Final Research Report for Narcotics Division, Security Bureau

Project title: Short and long term burden of COVID-19 in substance abusers: A cohort study

Project reference no.: BDF 220051

Principal investigator:

Dr. Eric Yuk Fai Wan

Assistant Professor, Department of Family Medicine and Primary Care, and Department of Pharmacology, and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong

Co-investigators and team members:

Professor Ian Chi Kei Wong

Lo Shiu Kwan Kan Po Ling Professor, Department of Pharmacology and Pharmacy, The University of Hong Kong

Professor Esther Wai Yin Chan

Professor, Department of Pharmacology and Pharmacy, The University of Hong Kong

Professor Celine Sze Ling Chui

Assistant Professor, School of Nursing, and School of Public Health, The University of Hong Kong

Professor Shirley Xue LI

Assistant Professor, Department of Medicine, and Department of Pharmacology and Pharmacy, The University of Hong Kong

Professor Carlos King Ho Wong

Associate Professor, Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine

Professor Francisco Tse Tsun Lai

Assistant Professor, Department of Pharmacology and Pharmacy, and Department of Family Medicine and Primary Care, The University of Hong Kong

Dr. Luna Yue WEI

Postdoctoral Fellow, Department of Pharmacology and Pharmacy, and Department of Family Medicine and Primary Care, The University of Hong Kong

Mr. Vincent Ka Chun Yan

PhD candidate, Department of Pharmacology and Pharmacy, The University of Hong Kong

Table of Contents

Abstract	5
Declaration	8
Acknowledgements	9
List of tables	10
List of figures	12
List of abbreviations	13
1. Introduction	14
2. Aim and objectives	16
2.1 Aims	16
2.2 Objectives	16
3. Methods	17
3.1 Research ethics	17
3.2 Data source	17
3.3 Patient identification	19
3.4 Outcome	24
3.5 Statistical analysis	25
4. Results	27
4.1 Result of Objective 1 (To investigate the risk of COVID-19 infection in substance abusers)	27
4.2 Result of Objective 2 (To evaluate the short-term burden of COVID-19 in individuals with substance abuse)	31
4.3 Result of Objective 3 (To assess the long-term burden of COVID-19 in individuals with substance abuse)	37
4.4 Result of Objective 4 (To compare vaccine effectiveness among vaccinated individuals with or without substance abuse)	43
5. Discussion	55
5.1 Interpretation of study results	
5.2 Clinical implications	58
5.3 Implication	58
6. Conclusion	59
7. References	60

Abstract

Introduction

Substance abuse can significantly increase the risk for infection and prognosis, potentially leading to more severe and longer lasting illnesses. Concurrently, the coronavirus disease 2019 (COVID-19) contributes to higher morbidity and mortality rates. Substance abusers may face heightened health risks due to compromised immune systems and co-occurring medical conditions. However, there is limited evidence on the interaction between substance abuse and COVID-19. Moreover, the evidence on the vaccine effectiveness against short- and long-term COVID-19 in substance abusers is lacking. Understanding the impact of substance abuse on COVID-19 infection and its related outcomes and vaccination effectiveness is crucial to the health management, social care, and education of this population.

Objectives

The objectives of this study were: 1) to investigate the risk of COVID-19 infection in substance abusers; 2) to evaluate the short-term burden of COVID-19 in substance abusers; 3) to assess the long-term burden of COVID-19 in substance abusers; 4) to compare vaccine effectiveness among vaccinated individuals with or without substance abuse.

Methods

The population-based cohort was based on electronic health records from the Hospital Authority and the Department of Health. For objective 1, patients who were not tested positive for COVID-19 on or before January 1, 2022 were identified and then divided into two groups based on whether had a history of substance abuse. Each patient in the exposure group (i.e., with substance abuse) was randomly matched to up to ten patients in the non-exposure group (i.e. controls without substance abuse) based on 5-year age group, sex, Charlson comorbidity index, and vaccination status. The outcomes included COVID-19 infection, COVID-19-related hospitalisation and COVID-19-related death. For Objective 2, we extracted individuals who had a diagnosis of substance abuse between January 1, 2016, and January 1, 2022. Those who tested positive for COVID-19 between April 1, 2020, and February 28, 2023, formed the COVID-19 group, while those who never tested positive before February 28, 2023, formed the Non-COVID-19 group. Each patient in the COVID-19 group was randomly matched to patients in the Non-COVID-19 group based on 5-year age group and sex. They were followed for up to 30 days. The outcomes included hospitalisation, accident and emergency (A&E) attendance,

cardiovascular disease, mental disorders, respiratory diseases, and all-cause mortality. For objective 3, the procedure for patient's identification was similar to that in objective 2. The index date was set as 30 days after the date of COVID-19 infection. The end of follow-up period extended to August 31, 2023. For objective 4, we identified patients who tested positive for COVID-19 between April 1, 2020, and August 31, 2022. They were divided into two cohorts based on whether had a diagnosis of substance abuse (substance abuse cohort and without substance abuse cohort). Within each cohort, those who received full vaccination (two doses or above) before infection formed the fully vaccinated group, while those who had not received full vaccination formed the control group. The outcomes were similar to that in objective 2. Covariates between exposed groups and controls were adjusted using propensity score-based inverse probability treatment weighting. Cox proportional hazards regression was employed to estimate the hazard ratio (HR) of outcomes for each objective.

Results

For objective 1, for individuals with substance use compared to those without substance use, no increased risk of COVID-19 infection (Adjusted HR [95% CI]: 0.89 [0.84,0.95]) was observed, but significantly increased risks of COVID-19-related hospitalisation (Adjusted HR [95% CI]: 2.27 [1.75,2.95]) and mortality (Adjusted HR [95% CI]: 2.75 [1.18,6.42]) were identified. For objectives 2 and 3, higher short- and long-term burdens of COVID-19 were also found among substance abusers. Compared with uninfected individuals with substance abuse, individuals with both substance abuse and COVID-19 infection were consistently associated with higher risks of hospitalisation (Adjusted HR: 4.22 [95% CI: 3.46, 5.13], $p<0.001$), A&E attendance (Adjusted HR: 3.27 [95% CI: 2.77, 3.86], $p<0.001$) and all-cause mortality (Adjusted HR: 3.99 [95% CI: 1.49,10.68], $p=0.006$) during the acute phase of COVID-19. No significant difference was observed in the risk of these outcomes during the post-acute phase of COVID-19, except for pneumonia (Adjusted HR: 1.79 [95% CI: 1.09,2.94], $p = 0.02$). For objective 4, significant risk reductions were observed in two exposures among fully-vaccinated individuals with substance abuse during acute phase of COVID-19, including hospitalisation (Adjusted HR: 0.60 [95% CI: 0.45,0.81]) and A&E attendance (Adjusted HR: 0.66 [95% CI: 0.51,0.87]). Similar risk reductions were observed but insignificant among fully-vaccinated individuals with substance abuse during post-acute phase of COVID-19. Among fully-vaccinated individuals without substance abuse, significant risk reductions were observed among hospitalisation (Adjusted HR: 0.52 [95% CI: 0.51, 0.53]), A&E attendance (Adjusted HR: 0.72 [95% CI: 0.71, 0.73]), all-cause mortality (Adjusted HR: 0.60 [95% CI: 0.56, 0.64]),

and major cardiovascular disease (Adjusted HR: 0.79 [95% CI: 0.69, 0.92]) during acute phase of COVID-19. Similar estimates of significant risk reductions were observed among fully-vaccinated individuals without substance abuse during post-acute phase of COVID-19.

Conclusion

This study found that patients with substance abuse had higher risk of COVID-19 related adverse outcomes compared to those without substance abuse and revealed the effectiveness of vaccination on reducing COVID-19 outcomes among this population. These findings highlight the important of COVID-19 vaccination among patients with substance abuse. Given the higher short-term and long-term burden of COVID-19 in patients with substance abuse, close monitoring of these patients is required after COVID-19 infection.

Declaration

The following work has been completed by the research team at the Centre for Safe Medication Practice and Research (CSMPR), the University of Hong Kong, as the final research report for Beat Drugs Fund 220051 under the Principal Investigator Dr. Eric Yuk Fai Wan.

Ethical approval for this study was granted by the Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster (CIRB-2021-005-4, UW20-556, UW21-138 and UW21-149) and Department of Health, HK (L/M21/2021 and L/M175/2022). As our data were all anonymised without any personal identification information, no informed consent was required for the study.

We hereby declare that the research report represents our own work and that, to the best of our knowledge, it contains no material that has been previously published or written by other persons nor submitted to Beat Drugs Fund or to any other institution, except where due acknowledgement has been made in the text.

Acknowledgement

This research was supported by the Beat Drugs Fund (BDF) Regular Funding Scheme, Narcotics Division, Security Bureau, the Government of the Hong Kong Special Administrative Region.

The research team would like to express our thanks to the Department of Health, and Hospital Authority for facilitating data access.

