THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 10

RESEARCH ARTICLE

Risk of COVID-19 reinfection and its severe complications in adults treated with long-term opioids for chronic non-cancer pain

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OPEN ACCESS

PUBLISHED
31 October 2024

CITATION
Tuan, WT., Partin, M., et al., 2024. Risk of COVID-19 reinfection and its severe complications in adults treated with long-term opioids for chronic non-cancer pain. Medical Research Archives, [online] 12(10). https://doi.org/10.18103/mra.v12i10.5931

DOI
https://doi.org/10.18103/mra.v12i10.5931

ISSN
2375-1924

ABSTRACT

Introduction: With the sequelae of the COVID-19 pandemic, many concerns remain about reinfection and waning immunity against the virus and its variants.

Objective: This study aimed to assess the risk of COVID-19 reinfection and its severe complications in adults treated with long-term opioid therapy (LTOT) for chronic non-cancer pain.

Methods: A retrospective cohort study was conducted using the TriNetX database of over 2,120,701 adults infected by COVID-19 between January 2020 and June 2022. The reinfection was defined as a new COVID-19 infection recorded after at least 30 days after the initial one. Logistic regression was applied to evaluate the probability of reinfection and severe COVID-19 illness (measured by emergence department (ED) visits, hospitalization, intensive care unit (ICU) care, or death) within 30 days of the reinfection, controlled for baseline demographic and comorbid conditions.

Results: The study included 36,265 adults treated with LTOT. Adults on LTOT, compared to those without LTOT, were 2.8 times more likely to have a COVID-19 reinfection, and, after re-infected, were 1.4-1.6 times more likely to be admitted to ED, hospital, and ICU, though no impact was found on a 30-day mortality.

Conclusion: the study findings can help guide clinical decisions about the level of monitoring and care for adults treated with LTOT for chronic non-cancer pain who experience a COVID-19 reinfection. Future prospective research is needed to fully understand the components of risk and optimal risk mitigation strategies of COVID-19 reinfection in adults on LTOT.

Keywords: Opioid, COVID-19 reinfection, COVID-19 outcomes, chronic pain.

1. Introduction

Since December 2019, over 770 million cases and over 6.9 million deaths attributed to SARS-CoV-2 infection have been reported globally[1]. The pandemic has disproportionately affected populations impacted by chronic health issues, including people with chronic non-cancer pain[2,3]. Research has shown the COVID-19 pandemic increased the burden of chronic pain, with worsened social isolation, economic stress, anxiety, and disrupted access to pain management contributing to this distress[2,4,5]. Pharmacological treatments, including long-term opioid therapy (LTOT), are a part of standard of care in chronic non-cancer pain,[6,7] with an increase in opioid medication use for managing chronic pain noted likely in compensation for stopping physical/psychological treatments due to the pandemic[5,8].

To date, research evaluating the relationship between opioid use and COVID-19 infection outcomes has primarily focused on persons with an opioid use disorder (OUD), showing increased risk of complications due to the COVID-19 infection in this population[9–11]. Opioids can cause acute respiratory depression and compromise immune system[12,13], which has been identified as a risk factor for severe COVID-19 complications[14]. As additional SARS-CoV-2 variants emerged that can evade prior immunity, rates of COVID-19 reinfection have increased over the past 3 years[15,16]. Reinfection with COVID-19 has been associated with greater risk of intensive care unit (ICU) admission, mechanical ventilation, and development of chronic physical and mental health sequelae[17,18]. Despite recent advancement in vaccines and treatments for COVID-19, concerns remain about waning immunity against SARS-CoV-2 virus and its variants and reinfection, especially among individuals at an already-higher risk of COVID-19 complications, such as adults treated for chronic pain with LTOT.

Moreover, the literature has shown elevated risk of mortality and healthcare utilization after initial COVID-19 infection among people prescribed opioids[19,20]. Many people on opioid treatment also experience medical comorbidities (diabetes, obesity/overweight, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, immune problems, sickle cell disease)[19,21], mental health conditions (anxiety, bipolar, dementia, depression)[10], and substance use (alcohol, drugs, tobacco/nicotine) disorders, which have been documented as important moderators for poor COVID-19 outcomes. To better understand the relationship between COVID-19 and opioid-related treatment, this retrospective cohort study leveraged TriNetX, a large existing database of electronic health records (EHRs), to assess the risk of COVID-19 reinfection and its severe complications within 30 days of the reinfection onset among adults treated with LTOT for chronic non-cancer pain in the U.S.

