 (46.7)	12,693(28)	391,318 (47.3)	2,584 (20.2)	401,427 (46.7)	381 (6.5)	403,630 (46.6)
40-64	353,590 (40.5)	762,587 (42.1)	61,007 (37.4)	292,583 (41.2)	17,504 (38.6)	336,086 (40.6)	5,573 (43.6)	348,017 (40.5)	1,753 (29.9)	351,837 (40.6)
65+	114,845 (13.2)	283,274 (15.7)	29,199 (17.9)	85,646 (12.1)	15,165 (33.4)	99,680 (12.1)	4,625 (36.2)	110,220 (12.8)	3,724 (63.6)	111,121 (12.8)
Female	517,916 (59.4)	966,370 (53.4)	100,293 (61.5)	417,623 (58.9)	24,690 (54.4)	493,226 (59.6)	5,997 (46.9)	511,919 (59.5)	2,699 (46.1)	515,217 (59.5)
Hispanic	53,381 (6.1)	126,502 (7)	16,168 (9.9)	37,213 (5.2)	5,009 (11)	48,372 (5.8)	1,255 (9.8)	52,126 (6.1)	373 (6.4)	53,008 (6.1)
Race										
White	410,391 (47)	809,554 (44.7)	97,110 (59.6)	313,281 (44.2)	29,984 (66.1)	380,407 (46)	8,151 (63.8)	402,240 (46.8)	3,915 (66.8)	406,476 (46.9)
Black	115,406 (13.2)	240,255 (13.3)	43,787 (26.9)	71,619 (10.1)	10,389 (22.9)	105,017 (12.7)	3,091 (24.2)	112,315 (13.1)	1,227 (20.9)	114,179 (13.2)
Other	346,649 (39.7)	760,178 (42)	22,115 (13.6)	324,534 (45.7)	4,989 (11)	341,660 (41.3)	1,540 (12)	345,109 (40.1)	716 (12.2)	345,933 (39.9)
Hypertension	152,909 (17.5)	255,440 (14.1)	51,182 (31.4)	101,727 (14.3)	20,779 (45.8)	132,130 (16)	6,699 (52.4)	146,210 (17)	3,348 (57.2)	149,561 (17.3)
Diabetes	74,105 (8.5)	128,342 (7.1)	27,554 (16.9)	46,551 (6.6)	12,533 (27.6)	61,572 (7.4)	4,377 (34.2)	69,728 (8.1)	2,195 (37.5)	71,910 (8.3)
Obesity/overweight	112,102 (12.8)	166,507 (9.2)	35,402 (21.7)	76,700 (10.8)	11,726 (25.8)	100,376 (12.1)	3,421 (26.8)	108,681 (12.6)	1,469 (25.1)	110,633 (12.8)
Chronic kidney disease	32,936 (3.8)	44,435 (2.5)	12,979 (8)	19,957 (2.8)	7,625 (16.8)	25,311 (3.1)	2,736 (21.4)	30,200 (3.5)	1,778 (30.4)	31,158 (3.6)
Heart Failure	23,458 (2.7)	30,654 (1.7)	10,966 (6.7)	12,492 (1.8)	6,745 (14.9)	16,713 (2)	2,636 (20.6)	20,822 (2.4)	1,639 (28)	21,819 (2.5)
Stroke	14,214 (1.6)	19,947 (1.1)	5,562 (3.4)	8,652 (1.2)	2,766 (6.1)	11,448 (1.4)	958 (7.5)	13,256 (1.5)	598 (10.2)	13,616 (1.6)
Ischemic Heart Disease	43,909 (5)	65,166 (3.6)	17,935 (11)	25,974 (3.7)	9,384 (20.7)	34,525 (4.2)	3,319 (26)	40,590 (4.7)	1,971 (33.6)	41,938 (4.8)
Asthma	69,883 (8)	90,818 (5)	24,551 (15.1)	45,332 (6.4)	6,512 (14.4)	63,371 (7.7)	1,895 (14.8)	67,988 (7.9)	636 (10.9)	69,247 (8)
COPD	22,857 (2.6)	31,103 (1.7)	10,541 (6.5)	12,316 (1.7)	5,484 (12.1)	17,373 (2.1)	2,061 (16.1)	20,796 (2.4)	1,148 (19.6)	21,709 (2.5)
Depression	95,776 (11)	117,360 (6.5)	33,688 (20.7)	62,088 (8.8)	11,025 (24.3)	84,751 (10.2)	3,133 (24.5)	92,643 (10.8)	1,300 (22.2)	94,476 (10.9)
Bipolar	13,976 (1.6)	15,537 (0.9)	7,096 (4.4)	6,880 (1)	2,457 (5.4)	11,519 (1.4)	672 (5.3)	13,304 (1.5)	217 (3.7)	13,759 (1.6)
Anxiety	121,345 (13.9)	154,624 (8.5)	37,970 (23.3)	83,375 (11.8)	11,359 (25)	109,986 (13.3)	3,146 (24.6)	118,199 (13.7)	1,179 (20.1)	120,166 (13.9)
Vaccine dose										
None	818,515 (93.8)	1,719,387 (95)	151,116 (92.7)	667,399 (94.1)	41,355 (91.2)	777,160 (94)	11,784 (92.2)	806,731 (93.8)	5,582 (95.3)	812,933 (93.8)
One	12,079 (1.4)	22,997 (1.3)	2,805 (1.7)	9,274 (1.3)	922 (2)	11,157 (1.3)	240 (1.9)	11,839 (1.4)	63 (1.1)	12,016 (1.4)