List of tables

Table 1.	ICD-9-CM diagnosis codes related to substance abuse
Table 2.	ICD-9-CM diagnosis codes for the outcome identification
Table 3.	ICD-9-CM diagnosis codes for the identification of baseline comorbidities
Table 4.	ICD-9-CM diagnosis codes for the identification of baseline medication
Table 5.	Baseline characteristics of matched individuals with or without substance abuse before and after weighting
Table 6.	Incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Without Substance Abuse and Substance Abuse groups before and after weighting
Table 7	Sensitivity analysis for incidence rate and hazard ratio of COVID-19-related outcomes in Without Substance Abuse and Substance Abuse groups after weighting (Adjusting SMD > 0.2)
Table 8.	Subgroup analysis for incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Without Substance Abuse and Substance Abuse groups before and after weighting
Table 9.	Baseline characteristics before and after weighting (Acute phase)
Table 10.	Acute phase Incidence rate and Adjusted hazard ratio of outcomes in Non-COVID-19 and COVID-19 groups after weighting
Table 11.	Subgroup analysis for incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Non-COVID-19 and COVID-19 groups after weighting (Acute phase)
Table 12.	Sensitivity analysis for incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Non-COVID-19 and COVID-19 groups after weighting (Acute phase)
Table 13.	Baseline characteristics before and after weighting (Post-acute phase)
Table 14.	Post-acute phase Incidence rate and Adjusted hazard ratio of outcomes in Non-COVID-19 and COVID-19 groups after weighting
Table 15.	Subgroup analysis for incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Non-COVID-19 and COVID-19 groups after weighting (Post-cute phase)
Table 16.	Sensitivity analysis for incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Non-COVID-19 and COVID-19 groups after weighting (Post-acute phase)
Table 17a.	Baseline characteristics for Substance Abuse cohort before and after matching (Acute phase)
Table 17b.	Baseline characteristics for Substance Abuse cohort before and after matching (Post-acute phase)
Table 17c.	Baseline characteristics for Without Substance Abuse cohort before and after matching (Acute phase)
Table 17d.	Baseline characteristics for Without Substance Abuse cohort before and after matching (Post-acute phase)
Table 18.	Vaccine effectiveness of full vaccination of COVID-19 Vaccine against COVID-19 outcomes during acute phase

Table 19. Vaccine effectiveness of full vaccination of COVID-19 Vaccine against COVID-19 outcomes during post-acute phase

List of figures

Figure 1. The structure and process of included data
Figure 2. Flowchart of selection procedure for objective 1
Figure 3. Flowchart of selection procedure for objective 2
Figure 4. Flowchart of selection procedure for objective 3
Figure 5. Flowchart of selection procedure for objective 4

List of abbreviations

A&E	Accident and Emergency
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CHP	Centre of Health Protection
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CVD	Cardiovascular Diseases
DH	Department of Health
DM	Diabetes mellitus
HA	Hospital Authority
HR	Hazard Ratio
ICD-9-CM	International Classification of Diseases Ninth Edition-Clinical Modification
NA	Not Applicable
PCR	Polymerase Chain Reaction
RAT	Rapid Antigen Test
SA	Substance Abuse
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SMD	Standard Mean Difference
VE	Vaccination Effectiveness

Chapter 1 Introduction

Substance abuse can significantly increase the risk for infection and prognosis, potentially leading to more severe and longer lasting illnesses. Concurrently, the coronavirus disease 2019 (COVID-19) contributes to higher morbidity and mortality rates. Substance abusers may face heightened health risks due to compromised immune systems and co-occurring medical conditions. The robust evidence showed that substance abuse results in greater susceptibility to infection, more severe and longer lasting illness, and lower levels of protective antibodies in the blood [1, 2]. Likewise, pulmonary and respiratory involvement may lead patients with substance abuse particularly vulnerable to the adverse respiratory effects of COVID-19 as it accounts for a major part of illicit drug-related morbidities [3, 4]. This effect of substance abuse on respiratory diseases was also reflected by the higher risk of hospitalisation and ventilator use among COVID-19 patients with substance use [5, 6].

Despite the pulmonary involvement, several extrapulmonary organs including the cardiovascular system may also be affected by substance abuse as substance use were found to have a higher risk of having prevalent cardiovascular disease [7]. Considering that cardiovascular complications are well-documented outcomes in both short- and long-term COVID-19 [8, 9], compromised cardiovascular function in individuals with substance abuse may accelerate the rate of acquiring such outcomes if infected with COVID-19. The effects of substance abuse were also found to be reciprocal. As individuals with substance abuse are more prone to infection, more severe and longer lasting illnesses, their risk of developing long-term COVID may also increase. Clear association between prolonged COVID-19 symptoms and premorbid health was established in a UK study conducting parallel analyses of the pooled data from multiple population-based longitudinal studies and electronic health records [10]. Nonetheless, despite the tremendous amount of data contributed to the knowledge pool of short- and long-term COVID-19, the underrepresentation of individuals with substance abuse in the study samples adds very little to current understanding.

Furthermore, although vaccination has proven effective against COVID-19 infection as well as hospitalisation, ICU admission, and mortality [11, 12], its effect on post-acute outcomes of COVID-19 is little known due to the inconsistent findings. A large study that analysed self-reported data from 1.2 million UK smartphone users found that two doses of a COVID-19 vaccine halved the risk of long-term COVID-19 [13], contrasting to another study concluded

effectiveness of COVID-19 vaccines against the risk of long-term COVID after infection [14] and a study analysing electronic health records that found no effect of vaccination on long-term COVID-19 at all [15]. The findings from these studies conducted in the general population may not translate to the individuals with substance abuse in particular, leaving this patient population unexplored and unprotected.

The existing literature base is narrow and most did not state clearly the proportion of individuals with substance abuse, impeding mechanistic understanding and intervention and evidence-based service planning. Given the aforementioned higher risk of COVID-19 infection and related complications among individuals with substance abuse, it is important to evaluate vaccine effectiveness against short- and long-term COVID-19 in this patient population for early intervention. Therefore, we propose a population-based study that includes patients with electronic health records stored in the Clinical Management System for Hospital Authority (HA) in Hong Kong to assess the magnitude of short- and long-term impact of COVID-19 on individuals with substance abuse. This study aims to evaluate the prevalence of long COVID and determine the vaccine effectiveness against risk of long COVID among individuals with substance abuse.

Chapter 2 Aim and objectives

2.1 Aim

The overall aim of this study is to determine the impact of substance abuse on COVID-19 infection, both short- and long-term COVID-19, as well as its interaction with the vaccine effectiveness against COVID-19 and related outcomes.

2.2 Objectives

1. To investigate the risk of COVID-19 infection in individuals with substance abuse;
2. To evaluate the short-term burden of COVID-19 in individuals with substance abuse;
3. To assess the long-term burden of COVID-19 in individuals with substance abuse;
4. To compare vaccine effectiveness among vaccinated individuals with or without substance abuse.

Chapter 3 Methodology

3.1 Research ethics

Each patient was assigned an anonymous identification number to protect patient confidentiality and facilitate data retrieval. Data were de-identified and only pooled data were reported. Data were securely stored via a password-protected server, accessible only by authorised research personnel.

There was no active recruitment of subjects nor direct patient contact for the study, as data had already been collected through electronic health records from the Department of Health and the Hospital Authority. No informed consent was required for the study.

Ethical approval for this study was granted by the Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster (CIRB-2021-005-4, UW20-556, UW21-138 and UW21-149) and Department of Health, HK (L/M21/2021 and L/M175/2022).

3.2 Data source

Territory-wide vaccination records from the Department of Health (DH) and COVID-19 confirmed case records from the Centre of Health Protection (CHP) of the Hong Kong Government were used in current study. These databases were linked with electronic health records provided by the HA, by matching the anonymised unique patient identifiers. The structure and the process of linking of these databases are shown in Figure 1. The matched database contains essential information for all vaccination records in Hong Kong and all confirmed COVID-19 cases, based on both mandatory and voluntary reporting of positive Polymerase Chain Reaction (PCR) and Rapid Antigen Test (RAT) test results. This big linked cohort has been applied in over 50 high-quality published studies related to the vaccine safety and effectiveness of COVID-19 vaccine [16-23].

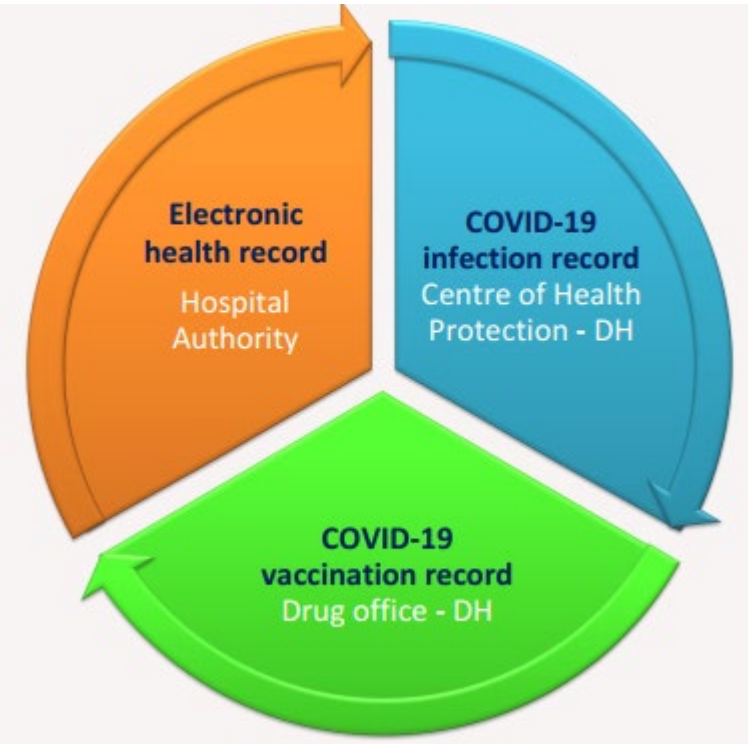

Figure 1. The structure and process of included data

3.2.1 Vaccination records from the DH

Vaccination records in this study were obtained from a COVID-19 database from the Drug Office of DH (Figure 1) in Hong Kong, which documented COVID-19 vaccination details linked by unique identifiers. The details include demographic and relevant medical information, including sex, date of birth, vaccine type and name as well as vaccination dates and locations [24].