2. Methods

2.1. STUDY DESIGN AND DATA SOURCE

This study utilized a retrospective cohort design using EHRs from the TriNetX database (Cambridge, MA), a global health data network containing de-identified EHRs (e.g., demographic, diagnosis, procedure, medication, and laboratory information) of more than 80 million patients from 57 participating healthcare organizations predominately from the U.S. TriNetX research data have 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.[22] Because the TriNetX database consists of deidentified standard data elements defined and processed in compliance with Sections §164.514(a) and §164.514(b)(1) of the HIPAA Privacy Rule, the Institutional Review Board of the Pennsylvania State University determined that the use of the TriNetX data does not require the IRB approval.

2.2. STUDY POPULATION

Individuals eligible for the analysis were adults ≥18 years old diagnosed with COVID-19 between January 1, 2020 and April 30, 2022 (study

enrollment period) and either meeting criteria for being classified to the LTOT or the Control cohorts. The diagnosis of a COVID-19 illness was based on the presence of both COVID-19 diagnosis and a positive laboratory test result documented in the EHR (see Supplemental Table S1 for details)[19,23]. Eligible patients' health data were extracted through June 30, 2022, yielding the study assessment period to span January 1, 2020 and June 30, 2022; this approach allowed to capture potential COVID-19 reinfection-related events, defined as occurring with 30 days of the initial infection, in all study participants. Individuals were ineligible if they had diagnoses of opioid use disorder (OUD) or cancer, or lived in nursing homes or palliative care facilities prior to their first COVID-19 infection to exclude those treated with opioids for OUD or cancer or terminal illness related care.

2.3. TREATMENT AND CONTROL COHORTS

The LTOT cohort comprised adults who had been issued at least three outpatient prescriptions for opioid medications, and the Control cohort included adults who were not prescribed any opioids within six months prior to their first COVID-19 infection noted during the study assessment period. Therefore, some of the opioid medications could have been prescribed before January 1, 2020 if study participants experienced the first COVID-19 illness in the first few months of the assessment period.

Prescription opioids included agonists and partial agonists prescribed as monotherapy or a combination medication in a form compatible with outpatient prescribing for chronic non-cancer pain[19,24]. Although buprenorphine and methadone are used to treat OUD, our analysis excluded patients with OUD diagnoses; in addition, methadone prescriptions are assumed to be issued for chronic pain, because only opioid treatment programs are allowed to dispense methadone as a treatment for OUD in the outpatient settings. The study identified opioid medications using normalized name and code sets for medications based on the Prescription for Electronic Drug Information Exchange (RxNorm)[25]. The list of RxNorm codes is provided in Supplemental Table S1.

2.4. OUTCOME MEASURES OF COVID-19 REINFECTION AND ITS SEVERITY

The first COVID-19 infection episode during the study assessment period was considered the "index" infection. A COVID-19 reinfection (i.e., a new infection with SARS-CoV-2) was defined as a COVID-19 infection documented at least 30 days after the index infection date. Severe COVID-19 complications were defined as presence of an emergency department (ED), hospital or intensive care unit (ICU) admission, or death within 30 days of the reinfection. Presence of COVID-19 reinfection and its severe complications were assessed through dichotomous (yes/no) metrics for each of the variables of interest.

2.5. BASELINE CHARACTERISTICS

Demographic and health comorbidity data were extracted at the time of the index COVID-19 infection date for each study participant. The available demographic data included sex (male/female), age group (18-39, 40-64, 65+), ethnicity (Hispanic/non-Hispanic) and race (White/Black/Other). Data on comorbid conditions known to be associated with the increased risk of severe COVID-19 complications included the diagnoses of chronic medical (diabetes, obesity /overweight, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, immune problems, sickle cell disease)[19,21], mental health (anxiety, bipolar, dementia, depression)[10], and substance use (alcohol, drugs, tobacco/nicotine) disorders. Presence of the tobacco/nicotine use disorder diagnoses served as the proxy of smoking/tobacco use status, which is not a part of available EHR data. Detailed information on the diagnostic codes for the conditions extracted in this study is provided in Supplemental Table S1.