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Two or more	41,852 (4.8)	67,603 (3.7)	9,091 (5.6)	32,761 (4.6)	3,085 (6.8)	38,767 (4.7)	758 (5.9)	41,094 (4.8)	213 (3.6)	41,639 (4.8)
Smoking	59,674 (6.8)	89,652 (5)	26,629 (16.3)	33,045 (4.7)	8,580 (18.9)	51,094 (6.2)	2,842 (22.2)	56,832 (6.5)	898 (15.3)	58,776 (6.8)
Substance use disorder										
Alcohol	15,801 (1.8)	18,422 (1)	7,986 (4.9)	7,815 (1.1)	3,373 (7.4)	12,428 (1.5)	1,200 (9.4)	14,601 (1.7)	392 (6.7)	15,409 (1.8)
Opioid	7,642 (0.9)	7,462 (0.4)	4,461 (2.7)	3,181 (0.4)	1,844 (4.1)	5,798 (0.7)	587 (4.6)	7,055 (0.8)	186 (3.2)	7,456 (0.9)
Cocaine	4,117 (0.5)	3,367 (0.2)	2,738 (1.7)	1,379 (0.2)	1,161 (2.6)	2,956 (0.4)	414 (3.2)	3,703 (0.4)	96 (1.6)	4,021 (0.5)
Stimulant	3,922 (0.4)	3,921 (0.2)	2,593 (1.6)	1,329 (0.2)	1,094 (2.4)	2,828 (0.3)	351 (2.7)	3,571 (0.4)	84 (1.4)	3,838 (0.4)
Cannabis	6,464 (0.7)	6,683 (0.4)	3,879 (2.4)	2,585 (0.4)	1,477 (3.3)	4,987 (0.6)	461 (3.6)	6,003 (0.7)	107 (1.8)	6,357 (0.7)
Other	13,533 (1.6)	13,848 (0.8)	7,256 (4.5)	6,277 (0.9)	2,651 (5.8)	10,882 (1.3)	897 (7)	12,636 (1.5)	276 (4.7)	13,257 (1.5)

†SD: standard deviation
All the differences were statistically significant at the 0.05 level

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Table S3. Risk of COVID-19 reinfection and outcomes