3.2.2 COVID-19 confirmed case from the CHP

The record of COVID-19 confirmed case in our study were extracted from the CHP. The CHP in Hong Kong maintains a database of confirmed COVID-19 cases, which includes both mandatory and voluntary reporting of positive PCR and RAT results. PCR tests and RAT kits, as affordable tools for COVID-19 infection testing, are widely used during the outbreak. The Government also distributes free RAT kits occasionally, and families often keep test kits at home to use in case of a suspected infection of household members. Individuals who test positive using RAT are required to report to the CHP. At earlier stages of the outbreak, a mandatory PCR test would follow to confirm the case.

3.2.3 Electronic health record from the HA

The Hospital Authority is the regulatory body for all public hospitals in HK, which include 43 hospitals and institutions, 49 specialist Out-patient Clinics, and 74 general Out-patient Clinics. Clinicians and related healthcare professionals have received training on using the electronic health records to record clinical information and patient demographics. HA maintains the comprehensive electronic health records database and providing real-time updated clinical data for routine practice across all clinics and hospitals. The validity and coding accuracy of the electronic health records were evaluated and applied in previous high-quality population-based epidemiological studies [25-27].

3.3 Patient identification

3.3.1 Cohort for objective 1 (To investigate the risk of COVID-19 infection in individuals with substance abuse)

Patients, who were not tested positive for COVID-19 on or before January 1, 2022, were included in the analysis. These individuals were then divided into two groups: the exposure group and the control group. The exposure cohort was defined as people with a history of substance abuse on or before January 1, 2022, identified based on a diagnosis with an International Classification of Diseases Ninth Edition-Clinical Modification (ICD-9-CM) diagnosis code for substance abuse (Table 1), including the codes for drug-induced mental disorders, drug dependence, nondependent abuse of substances. This definition is widely adapted in the our previous studies [28, 29]. To compare the risk of COVID-19 outcomes between individuals with and without substance abuse, each individual with substance abuse was randomly matched with up to 10 individuals without a diagnosis of substance abuse before the end of follow up period and based on 5-year age group, sex, Charlson Comorbidity Index (CCI) group (<3, 3-4, 5-6, 7-8, ⩾9) and baseline vaccination status to form the non-exposure cohort. Both cohorts were followed from January 1, 2022, which is the index date, to the first date of COVID-19 infection, death, or the date of the end of follow up period (May 31, 2022), whichever occurs first.

Table 1. ICD-9-CM diagnosis codes related to substance abuse

ICD-9-CM diagnosis codes	**Descriptions**
Drug-induced mental disorders	
292	Drug-induced mental disorders
292.0	Drug withdrawal

292.1	Drug-induced psychotic disorders
292.11	Drug-induced psychotic disorder with delusions
292.12	Drug-induced psychotic disorder with hallucinations
292.2	Pathological drug intoxication
292.8	Other specified drug-induced mental disorders
292.81	Drug-induced delirium
292.82	Drug-induced persisting dementia
292.83	Drug-induced persisting amnestic disorder
292.84	Drug-induced mood disorder
292.85	Drug induced sleep disorders
292.89	Other specified drug-induced mental disorders
292.9	Unspecified drug-induced mental disorder
Drug dependence	
304	Drug dependence
304.0	Opioid type dependence
304.00	Opioid type dependence, unspecified
304.01	Opioid type dependence, continuous
304.02	Opioid type dependence, episodic
304.03	Opioid type dependence, in remission
304.1	Sedative, hypnotic or anxiolytic dependence
304.10	Sedative, hypnotic or anxiolytic dependence, unspecified
304.11	Sedative, hypnotic or anxiolytic dependence, continuous
304.12	Sedative, hypnotic or anxiolytic dependence, episodic
304.13	Sedative, hypnotic or anxiolytic dependence, in remission
304.2	Cocaine dependence
304.20	Cocaine dependence, unspecified
304.21	Cocaine dependence, continuous
304.22	Cocaine dependence, episodic
304.23	Cocaine dependence, in remission
304.3	Cannabis dependence
304.30	Cannabis dependence, unspecified
304.31	Cannabis dependence, continuous
304.32	Cannabis dependence, episodic
304.33	Cannabis dependence, in remission
304.4	Amphetamine and other psychostimulant dependence
304.40	Amphetamine and other psychostimulant dependence, unspecified
304.41	Amphetamine and other psychostimulant dependence, continuous
304.42	Amphetamine and other psychostimulant dependence, episodic
304.43	Amphetamine and other psychostimulant dependence, in remission
304.5	Hallucinogen dependence
304.50	Hallucinogen dependence, unspecified
304.51	Hallucinogen dependence, continuous
304.52	Hallucinogen dependence, episodic

304.53	Hallucinogen dependence, in remission
304.6	Other specified drug dependence
304.60	Other specified drug dependence, unspecified
304.61	Other specified drug dependence, continuous
304.62	Other specified drug dependence, episodic
304.63	Other specified drug dependence, in remission
304.7	Combinations of opioid type drug with any other drug dependence
304.70	Combinations of opioid type drug with any other drug dependence, unspecified
304.71	Combinations of opioid type drug with any other drug dependence, continuous
304.72	Combinations of opioid type drug with any other drug dependence, episodic
304.73	Combinations of opioid type drug with any other drug dependence, in remission
304.8	Combinations of drug dependence excluding opioid type drug
304.80	Combinations of drug dependence excluding opioid type drug, unspecified
304.81	Combinations of drug dependence excluding opioid type drug, continuous
304.82	Combinations of drug dependence excluding opioid type drug, episodic
304.83	Combinations of drug dependence excluding opioid type drug, in remission
304.9	Unspecified drug dependence
304.90	Unspecified drug dependence, unspecified
304.91	Unspecified drug dependence, continuous
304.92	Unspecified drug dependence, episodic
304.93	Unspecified drug dependence, in remission
Nondependent abuse of drugs	
305.2	Nondependent cannabis abuse
305.20	Cannabis abuse, unspecified
305.21	Cannabis abuse, continuous
305.22	Cannabis abuse, episodic
305.23	Cannabis abuse, in remission
305.3	Nondependent hallucinogen abuse
305.30	Hallucinogen abuse, unspecified
305.31	Hallucinogen abuse, continuous
305.32	Hallucinogen abuse, episodic
305.33	Hallucinogen abuse, in remission
305.4	Nondependent sedative, hypnotic or anxiolytic abuse
305.40	Sedative, hypnotic or anxiolytic abuse, unspecified
305.41	Sedative, hypnotic or anxiolytic abuse, continuous
305.42	Sedative, hypnotic or anxiolytic abuse, episodic
305.43	Sedative, hypnotic or anxiolytic abuse, in remission
305.5	Nondependent opioid abuse
305.50	Opioid abuse, unspecified
305.51	Opioid abuse, continuous
305.52	Opioid abuse, episodic
305.53	Opioid abuse, in remission
305.6	Nondependent cocaine abuse

305.60	Cocaine abuse, unspecified
305.61	Cocaine abuse, continuous
305.62	Cocaine abuse, episodic
305.63	Cocaine abuse, in remission
305.7	Nondependent amphetamine or related acting sympathomimetic abuse
305.70	Amphetamine or related acting sympathomimetic abuse, unspecified
305.71	Amphetamine or related acting sympathomimetic abuse, continuous
305.72	Amphetamine or related acting sympathomimetic abuse, episodic
305.73	Amphetamine or related acting sympathomimetic abuse, in remission
305.8	Nondependent antidepressant type abuse
305.80	Antidepressant type abuse, unspecified
305.81	Antidepressant type abuse, continuous
305.82	Antidepressant type abuse, episodic
305.83	Antidepressant type abuse, in remission
305.9	Nondependent other mixed or unspecified drug abuse
305.90	Other, mixed, or unspecified drug abuse, unspecified
305.91	Other, mixed, or unspecified drug abuse, continuous
305.92	Other, mixed, or unspecified drug abuse, episodic
305.93	Other, mixed, or unspecified drug abuse, in remission

3.3.2 Cohort for objective 2 (To evaluate the short-term burden of COVID-19 in individuals with substance abuse) and 3 (To assess the long-term burden of COVID-19 in individuals with substance abuse)

We retrospectively studied a cohort of individual who had a diagnosis of substance abuse on or before January 1, 2022; these individuals were identified based on a diagnosis with an International Classification of Diseases Ninth Edition-Clinical Modification (ICD-9-CM) diagnosis code for substance abuse (Table 1).