2.6. STATISTICAL ANALYSIS

Summary statistics were computed to describe the baseline characteristics and outcome measures of the study sample and by the cohort status. Between-cohort differences at baseline were

compared using the t-test for continuous and chi-square for categorical normally-distributed variables (or equivalent non-parametric tests for non-normally distributed variables). Multiple logistic regression modeling was utilized to assess the risk of COVID-19 reinfection and its severe complications, when controlling for baseline demographic and comorbid condition characteristics. The regression analysis was conducted using the Maximum Likelihood Estimation method to estimate the adjusted odds ratios (aORs), Wald 95% confidence intervals (CIs) for the coefficients, and p-values for each outcome variable to estimate the risk of a given outcome. 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).

3. Results

3.1. STUDY SAMPLE CHARACTERISTICS

The study sample consisted of 2,120,701 adults diagnosed with COVID-19 between January 1, 2020 and June 30, 2022, including 36,265 individuals in the LTOT and 2,084,436 individuals in the Control cohort. Compared to the Control cohort, the LTOT cohort had a statistically significantly greater percentage of individuals who were younger, males, non-Whites, and had a higher burden of chronic medical/mental health conditions and substance use disorders, known risk factors for COVID-19 complications (Table 1).

3.2. RISK OF COVID-19 REINFECTION AND ITS SEVERE COMPLICATIONS

During the study assessment period, approximately 50.1% (18,150) of patients in the LTOT cohort had a documented COVID-19 reinfection compared to 28.6% (596,790) of patients in the Control cohort (p<0.01). Among those with COVID-19 re-infection, adults in the LTOT cohort, compared to the Control cohort, also had a greater frequency (p<0.01) of the ED visits, hospital and ICU admissions, and mortality within 30 days of COVID-19 reinfection (Table 2).

Table 1. Baseline characteristics of the study sample: Adults with COVID-19 infection

Characteristics, n (%)	Total, N=2,120,701	LTOT Cohort, N=36,265	Control Cohort, N=2,084,436	p-value[†]
Female	1,148,766 (54.2)	23,075 (63.7)	1,125,691 (54.0)	<0.01
Age category				
18-39	969,601 (45.7)	9,955 (27.5)	959,646 (46.0)	<0.01
40-64	866,424 (40.9)	17,567 (48.4)	848,857 (40.7)	
65+	284,676 (13.4)	8,743 (24.1)	275,933 (13.2)	
Hispanic	136,174 (6.4)	2,877 (7.9)	133,297 (6.4)	<0.01
Race				<0.01
White	857,656 (40.4)	25,264 (69.7)	832,392 (39.9)	
Black	259,342 (12.2)	7,430 (20.5)	251,912 (12.1)	
Other	1,003,703 (47.3)	3,571 (9.8)	1,000,132 (48.0)	
Medical/mental health conditions				
Diabetes	120,915 (5.7)	8,643 (23.8)	112,272 (5.4)	<0.01
Obesity/overweight	155,358 (7.3)	11,285 (31.1)	144,073 (6.9)	<0.01
Cardiovascular disease	287,419 (13.6)	19,351 (53.4)	268,068 (12.9)	<0.01
Chronic kidney disease	41,463 (2.0)	4,778 (13.2)	36,685 (1.8)	<0.01
Chronic liver disease	6,831 (0.3)	757 (2.1)	6,074 (0.3)	<0.01
Chronic lung disease	141,018 (6.6)	10,155 (28.0)	130,863 (6.3)	<0.01
Immune problem	12,878 (0.6)	1,491 (4.1)	11,387 (0.5)	<0.01
Sickle cell disease	3,021 (0.1)	556 (1.5)	2,465 (0.1)	<0.01
Mental health problem[1]	212,906 (10.0)	15,685 (43.3)	197,221 (9.5)	<0.01

Characteristics, n (%)	Total, N=2,120,701	LTOT Cohort, N=36,265	Control Cohort, N=2,084,436	p-value†
Nicotine/tobacco use disorder	84,084 (4.0)	5,350 (14.8)	78,734 (3.8)	<0.01
Alcohol use disorder	20,898 (1.0)	1,233 (3.4)	19,665 (0.9)	<0.01
Other drug use disorder[2]	41,418 (1.6)	1,474 (4.1)	21,288 (1.0)	<0.01

†Chi-square statistics were computed to evaluate differences in proportions between the cohorts.

[1]Mental health problem included anxiety, bipolar disorder, dementia, depression, and ADHD.