Factors	Reinfection, aOR (95% CI)	Individuals with COVID-19 Reinfection: Outcomes within 30 days of reinfection			
		Emergency Department, aOR (95% CI)	Hospitalization, aOR (95% CI)	Intensive Care, aOR (95% CI)	Death, aOR (95% CI)
Intercept					
Female	1.11** (1.08,1.15)	0.96 (0.91,1.01)	0.85** (0.8,0.91)	0.80** (0.72,0.89)	0.99 (0.83,1.19)
Age (ref: 18-39 yrs)					
40-64 yrs	0.97 (0.94,1.01)	0.91** (0.86,0.97)	1.20** (1.12,1.30)	1.36** (1.20,1.54)	2.41** (1.87,3.13)
65+ yrs	0.88** (0.83,0.94)	0.89* (0.82,0.98)	1.43** (1.27,1.60)	1.38** (1.16,1.66)	4.42** (3.31,6.09)
Hispanic	1.46** (1.38,1.56)	1.07 (0.98,1.17)	1.21** (1.08,1.36)	0.99 (0.83,1.21)	0.65* (0.45,0.95)
Race (ref: White)					
Black	1.09** (1.05,1.14)	1.52** (1.43,1.61)	1.11** (1.03,1.20)	1.08 (0.95,1.22)	0.86 (0.69,1.06)
Other	0.71** (0.67,0.74)	1.42** (1.31,1.54)	0.93 (0.84,1.04)	1.37** (1.17,1.61)	1.46** (1.12,1.89)
Hypertension	1.10** (1.06,1.15)	1.14** (1.07,1.20)	1.34** (1.24,1.45)	1.44** (1.27,1.62)	0.97 (0.78,1.20)
Diabetes	1.07** (1.02,1.12)	1.17** (1.09,1.24)	1.30** (1.20,1.41)	1.64** (1.46,1.85)	1.30** (1.07,1.58)
Obesity/overweight	1.10** (1.05,1.14)	0.94* (0.89,0.99)	0.87** (0.81,0.94)	0.76** (0.68,0.86)	0.85 (0.70,1.03)
Chronic kidney disease	1.11** (1.05,1.17)	0.93 (0.86,1.01)	1.29** (1.17,1.42)	1.34** (1.17,1.54)	2.11** (1.72,2.58)
Heart failure	1.18 (1.10,1.26)	1.25** (1.14,1.38)	1.39** (1.25,1.54)	1.53** (1.32,1.77)	1.84** (1.48,2.29)
Stroke	0.99 (0.93,1.06)	0.86** (0.78,0.94)	0.98 (0.87,1.10)	1.01 (0.85,1.19)	1.43** (1.13,1.81)
Ischemic heart disease	1.02 (0.96,1.07)	1.27** (1.18,1.38)	1.20** (1.10,1.31)	1.18* (1.03,1.35)	1.28* (1.04,1.58)
Asthma	1.28** (1.23,1.34)	1.20** (1.13,1.27)	0.98 (0.90,1.06)	0.99 (0.88,1.12)	0.86 (0.69,1.07)
COPD	1.20** (1.13,1.27)	1.16** (1.06,1.26)	1.45** (1.32,1.59)	1.63** (1.43,1.87)	1.58** (1.29,1.94)
Depression	1.20 (1.16,1.24)	1.00 (0.95,1.05)	1.04 (0.97,1.12)	0.93 (0.83,1.03)	0.93 (0.78,1.12)
Anxiety	1.11** (1.07,1.15)	0.95 (0.90,1.00)	1.06 (0.99,1.13)	1.10 (0.98,1.23)	0.88 (0.73,1.06)
Bipolar	1.13** (1.07,1.18)	1.46** (1.36,1.56)	1.25** (1.15,1.36)	0.93 (0.80,1.07)	0.95 (0.73,1.23)
Smoking	0.96* (0.93,0.99)	1.42 (1.35,1.49)	1.29** (1.21,1.38)	1.29** (1.16,1.44)	1.15 (0.96,1.37)
Vaccine dose (ref: none)					
1	0.89* (0.79,0.99)	0.94 (0.79,1.11)	0.98 (0.79,1.22)	0.86 (0.60,1.22)	0.87 (0.48,1.56)
2+	1.05 (0.97,1.12)	0.72** (0.64,0.80)	0.71** (0.61,0.83)	0.50** (0.37,0.66)	0.50** (0.31,0.80)

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Alcohol use disorder	1.26** (1.21,1.30)	1.41** (1.34,1.49)	1.77** (1.66,1.89)	1.86** (1.67,2.07)	1.76** (1.46,2.12)
Opioid use disorder	1.29** (1.24,1.34)	1.56** (1.47,1.65)	1.69** (1.58,1.82)	1.49** (1.33,1.67)	1.61** (1.33,1.96)
Cocaine use disorder	1.28** (1.21,1.35)	1.37** (1.27,1.48)	1.22** (1.12,1.33)	1.21** (1.06,1.39)	0.90 (0.70,1.16)
Stimulant use disorder	1.13** (1.07,1.19)	1.69** (1.57,1.83)	1.63** (1.49,1.78)	1.50** (1.30,1.72)	1.33* (1.02,1.73)
Cannabis use disorder	1.18** (1.13,1.23)	1.51** (1.42,1.61)	1.49** (1.38,1.61)	1.34** (1.18,1.52)	1.08 (0.94,1.50)
Other use disorder	1.22** (1.18,1.26)	1.26** (1.20,1.33)	1.07 (1.00,1.14)	1.13* (1.02,1.26)	1.11 (0.92,1.33)

*p<0.05; **p<0.01

aOR: Adjusted odds ratio; 95% CI: 95% conference intervals

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The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title and abstract PP:1, 2 Geographic region: title and abstract Timeframe: abstract PP: 1, 2 Not applicable
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction PP: 5, 6

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Objectives	3	State specific objectives, including any pre-specified hypotheses			P: 6
Methods					
Study Design	4	Present key elements of study design early in the paper			PP: 6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			P: 7
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published	Methods, Cohort Description PP: 7-8 P: 7

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		Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	PP: 7-8
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of			PP: 7-8

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		assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias			P: 9 (Regression analysis controlled for baseline characters to address bias from observable covariate differences)
Study size	10	Explain how the study size was arrived at			P: 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			PP: 9-10 Appendix
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed			PP: 9-10

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		Case-control study - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	P: 6 P: 7
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases.	N/A

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				The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Cohort Description PP: 10-11, and Table 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for			PP: 10-11

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		each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			Outcome indicators PP: 10-11, Table 1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included			Results PP: 11-13 Figure 1 Table 2

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		(b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			N/A
Discussion					
Key results	18	Summarise key results with reference to study objectives			P: 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Strength and Limitations of this study P: 3 Limitation PP: 16-17

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Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			PP: 13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results			P: 16
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			P: 16
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	P: 18

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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