For Objective 2, individuals with substance abuse who tested for COVID-19 between April 1, 2020 and February 28, 2023 was defined as exposure cohort, and individuals with substance abuse who did not test for COVID-19 on or before February 28, 2023 was defined as the non-exposure cohort (Controls). The index date of the exposure cohort was defined as the first date of COVID-19 infection. Controls were randomly matched to each COVID-19 cases by 5-year age group and sex with the same index date assigned to individual controls of the same 5-year age group and sex as pseudo index date. Both cohorts were followed from the index date to the first date of the corresponding outcome event, death or 30 days after the index date, whichever occurs first. In addition, individuals in the Controls were censored at the date of COVID-19 infection.

For Objective 3, the procedure for patient identification was similar to that in Objective 2. The index date was set as 30 days after the date of COVID-19 infection, and the end of follow-up period was extended to August 31, 2023.

3.3.3 Cohort for objective 4 (To compare vaccine effectiveness among vaccinated individuals with or without substance abuse)

The retrospective cohort included individual who tested positive for COVID-19 on or before August 31, 2022. They were divided into two cohorts based on whether had a diagnosis of substance abuse (substance abuse cohort and without substance abuse cohort). Within each cohort, these individuals were then divided into two groups: the exposure group and the control group. The exposure cohort was defined as individual with a diagnosis of substance abuse on or before January 1, 2022, based on a diagnosis with an International Classification of Diseases Ninth Edition-Clinical Modification (ICD-9-CM) diagnosis code for substance abuse (Table 1). The index date of each individual in both groups was their first date of COVID-19 infection. COVID-19 outcomes among fully-vaccinated COVID-19 patients were compared with similar COVID-19 patients without full vaccination. Two COVID-19 vaccines were provided by the Hong Kong Government, namely BNT162b2 and CoronaVac. Patients in this study were classified into two mutually exclusive groups based on their vaccination status: (i) Without fully vaccination (unvaccinated or received one doses of BNT162b2 or CoronaVac); (ii) full vaccination (received two or more doses of BNT162b2 or CoronaVac). Vaccine recipients were defined as individuals who received the latest dose of vaccination within 180 days before the index date [30]. Based on 5-year age group, sex and baseline comorbidities, each fully vaccinated patient was randomly matched with patients without full vaccination before their infection date with a 1:1 ratio to form the non-exposure cohort. Both cohorts were followed from the date of the first COVID-19 infection, which is the index date, to the first date of the corresponding outcome event or death or the date of the end of the follow-up period (August 31, 2023), whichever occurs first.

3.4 Outcomes

For Objective 1, the outcomes included: (a) COVID-19 infection, which was defined as a positive PCR or RAT test result for coronavirus confirmed by the Centre of Health Protection of the HKSAR government; (b) COVID-19-related hospitalisation, which was defined as had

a record of hospital admission within 28 days after the first date of COVID-19 infection; (c) COVID-19-related death, which was defined as had a record of death within 28 days after the first date of COVID-19 infection.

For Objective 2-4, the primary outcomes included (a) hospitalisations, (b) A&E attendance, and (c) mortality. The secondary outcomes included (a) major cardiovascular disease (CVD), including heart failure, stroke and coronary heart disease; (b) mental disorders including depression, anxiety and suicide; (c) respiratory disease, including chronic obstructive pulmonary disease (COPD) and pneumonia. All these outcomes were defined using the ICD-9-CM classification (Table 2). The acute phase was defined as the 30 days following the initial COVID-19 infection, while the post-acute phase was defined as the period starting from the 31 day after the initial COVID-19 infection until censoring.

Table 2. ICD-9-CM diagnosis codes for the outcome identification

Descriptions	**ICD-9-CM diagnosis codes**
Major Cardiovascular Disease	36.0,36.1,398.91,402.01,402.11,402.91,404.01,404.03,404.11,404.13,404.91,404.93,410-414, 428, 430-438
Coronary artery disease	410-414, 36.0, 36.1
Heart failure	428,398.91,402.01,402.11,402.91,404.01,404.03,404.11,404.13,404.91,404.93
Stroke	430-438
Depression	296.2, 296.3, 311
Anxiety	300
Suicide	E950-E959
Chronic Obstructive Pulmonary Disease	490-496, 500-505, 506.4
Pneumonia	480-486

3.5 Statistical analysis

To further adjust for the selection bias among patients in the exposure and non-exposure groups, Inverse Probability Treatment Weighting using propensity score will be applied. The propensity score will be estimated using logistic regression with the treatment group as dependent variable and all confounders as independent variables [31]. The confounders included age, sex, CCI, pre-existing of comorbidities (Table 3), and medication use within 90 days before index date (Table 4). After weighting, the baseline characteristics will be summarised using descriptive statistics. The standard mean difference (SMD) between the exposure group and the non-exposure group will be described, and an SMD of less than 0.2 will be considered as a sufficient balance between the two groups [32].

For Objective 1, the incidence rates (per 1000 person-days) of COVID-19 infection and their corresponding 95% confidence intervals (CIs) were assessed based on their Poisson distribution. The hazard ratio (HR) and 95% CI of each outcome were estimated using Cox proportional hazard regression. The sensitivity analysis adjusting baseline characteristics with SMD > 0.2 was conducted.

For Objective 2 & 3, the incidence rates (per 1000 person-days) of the outcomes after the index date and their corresponding 95% CIs were assessed based on their Poisson distribution. When measuring the separate incidences of outcomes, the patients who had a history of a particular outcome were excluded from the corresponding analysis. The HR and 95% CI of each outcome were estimated using Cox proportional hazard regression. Considering the competing risk between death and the other outcomes, the sensitivity analysis using competing risk Cox regression by Fine and Gray method adjusted mortality as the competing risk was conducted for the evaluation of associations.

For Objective 4, the incidence rates (per 1000 person-days) of COVID-19 outcomes and their corresponding 95% CIs) were assessed based on their Poisson distribution. The HR and 95% CI of each outcome were estimated using Cox proportional hazard regression. We calculated estimates for vaccine effectiveness against clinical outcomes and all-cause mortality after the infection as 100 × (1–adjusted HR).

Two-tail tests were adopted for analysing the results from this study and a P value less than 0.05 implied a result to be statistically significant. The statistical analyses were performed using R software (RStudio, Boston, Massachusetts), and an independent crosscheck of analysis was conducted by two analysts for quality assurance.

Table 3. ICD-9-CM diagnosis codes for the identification of baseline comorbidities

Descriptions	**ICD-9-CM diagnosis codes**
Tobacco abuse	305.1
Alcohol abuse	291, 303, 305.0
Myocardial infarction	410
Congestive Heart Failure	398.91, 402.0, 402.1, 402.91, 404.0-404.03, 404.11-404.13, 404.91-404.93, 428
Peripheral vascular disease	441, 443.9, 785.4, V43.4
Cerebrovascular disease	430-438
Chronic obstructive pulmonary disease	490-496, 500-505, 506.4
Dementia	290
Paralysis	342, 344.1
Chronic renal failure	582, 585, 586, 588, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7

Major Mental Illness	295, 296.0-296.8
Mild liver disease	571.2, 571.4, 571.5, 571.6
Moderate-severe liver disease	456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8
Ulcers	531-534
Rheumatoid arthritis and other inflammatory polyarthropathies	710.0, 710.1, 710.4, 714.0, 714.1, 714.2, 714.81, 725
Malignancy	140-149, 150-159, 180-189, 170-172, 174-176, 179, 160-165,190-195, 200-208
Metastatic solid tumour	196-199
Coronary artery disease	410-414, 36.0, 36.1
Heart failure	428,398.91,402.01,402.11,402.91,404.01,404.03,404.11,404.13,404.91,404.93
Stroke	430-438
Stroke or systemic embolism	433.01-433.31, 433.81, 433.91, 434-436, 437.0, 437.1, 444, 445
Cardiovascular Disease	398.91, 401-405, 410-412, 425.4, 425.5, 425.7-425.9, 427.3, 428, 433, 434, 436-438, 453.8
Asthma	493
Hypertension	401-405, 437.2
Diabetes	250
Hyperlipidemia	272.0-272.4
Neoplasms	140-149, 190-199, 200-209
Type 2 diabetes mellitus	250.00-250.02, 250.10-250.12, 250.20-250.22, 250.30-250.32, 250.40-250.42, 250.50-250.52, 250.60-250.62, 250.70-250.72, 250.80-250.82, 250.90-250.92, T90
Respiratory diseases	416.8, 416.9, 490-496, 500-505, 506.4, 508.1-508.8

Table 4. ICD-9-CM diagnosis codes for the identification of baseline medication

Descriptions	**British National Formulary**
Renin-angiotensin-system agents	2.5.5
Beta blockers	2.4
Calcium channel blockers	2.6.2
Diuretics	2.2
Nitrates	2.6.1
Lipid lowering agents	2.12
Insulins	6.1.1
Antidiabetic drugs	6.1.2
Oral anticoagulants	2.8.2
Antiplatelets	2.9
Immunosupressants	8.2