[2]Other drug use disorders included cannabis, sedative, cocaine, stimulant, hallucinogen, inhalant, or psychoactive drug use disorders, and excluded opioid, alcohol, and nicotine/tobacco use disorders

Table 2. COVID-19 reinfection and its severe complications: frequency within the study sample and by the cohort status

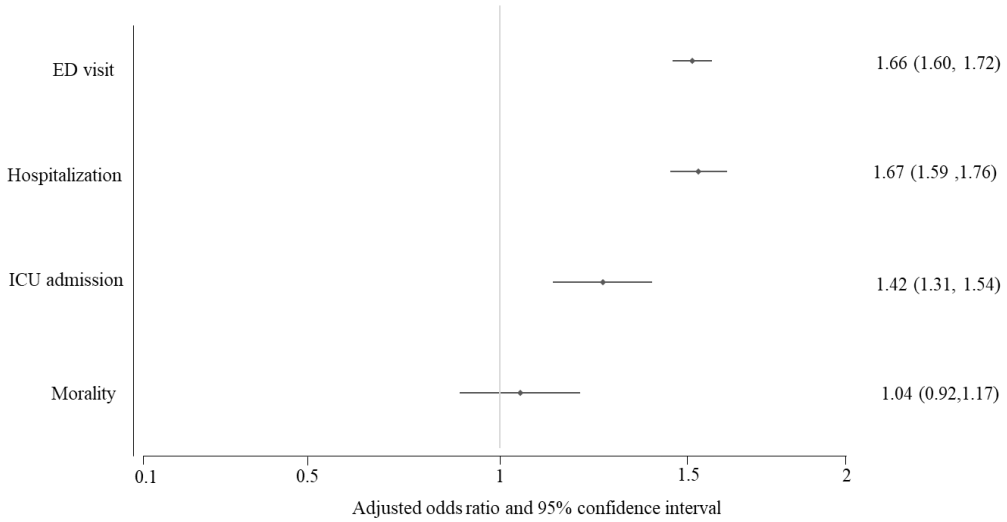
Characteristics, n (%)	Total, N=2,120,701	LTOT Cohort, N=36,265	Control Cohort, N=2,084,436	p-value†
Reinfection	614,940 (29.0)	18,150 (50.1)	596,790 (28.6)	<0.01
Of those with re-infection:				
ED visit	84,303 (13.7)	7,255 (40.0)	77,048 (12.9)	<0.01
Hospital admission	20,181 (3.3)	2,730 (15.0)	17,451 (2.9)	<0.01
ICU admission	5,854 (1.0)	816 (4.5)	5,038 (0.8)	<0.01
Death	3,178 (0.5)	378 (2.1)	2,800 (0.5)	<0.01

ED: Emergency department; ICU: Intensive care unit

†Chi-square statistics were computed to evaluate differences in proportions between the cohorts.

The logistic regression analysis, controlling for baseline characteristics, revealed that, compared to the Control cohort, the LTOT cohort had an increased likelihood of COVID-19 re-infection (aOR=2.75, 95% CI: 2.69, 2.81; p<0.01). After being re-infected, the LTOT cohort, compared to those in the Control cohort, was also more likely to have an ED visit (aOR=1.66, 95% CI: 1.60, 1.72; p<0.01), and be admitted to a hospital (aOR=1.67, 95% CI: 1.59, 1.76; p<0.01) and ICU (aOR=1.42, 95% CI: 1.31, 1.54; p<0.01) within 30 days of reinfection (Figure 1). No statistically significant differences in 30-day mortality rates were noted between the cohorts (aOR=1.04, 95% CI: 0.92, 1.17; p=0.50). The details of the statistical models and their outputs for each outcome measure are provided in Supplemental Table S2.

Figure 1. Logistic regression analysis: the likelihood of severe complications within 30 days of the COVID-19 reinfection among adults treated with long-term opioid therapy versus those not treated with opioid medications.



4. Discussion

This retrospective cohort study, based on a secondary analysis of large EHR research database with over 2.1 million adults with COVID-19 infection in the U.S., revealed that adults with LTOT-treated chronic non-cancer pain are at a greater risk of reinfection with COVID-19 and, once re-infected, were more likely to require ED, hospital, and ICU care. These findings extend the evidence from prior research, which indicated that individuals on LTOT were at increased risk to experience a COVID-19 illness and associated worse outcomes[19,26]. Together, these results suggest that persons on LTOT are more likely to become infected and re-infected, and, once infected by SARS-CoV-2, are more likely to become severely ill. The increased utilization of emergency, hospital and critical care services, caused by these infections and reinfections has imposed additional strain on limited healthcare resources, especially in communities that are already underserved and disproportionately affected by the pandemic.

The COVID-19 pandemic has led to unprecedented public health challenges and harms, with an especially heavy toll among individuals treated with LTOT for refractory, severe chronic pain[8,19]. Prior research has shown that individuals on long-term opioid treatment often experience underlying health issues that can compromise their immune system or overall health, making it harder for the body to cope with additional stressors like a severe viral infection. Essentially, the combination of compromised respiratory function, underlying health issues, potential impacts on immune response, and lifestyle factors contribute to the increased risk of severe COVID-19 infection in those prescribed opioid medication[19]. Together with the findings of increased risk for both COVID-19 illness and its severe complications among adults with LTOT, this underscores the need to consider LTOT prescribed for chronic pain as a risk factor for worse outcomes when evaluating and managing patients with a COVID-19 infection. Although chronic non-cancer pain treated with LTOT is not currently listed by the Centers for Disease Control and Prevention as one of recognized risk factors for more severe COVID-19 illness[27], the finding of the study can be clinically applied when counseling adults with LTOT-treated chronic pain about the importance of COVID-19 prevention strategies.

The strengths of this study include a large sample size and reliance on clinically-relevant, real-life data. Utilizing a large database enabled us to estimate the risk for COVID-19 reinfection and its sequelae in individuals prescribed LTOT while accounting for a range of demographic, medical, and mental health characteristics to strengthen the validity of our findings, and minimize the potential impact of confounding and bias.

Despite its strengths, this study has several important limitations. First, the COVID-19 diagnosis and testing records would not have been captured in the TriNetX database if the diagnosis was established at facilities outside of the participating research data network, potentially causing selection bias. Second, the study used retrospective observational data; the lack of prospective, randomized design could have affected the outcome validity. In addition, although the existing social determinants of health are critical for predicting future health outcomes[28,29], the TriNetX-based research data do not contain information on patient socioeconomic contexts (e.g., health insurance, education or income levels) that could be important confounders in the analyses. Future prospective studies and secondary database analyses using advanced data mining techniques or machine learning algorithms, and accounting for social determinants of health information could provide more insight and better account for important confounders.

5. Conclusion

Findings from this retrospective cohort study, leveraging EHRs from a large national research database, indicated that adults treated with LTOT

for chronic non-cancer pain are at increased risk for COVID-19 reinfection and its severe complications, requiring ED, hospital, and ICU care. These results can help guide clinical decisions when caring for patients treated with LTOT regarding the prevention as well as monitoring and treatment of COVID-19 re-infection.

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. MP, CH, GH, KB, AVR contributed to literature review, data analysis, interpretation, and writing the manuscript. AEZ contributed to study design, data analysis, interpretation, and writing the manuscript.

Funding

The author(s) received no funding support for the research, authorship, and/or publication of this article.

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.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

No data are available

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Supplemental Material

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
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
Prescription opioids		
RxNorm	10689,1819,1841,19860,2001352,22713,23088,2670,3423,4337,480,5489,56795,6378,6754,6813,7052,7238,73032,7804,7814,787390,8001	Opioid medication
Baseline characteristics		
ICD-10	E10-E11	Diabetes (type I and II)
ICD-10	E66	Obesity/overweight,
ICD-10	I10, I20, I21, I22, I23, I24, I25, I26, I27, I28, I48, I49, I50, I63	Cardiovascular diseases
ICD-10	N18	Chronic kidney diseases
ICD-10	K70, K73, K74, K721, K754	Chronic liver diseases
ICD-10	J40, J41, J42, J43, J44, J45, J46, J47, J44, E84, A15	Chronic lung diseases
ICD-10	B20, D849, T86, Z94	Immune problem
ICD-10	D56, D57	Sickle cell disease
ICD-10	F03, F31, F32, F33, F41, F90	Mental health disorders
ICD-10	F17.1, F17.2	Tobacco/nicotine 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, F13.1, F13.2, F14.1, F14.2, F15.1, F15.2, F16.1, F16.2, F18.1, F18.2, F19.1, F19.2	Other drug use disorder, including cannabis, sedative, cocaine, stimulant, hallucinogen, inhalant, or psychoactive drug use disorders, and excluding opioid, alcohol, and nicotine/tobacco use disorders