Chapter 4 Results

4.1 Result of Objective 1 (To investigate the risk of COVID-19 infection in substance abusers)

Figure 2 shows the flowchart of selection procedure. After applying the exclusion criteria and matching, we have identified 85,085 eligible patients who tested positive for COVID-19 after January 1, 2022, where 7,740 individuals with substance abuse were randomly matched to 77,345 individuals without substance abuse in the non-exposure cohort (Table 5). The baseline characteristics before and after inverse probability treatment weighting were presented in Table 5. After weighting, the baseline characteristics were well-balanced between substance abuse and without substance abuse groups except alcohol (SMD = 0.217), pulmonary disease (SMD = 0.195), and major mental illness (SMD = 0.243). The average age was approximately 47 (SD: 14) years, the proportion of males was around 60%, and the CCI was approximately 1 (SD: 1.5) across the groups. The incidence rate and hazard ratio of COVID-19-related outcomes were presented in Table 6. The incidence rate for individuals with and without substance use are 479.16 vs. 539.63 per 1000 person-days in COVID-19 infection, 27.53 vs. 11.54 per 1000 person-days in COVID-19-related hospitalisation, and 2.54 vs. 0.95 per 1000 person-days in COVID-19-related mortality. For the adjusted HR, lower risk of COVID-19 infection (Adjusted HR [95% CI]: 0.89 [0.84,0.95]) was observed, but significantly increased risks of COVID-19-related hospitalisation (Adjusted HR [95% CI]: 2.27 [1.75,2.95]) and mortality (Adjusted HR [95% CI]: 2.75 [1.18,6.42]) were identified. In sensitivity analysis adjusting baseline characteristics with SMD > 0.2, similar estimates for risk reduction and increase were also observed (Adjusted HR for COVID-19 infection: 0.89 [95% CI: 0.84,0.95]; for COVID-19-related hospitalisation: 2.06 [95% CI: 1.54,2.74]; for COVID-19-related mortality: 2.72 [95% CI: 1.13,6.53]) (Table 7). The results of subgroup analysis for incidence rate and hazard ratio were presented in Table 8. Similar findings compared to the main analysis were observed regarding age (<65/≥65), gender, and CCI (<3/≥3).

Figure 2. Flowchart of selection procedure for objective 1

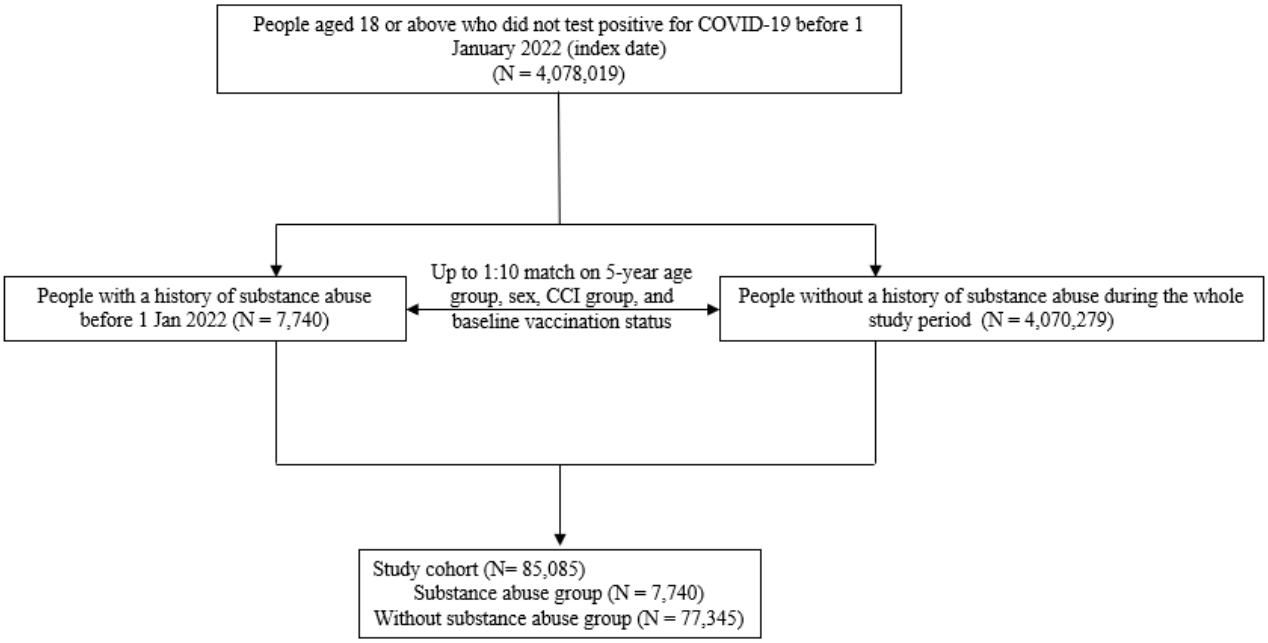
People aged 18 or above who did not test positive for COVID-19 before 1 January 2022 (index date)
(N = 4,078,019)
People with a history of substance abuse before 1 Jan 2022 (N = 7,740)
Up to 1:10 match on 5-year age group, sex, CCI group, and baseline vaccination status
People without a history of substance abuse during the whole study period (N = 4,070,279)
Study cohort (N= 85,085)
Substance abuse group (N = 7,740)
Without substance abuse group (N = 77,345)

Table 5. Baseline characteristics of matched individuals with or without substance abuse before and after weighting

	Before weighting			After weighting		
Baseline characteristics	**SA (N=7,740)**	**Without SA (N=77,345)**	**SMD**	**SA (N=7,740)**	**Without SA (N=77,345)**	**SMD**
Age, years (mean (SD))	47.17 (14.14)	47.23 (14.22)	0.005	48.32 (14.07)	46.86 (14.43)	0.102
Sex, male (%)	4556 (58.9)	45535 (58.9)	<0.001	4573.6 (59.1)	45463.0 (58.8)	0.006
Charlson Comorbidity Index (mean (SD))	0.96 (1.45)	0.92 (1.44)	0.024	1.02 (1.52)	0.91 (1.44)	0.072
Pre-existing comorbidities						
Tobacco abuse(%)	143 (1.8)	609 (0.8)	0.093	150.8 (1.9)	600.4 (0.8)	0.101
Alcohol abuse(%)	715 (9.2)	255 (0.3)	0.427	258.6 (3.3)	318.3 (0.4)	0.217
Myocardial infarction (%)	39 (0.5)	472 (0.6)	0.014	37.5 (0.5)	465.6 (0.6)	0.016
Congestive Heart Failure (%)	81 (1.0)	457 (0.6)	0.051	66.8 (0.9)	473.1 (0.6)	0.029
Cerebrovascular disease (%)	249 (3.2)	1692 (2.2)	0.064	230.6 (3.0)	1750.9 (2.3)	0.045
Chronic obstructive pulmonary disease (%)	391 (5.1)	1047 (1.4)	0.211	374.3 (4.8)	1124.6 (1.5)	0.195
Dementia (%)	25 (0.3)	87 (0.1)	0.045	20.9 (0.3)	86.9 (0.1)	0.036
Paralysis (%)	18 (0.2)	190 (0.2)	0.003	17.8 (0.2)	190.4 (0.2)	0.003
Chronic renal failure (%)	53 (0.7)	772 (1.0)	0.034	65.5 (0.8)	758.6 (1.0)	0.014
Mild liver disease (%)	54 (0.7)	116 (0.1)	0.084	47.6 (0.6)	125.2 (0.2)	0.073
Moderate-severe liver disease (%)	32 (0.4)	113 (0.1)	0.051	34.3 (0.4)	119.5 (0.2)	0.053
Ulcers (%)	139 (1.8)	614 (0.8)	0.089	139.4 (1.8)	614.0 (0.8)	0.089
Rheumatoid arthritis and other inflammatory polyarthropathies (%)	17 (0.2)	258 (0.3)	0.022	18.6 (0.2)	253.3 (0.3)	0.016
Malignancy (%)	92 (1.2)	1683 (2.2)	0.077	115.5 (1.5)	1652.5 (2.1)	0.048
Metastatic solid tumour (%)	17 (0.2)	158 (0.2)	0.003	22.0 (0.3)	161.4 (0.2)	0.015
Major cardiovascular diseases (%)	481 (6.2)	3690 (4.8)	0.063	458.5 (5.9)	3743.5 (4.8)	0.048
Coronary artery disease (%)	186 (2.4)	1852 (2.4)	0.001	194.0 (2.5)	1840.8 (2.4)	0.008
Stroke (%)	258 (3.3)	1760 (2.3)	0.064	237.8 (3.1)	1817.9 (2.4)	0.044
Heart failure (%)	83 (1.1)	476 (0.6)	0.050	69.7 (0.9)	491.9 (0.6)	0.030
Asthma (%)	226 (2.9)	680 (0.9)	0.150	146.6 (1.9)	768.3 (1.0)	0.076
Hypertension (%)	1096 (14.2)	11500 (14.9)	0.020	1152.7 (14.9)	11350.9 (14.7)	0.006
Diabetes (%)	589 (7.6)	6778 (8.8)	0.042	580.9 (7.5)	6696.4 (8.7)	0.042
Hyperlipidemia (%)	644 (8.3)	7285 (9.4)	0.039	654.9 (8.5)	7194.3 (9.3)	0.030
Cardiovascular diseases (%)	1355 (17.5)	12697 (16.4)	0.029	1349.9 (17.4)	12656.2 (16.4)	0.029
Neoplasms (%)	95 (1.2)	1735 (2.2)	0.078	119.8 (1.5)	1703.7 (2.2)	0.048
Major Mental Illness (%)	2001 (25.9)	1488 (1.9)	0.737	611.1 (7.9)	1959.8 (2.5)	0.243
Medication use within 90 days						
Renin-angiotensin-system agents (%)	611 (7.9)	8101 (10.5)	0.089	648.7 (8.4)	7983.7 (10.3)	0.067
Beta blockers (%)	896 (11.6)	5274 (6.8)	0.165	728.5 (9.4)	5338.4 (6.9)	0.092

Calcium channel blockers (%)	949 (12.3)	10187 (13.2)	0.027	976.9 (12.6)	10057.2 (13.0)	0.011
Diuretics (%)	198 (2.6)	1568 (2.0)	0.035	199.8 (2.6)	1580.4 (2.0)	0.036
Nitrates (%)	107 (1.4)	1044 (1.3)	0.003	123.3 (1.6)	1039.8 (1.3)	0.021
Lipid lowering agents (%)	933 (12.1)	10541 (13.6)	0.047	950.6 (12.3)	10428.6 (13.5)	0.036
Insulins (%)	150 (1.9)	1205 (1.6)	0.029	139.2 (1.8)	1206.3 (1.6)	0.019
Antidiabetic drugs (%)	548 (7.1)	6626 (8.6)	0.055	537.2 (6.9)	6538.4 (8.5)	0.057
Oral anticoagulants (%)	72 (0.9)	486 (0.6)	0.034	71.0 (0.9)	500.2 (0.6)	0.031
Antiplatelets (%)	430 (5.6)	3929 (5.1)	0.021	423.2 (5.5)	3924.8 (5.1)	0.018
Immunosupressants (%)	23 (0.3)	431 (0.6)	0.040	24.9 (0.3)	422.3 (0.5)	0.034
Vaccination status						
Dose status (%)			0.002			0.072
…No vaccination before	3121 (40.3)	31210 (40.4)		3304.9 (42.7)	30694.4 (39.7)	
…First dose before	382 (4.9)	3786 (4.9)		405.8 (5.2)	3716.7 (4.8)	
…Second dose before	4014 (51.9)	40140 (51.9)		3800.7 (49.1)	40774.6 (52.7)	
…Booster dose before	223 (2.9)	2209 (2.9)		228.7 (3.0)	2159.4 (2.8)	

Notes: SA = substance abuse; SMD = standard mean difference; SD = standard deviation

Table 6. Incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Without Substance Abuse and Substance Abuse groups before and after weighting

	Substance Abuse		**Without Substance Abuse**		Adjusted Hazard Ratio (95% CI)	P value
	Event	Incidence Rate† (95% CI)	Event	Incidence Rate† (95% CI)		
COVID-19 Infection	1529	479.16 (455.44,503.79)	15149	539.63 (531.07,548.29)	0.89 (0.84,0.95)	<0.001
COVID-19-related Hospitalisation	97	27.53 (22.33,33.59)	364	11.54 (10.38,12.78)	2.27 (1.75,2.95)	<0.001
COVID-19-related Mortality	9	2.54 (1.16,4.82)	30	0.95 (0.64,1.35)	2.75 (1.18,6.42)	0.019

Notes: CI = confidence interval; † per 1000 person-days

Table 7. Sensitivity analysis for incidence rate and hazard ratio of COVID-19-related outcomes in Without Substance Abuse and Substance Abuse groups after weighting (Adjusting SMD > 0.2)

	Substance Abuse		**Without Substance Abuse**		Adjusted Hazard Ratio (95% CI)	P value
	Event	Incidence Rate† (95% CI)	Event	Incidence Rate† (95% CI)		
COVID-19 Infection	1529	479.16 (455.44,503.79)	15149	539.63 (531.07,548.29)	0.89 (0.84,0.95)	<0.001
COVID-19-related Hospitalisation	97	27.53 (22.33,33.59)	364	11.54 (10.38,12.78)	2.06 (1.54,2.74)	<0.001
COVID-19-related Mortality	9	2.54 (1.16,4.82)	30	0.95 (0.64,1.35)	2.72 (1.13,6.53)	0.025

Notes: SMD = standard mean difference; CI = confidence interval; † per 1000 person-days

Table 8. Subgroup analysis for incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Without Substance Abuse and Substance Abuse groups before and after weighting

	Substance Abuse		Without Substance Abuse		Adjusted Hazard Ratio (95% CI)	P value
	Event	Incidence Rate† (95% CI)	Event	Incidence Rate† (95% CI)		
Age < 65						
COVID-19 Infection	1295	471.08 (445.77,497.45)	13353	545.11 (535.90,554.43)	0.86 (0.81,0.92)	<0.001
COVID-19-related Hospitalisation	56	18.44 (13.93,23.94)	229	8.30 (7.26,9.45)	2.02 (1.43,2.86)	<0.001
COVID-19-related Mortality	3	0.98 (0.20,2.88)	11	0.40 (0.20,0.71)	0.38 (0.10,1.38)	0.141
Age ≥ 65						
COVID-19 Infection	234	528.22 (462.70,600.41)	1796	502.10 (479.14,525.87)	1.05 (0.91,1.22)	0.5
COVID-19-related Hospitalisation	41	84.36 (60.54,114.45)	135	34.13 (28.62,40.40)	2.53 (1.73,3.69)	<0.001
COVID-19-related Mortality	6	12.15 (4.46,26.44)	19	4.77 (2.87,7.45)	2.76 (1.06,7.17)	0.037
Female						
COVID-19 Infection	526	427.99 (392.19,466.18)	6022	514.17 (501.27,527.33)	0.85 (0.77,0.94)	0.002
COVID-19-related Hospitalisation	29	21.58 (14.45,30.99)	137	10.47 (8.79,12.37)	2.30 (1.49,3.54)	<0.001
COVID-19-related Mortality	2	1.48 (0.18,5.35)	7	0.53 (0.21,1.10)	0.53 (0.11,2.53)	0.422
Male						
COVID-19 Infection	1003	510.95 (479.82,543.58)	9127	557.85 (546.46,569.42)	0.89 (0.82,0.95)	0.001
COVID-19-related Hospitalisation	68	31.21 (24.23,39.56)	227	12.30 (10.75,14.00)	1.89 (1.37,2.62)	<0.001
COVID-19-related Mortality	7	3.19 (1.28,6.58)	23	1.24 (0.79,1.86)	2.85 (1.17,6.94)	0.021
CCI < 3						
COVID-19 Infection	1253	463.39 (438.08,489.77)	13199	541.79 (532.58,551.11)	0.85 (0.79,0.91)	<0.001
COVID-19-related Hospitalisation	53	17.77 (13.31,23.24)	212	7.73 (6.72,8.84)	2.05 (1.43,2.94)	<0.001
COVID-19-related Mortality	4	1.34 (0.36,3.42)	5	0.18 (0.06,0.42)	3.52 (0.62,19.88)	0.155
CCI ⩾ 3						
COVID-19 Infection	276	565.57 (500.81,636.39)	1950	525.46 (502.40,549.32)	1.03 (0.89,1.20)	0.664
COVID-19-related Hospitalisation	44	81.48 (59.20,109.39)	152	36.89 (31.26,43.25)	2.28 (1.56,3.33)	<0.001
COVID-19-related Mortality	5	9.11 (2.96,21.25)	25	6.03 (3.90,8.89)	2.00 (0.73,5.47)	0.18

Notes: CCI = Charlson Comorbidity Index. † per 1000 person-days

4.2 Result of Objective 2 (To evaluate the short-term burden of COVID-19 in individuals with substance abuse)

Figure 3 shows the flowchart of selection procedure. In total, 7,729 patients were included after matching on 5-year age group and sex and exclusion. We identified 2,419 individuals with substance abuse who tested positive for COVID-19 between April 1, 2020 and February 28, 2023, matched with 5,310 controls. The baseline characteristics before and after inverse probability treatment weighting were presented in Table 9. The characteristics between the exposed group and unexposed group after weighting were well balanced (SMD < 0.2). The average age was approximately 47 (SD: 14) years, the proportion of males was around 60%, and the CCI was approximately 0.3 (SD: 0.8) across the groups. The incidence rate and HR with 95% CI for each of the outcomes during the acute phase among individuals with substance abuse with and without a COVID-19 diagnosis are summarised in Table 10. During the initial 30 days after the index date, infected patients displayed higher incidence rates (per 1000 person-days) in all-cause hospitalisation (1,659.22 [95% CI: 1,475.86, 1,859.06]) and A&E attendance (2,011.36 [95% CI: 1,807.27, 2,232.20]), as well as all-cause mortality (65.66 [95% CI: 34.96, 112.27)), compared with the uninfected unexposed group in both cohorts, while for secondary outcomes, there were a small number of cases (≤ 2) and no significant results were observed. Compared with uninfected individuals with substance abuse, infected patients were associated with higher risks of hospitalisation (Adjusted HR: 4.22 [95% CI: 3.46, 5.13], p<0.001), A&E attendance (Adjusted HR: 3.27 [95% CI: 2.77, 3.86], p<0.001) and all-cause mortality (Adjusted HR: 3.99 [95% CI: 1.49, 10.68], p=0.006) during the acute phase of COVID-19 (Table 10).