Table S2. Likelihood of COVID-19 reinfection and its severe complications among adults treated with long-term opioid therapy (LTOT) versus those not treated with opioid medications

		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)
Opioid therapy	2.75** (2.69,2.81)	1.66** (1.60,1.72)	1.67** (1.59,1.76)	1.42** (1.31,1.54)	1.04 (0.92,1.17)
Female	1.21** (1.2,1.22)	1.04** (1.02,1.06)	0.82** (0.80,0.85)	0.67** (0.64,0.71)	0.62** (0.58,0.67)
Age (ref: 18-39 yrs)					
40-64 yrs	0.82** (0.82,0.83)	0.78** (0.76,0.79)	1.33** (1.28,1.38)	1.92** (1.78,2.06)	5.02** (4.28,5.88)
65+ yrs	0.64** (0.63,0.64)	1.09** (1.06,1.12)	3.45** (3.30,3.60)	3.90** (3.59,4.23)	27.83** (23.79,32.55)
Hispanic	0.72** (0.71,0.73)	2.69** (2.62,2.77)	2.75** (2.62,2.88)	2.26** (2.07,2.47)	1.61** (1.4,1.86)
Race (ref: White)					
Black	0.94** (0.93,0.95)	2.40** (2.35,2.45)	1.41** (1.36,1.46)	1.43** (1.34,1.53)	1.24** (1.13,1.36)
Other	1.33** (1.32,1.34)	0.23** (0.23,0.24)	0.24** (0.23,0.25)	0.31** (0.29,0.34)	0.36** (0.32,0.4)
Medical/mental conditions					
Diabetes	0.89** (0.87,0.9)	1.39** (1.35,1.44)	1.57** (1.50,1.64)	1.86** (1.74,2.00)	1.45** (1.32,1.59)
Obesity/overweight	1.00 (0.99,1.01)	0.97* (0.95,0.99)	0.98 (0.94,1.03)	0.96 (0.90,1.03)	0.83** (0.75,0.92)
Chronic vascular disease	0.96** (0.95,0.97)	1.53** (1.50,1.57)	1.86** (1.79,1.93)	2.02** (1.88,2.17)	1.65** (1.5,1.81)
Chronic kidney disease	1.11** (1.08,1.13)	1.13** (1.08,1.18)	1.63** (1.55,1.73)	1.79** (1.65,1.94)	2.65** (2.4,2.92)
Chronic liver Disease	1.24** (1.17,1.3)	1.29** (1.18,1.42)	2.03** (1.82,2.26)	2.16** (1.86,2.51)	2.69** (2.22,3.26)
Chronic lung Disease	1.16** (1.14,1.17)	1.51** (1.47,1.55)	1.23** (1.18,1.28)	1.37** (1.28,1.47)	1.39** (1.26,1.52)
Immunodeficiency	1.19** (1.15,1.24)	0.78** (0.72,0.84)	1.36** (1.24,1.5)	1.02 (0.87,1.20)	1.44** (1.18,1.77)
Sickle cell disease	1.21** (1.13,1.29)	1.02 (0.91,1.14)	2.56** (2.22,2.96)	1.54** (1.15,2.06)	2.24** (1.45,3.48)
Mental health problem	1.16** (1.15,1.18)	1.39** (1.36,1.42)	1.35** (1.30,1.40)	1.19** (1.11,1.27)	1.15** (1.05,1.26)
Nicotine/tobacco use disorders	1.07** (1.06,1.09)	2.09** (2.03,2.15)	1.63** (1.55,1.71)	1.69** (1.56,1.83)	1.17* (1.03,1.33)
Alcohol use disorders	1.19** (1.15,1.23)	1.84** (1.74,1.95)	2.11** (1.96,2.27)	2.09** (1.86,2.34)	1.53** (1.27,1.85)
Other drug use disorder±	1.04** (1.01,1.07)	1.80** (1.70,1.89)	1.59** (1.47,1.72)	1.54** (1.36,1.75)	1.18** (0.95,1.46)

*$p<0.05$; **$p<0.01$;

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

† included persons who had the index infection (n=36,265 for the LTOT cohort; n=2,084,436 for the control cohort)

‡ included persons with reinfection (n=18,150 for the LTOT cohort; n=596,790 for the control cohort)

±Other drug use disorders included cannabis, sedative, cocaine, stimulant, hallucinogen, inhalant, or psychoactive drug use disorders, and excluded opioid, alcohol, and nicotine/tobacco use disorders