Table 11 provides the results from the subgroup analyses. In both cohorts, results largely consistent with the main analysis were observed for different subgroups. Moreover, patients who were older than 65 years and received less than two doses of COVID-19 vaccines were more likely to have a higher risk of hospitalisation and A&E attendance than their opposing subgroup of patients.

Table 12 summarises the results from the sensitivity analysis and these remain consistent with the main analysis.

Figure 3. Flowchart of selection procedure for objective 2

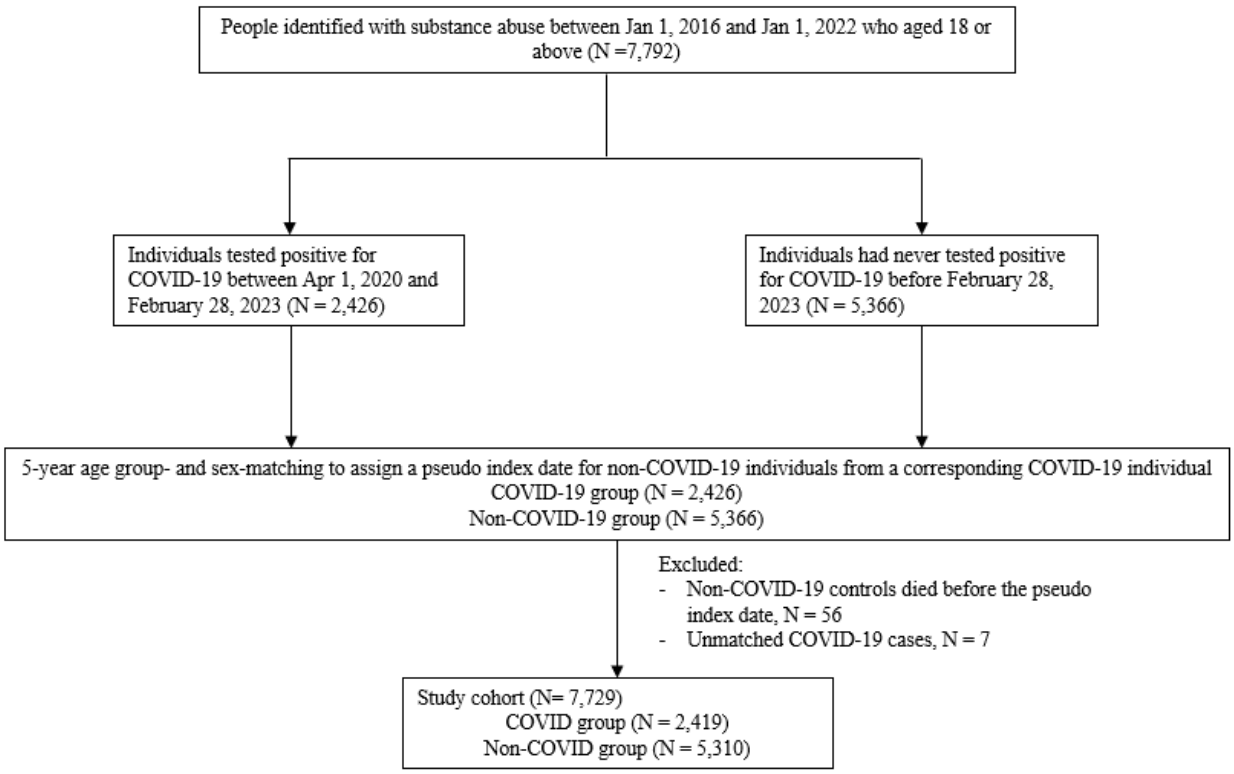

Table 9. Baseline characteristics before and after weighting (Acute phase)

	Before weighting			After weighting		
Baseline characteristics	COVID-19 (N=2,419)	Non-COVID-19 (N=5,310)	SMD	COVID-19 (N=2,419)	Non-COVID-19 (N=5,310)	SMD
Age, years (mean (SD))	46.80 (14.64)	47.31 (13.83)	0.036	47.20 (14.42)	47.12 (13.91)	0.005
Sex, male (%)	1424 (58.9)	3120 (58.8)	0.002	1423.9 (58.9)	3117.4 (58.7)	0.003
Charlson Comorbidity Index (mean (SD))	0.36 (0.88)	0.27 (0.79)	0.104	0.30 (0.81)	0.30 (0.82)	<0.001
Pre-existing comorbidities						
Tobacco abuse (%)	40 (1.7)	105 (2.0)	0.024	44.1 (1.8)	99.3 (1.9)	0.003
Alcohol abuse (%)	229 (9.5)	483 (9.1)	0.013	228.7 (9.5)	489.1 (9.2)	0.008
Myocardial infarction (%)	20 (0.8)	24 (0.5)	0.047	13.5 (0.6)	29.3 (0.6)	0.001
Congestive Heart Failure (%)	24 (1.0)	66 (1.2)	0.024	27.8 (1.2)	62.4 (1.2)	0.002
Cerebrovascular disease (%)	98 (4.1)	171 (3.2)	0.044	83.7 (3.5)	184.5 (3.5)	0.001
Chronic obstructive pulmonary disease (%)	157 (6.5)	250 (4.7)	0.078	129.4 (5.3)	281.2 (5.3)	0.002
Dementia (%)	14 (0.6)	16 (0.3)	0.042	9.7 (0.4)	19.7 (0.4)	0.005
Paralysis (%)	5 (0.2)	14 (0.3)	0.012	5.6 (0.2)	12.7 (0.2)	0.002
Chronic renal failure (%)	31 (1.3)	29 (0.5)	0.077	19.2 (0.8)	39.6 (0.7)	0.005
Mild liver disease (%)	25 (1.0)	29 (0.5)	0.055	16.7 (0.7)	35.2 (0.7)	0.003
Moderate-severe liver disease (%)	9 (0.4)	27 (0.5)	0.021	10.4 (0.4)	25.7 (0.5)	0.008
Ulcers (%)	62 (2.6)	87 (1.6)	0.065	46.4 (1.9)	102.4 (1.9)	0.001
Rheumatoid arthritis and other inflammatory polyarthropathies (%)	6 (0.2)	11 (0.2)	0.009	5.9 (0.2)	11.6 (0.2)	0.005
Malignancy (%)	37 (1.5)	68 (1.3)	0.021	32.3 (1.3)	71.7 (1.3)	0.001
Metastatic solid tumour (%)	7 (0.3)	14 (0.3)	0.005	6.3 (0.3)	14.5 (0.3)	0.002
Major Cardiovascular Diseases (%)	175 (7.2)	338 (6.4)	0.035	160.8 (6.6)	351.9 (6.6)	0.001
Coronary artery disease (%)	66 (2.7)	132 (2.5)	0.015	59.9 (2.5)	139.0 (2.6)	0.009
Stroke (%)	99 (4.1)	178 (3.4)	0.039	84.5 (3.5)	191.0 (3.6)	0.006
Heart failure (%)	24 (1.0)	69 (1.3)	0.029	27.8 (1.2)	65.8 (1.2)	0.008
Asthma (%)	80 (3.3)	155 (2.9)	0.022	73.3 (3.0)	163.1 (3.1)	0.002
Hypertension (%)	377 (15.6)	753 (14.2)	0.039	357.2 (14.8)	780.5 (14.7)	0.002
Diabetes (%)	233 (9.6)	396 (7.5)	0.078	197.1 (8.1)	432.8 (8.2)	<0.001
Hyperlipidemia (%)	246 (10.2)	454 (8.5)	0.056	220.5 (9.1)	485.5 (9.1)	0.001
Cardiovascular diseases (%)	468 (19.3)	930 (17.5)	0.047	442.2 (18.3)	963.5 (18.1)	0.004
Neoplasms (%)	39 (1.6)	70 (1.3)	0.024	34.7 (1.4)	73.6 (1.4)	0.004
Major Mental Illness (%)	662 (27.4)	1376 (25.9)	0.033	634.8 (26.2)	1404.2 (26.4)	0.005
Medication use within 90 days						
Renin-angiotensin-system agents (%)	211 (8.7)	415 (7.8)	0.033	190.5 (7.9)	429.5 (8.1)	0.008
Beta blockers (%)	315 (13.0)	588 (11.1)	0.060	284.1 (11.7)	621.5 (11.7)	0.001
Calcium channel blockers (%)	338 (14.0)	593 (11.2)	0.085	290.6 (12.0)	638.2 (12.0)	<0.001
Diuretics (%)	65 (2.7)	133 (2.5)	0.011	61.6 (2.5)	136.5 (2.6)	0.002
Nitrates (%)	45 (1.9)	73 (1.4)	0.038	35.8 (1.5)	81.9 (1.5)	0.005
Lipid lowering agents (%)	338 (14.0)	633 (11.9)	0.061	311.7 (12.9)	668.3 (12.6)	0.009
Insulins (%)	56 (2.3)	91 (1.7)	0.043	47.7 (2.0)	102.5 (1.9)	0.003

Antidiabetic drugs (%)	211 (8.7)	369 (6.9)	0.066	183.0 (7.6)	400.0 (7.5)	0.001
Oral anticoagulants (%)	32 (1.3)	47 (0.9)	0.042	23.6 (1.0)	52.1 (1.0)	<0.001
Antiplatelets (%)	161 (6.7)	277 (5.2)	0.061	138.1 (5.7)	300.3 (5.7)	0.002
Immunosupressants (%)	14 (0.6)	9 (0.2)	0.067	8.1 (0.3)	13.6 (0.3)	0.015
Vaccination status			0.080			0.008
Dose status (%)	219 (9.1)	509 (9.6)		226.9 (9.4)	493.3 (9.3)	
…No vaccination before	260 (10.7)	586 (11.0)		265.4 (11.0)	578.7 (10.9)	
…First dose before	857 (35.4)	1797 (33.8)		834.6 (34.5)	1832.1 (34.5)	
…Second dose before	965 (39.9)	2230 (42.0)		997.9 (41.3)	2191.4 (41.3)	
…Booster dose before	118 (4.9)	188 (3.5)		94.2 (3.9)	214.5 (4.0)	

Notes: SMD = standard mean difference; SD = standard deviation

Table 10. Acute phase Incidence rate and Adjusted hazard ratio of outcomes in Non-COVID-19 and COVID-19 groups after weighting

	COVID-19		**Non-COVID-19**			
	Event	Incidence Rate† (95% CI)	Event	Incidence Rate† (95% CI)	Adjusted hazard ratio (95% CI)	P-value
Hospitalisations	297	1,659.22 (1,475.86,1,859.06)	156	362.79 (308.09,424.40)	4.22 (3.46,5.13)	<0.001
A&E attendance	354	2,011.36 (1,807.27,2,232.20)	248	582.16 (511.95,659.30)	3.27 (2.77,3.86)	<0.001
All-cause mortality	13	65.66 (34.96,112.27)	6	13.76 (5.05,29.95)	3.99 (1.49,10.68)	0.006
Major Cardiovascular Disease	1	5.43 (0.14,30.28)	2	4.90 (0.59,17.71)	1.20 (0.11,13.31)	0.88
Coronary artery disease	1	5.18 (0.13,28.87)	1	2.35 (0.06,13.11)	2.18 (0.14,34.74)	0.582
Heart failure	1	5.10 (0.13,28.43)	1	2.33 (0.06,12.96)	2.68 (0.17,42.89)	0.485
Stroke	1	5.26 (0.13,29.32)	0	0 (NA)	NA	NA
Depression	0	0 (NA)	1	2.91 (0.07,16.20)	NA	NA
Anxiety	0	0 (NA)	0	0 (NA)	NA	NA
Suicide	0	0 (NA)	0	0 (NA)	NA	NA
COPD	0	0 (NA)	0	0 (NA)	NA	NA
Pneumonia	2	10.87 (1.32,39.26)	0	0 (NA)	NA	NA

Notes: CI = confidence interval; A&E = Accident and Emergency; COPD = Chronic obstructive pulmonary disease; NA = Not applicable; † per 1000 person-days

Table 11. Subgroup analysis for incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Non-COVID-19 and COVID-19 groups after weighting (Acute phase)

	Sex				
	Female		**Male**		P value for interaction
	Events	Adjusted hazard ratio (95% CI)	Events	Adjusted hazard ratio (95% CI)	
Hospitalisation	112	3.37 (2.50,4.54)	185	4.99 (3.83,6.51)	0.055
A&E attendance	134	2.73 (2.11,3.52)	220	3.73 (3.00,4.63)	0.07
All-cause mortality	2	3.52 (0.32,39.04)	11	4.06 (1.38,11.93)	0.916
Major Cardiovascular Disease	0	NA	1	1.21 (0.11,13.32)	0.879
Coronary artery disease	0	NA	1	NA	NA
Heart failure	0	NA	1	NA	NA
Stroke	0	NA	1	NA	NA
Depression	0	NA	0	NA	NA
Anxiety	0	NA	0	NA	NA
Suicide	0	NA	0	NA	NA
COPD	0	NA	0	NA	NA
Pneumonia	1	NA	1	NA	NA
	Age				
	< 65 years old		**⩾65 years old**		P value for interaction
	Events	Adjusted hazard ratio (95% CI)	Events	Adjusted hazard ratio (95% CI)	
Hospitalisation	205	3.52 (2.82,4.40)	92	7.54 (4.83,11.78)	0.003
A&E attendance	269	2.82 (2.36,3.38)	85	6.83 (4.40,10.61)	<0.001
All-cause mortality	4	1.66 (0.41,6.72)	9	7.93 (1.69,37.23)	0.142
Major Cardiovascular Disease	0	NA	1	2.31 (0.15,36.63)	NA
Coronary artery disease	0	NA	1	NA	NA
Heart failure	0	NA	1	NA	NA
Stroke	0	NA	1	NA	NA
Depression	0	NA	0	NA	NA
Anxiety	0	NA	0	NA	NA
Suicide	0	NA	0	NA	NA
COPD	0	NA	0	NA	NA
Pneumonia	1	NA	1	NA	NA
	Vaccination status				
	< 2 dose		**⩾ 2 doses**		P value for interaction
	Events	Adjusted hazard ratio (95% CI)	Events	Adjusted hazard ratio (95% CI)	
Hospitalisation	100	6.88 (4.62,10.23)	197	3.51 (2.79,4.42)	0.004
A&E attendance	113	5.88 (4.16,8.30)	241	2.70 (2.23,3.27)	<0.001
All-cause mortality	7	3.76 (0.96,14.77)	6	4.21 (1.02,17.31)	0.912
Major Cardiovascular Disease	0	1.00 (0.89,1.12)	1	1.20 (0.11,13.24)	0.884
Coronary artery disease	0	NA	1	NA	NA
Heart failure	0	NA	1	NA	NA
Stroke	0	NA	1	NA	NA
Depression	0	NA	0	NA	NA
Anxiety	0	NA	0	NA	NA
Suicide	0	NA	0	NA	NA
COPD	0	NA	0	NA	NA
Pneumonia	0	NA	0	NA	NA
	CCI group				

	CCI < 3		CCI ⩾3		P value for interaction
	Events	Adjusted hazard ratio (95% CI)	Events	Adjusted hazard ratio (95% CI)	
Hospitalisation	272	4.50 (3.66,5.54)	25	2.54 (1.36,4.75)	0.089
A&E attendance	333	3.35 (2.83,3.98)	21	2.32 (1.17,4.61)	0.308
All-cause mortality	11	4.30 (1.47,12.61)	2	2.83 (0.26,31.36)	0.755
Major Cardiovascular Disease	1	1.20 (0.11,13.31)	0	1.00 (0.66,1.52)	0.882
Coronary artery disease	1	NA	0	NA	NA
Heart failure	1	NA	0	NA	NA
Stroke	0	NA	1	NA	NA
Depression	0	NA	0	NA	NA
Anxiety	0	NA	0	NA	NA
Suicide	0	NA	0	NA	NA
COPD	0	NA	0	NA	NA
Pneumonia	2	NA	0	NA	NA

Notes: CI = confidence interval; A&E = Accident and Emergency; COPD = Chronic obstructive pulmonary disease; CCI = Charlson Comorbidity Index; NA = Not applicable

Table 12. Sensitivity analysis for incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Non-COVID-19 and COVID-19 groups after weighting (Acute phase)

Changing the duration of the acute phase to 21 days		
	Adjusted hazard ratio (95% CI)	P-value
Hospitalisations	5.19 (4.14,6.49)	<0.001
A&E attendance	3.76 (3.12,4.52)	<0.001
All-cause mortality	4.65 (1.61,13.41)	0.004
Major Cardiovascular Disease	2.18 (0.14,34.80)	0.581
Coronary artery disease	2.18 (0.14,34.74)	0.582
Heart failure	NA	NA
Stroke	NA	NA
Depression	NA	NA
Anxiety	NA	NA
Suicide	NA	NA
COPD	NA	NA
Pneumonia	NA	NA
Considering all-cause mortality as the competing risk		
	Adjusted hazard ratio (95% CI)	P-value
Hospitalisation	4.21 (3.46,5.13)	<0.001
A&E attendance	3.27 (2.77,3.86)	<0.001
Major Cardiovascular Disease	1.20 (0.11,13.30)	0.881
Coronary artery disease	2.17 (0.14,34.75)	0.583
Heart failure	2.68 (0.17,42.77)	0.486
Stroke	NA	NA
Depression	NA	NA
Anxiety	NA	NA
Suicide	NA	NA
COPD	NA	NA
Pneumonia	NA	NA

Notes: CI = confidence interval; A&E = Accident and Emergency; COPD = Chronic obstructive pulmonary disease; NA = Not applicable;

4.3 Result of Objective 3 (To assess the long-term burden of COVID-19 in individuals with substance abuse)

Figure 4 shows the flowchart of selection procedure. In total, 7,706 patients were included after matching on 5-year age group and sex and exclusion. We identified 2,405 individuals with substance abuse who tested positive for COVID-19 between April 1, 2020 and February 28, 2023 and survived 30 days after the infection, matched with 5,301 controls. The average age was approximately 47 (SD: 14) years, the proportion of males was around 60%, and the CCI was approximately 0.3 (SD: 0.8) across the groups. The baseline characteristics before and after inverse probability treatment weighting were presented in Table 13. The characteristics between the exposed group and unexposed group after weighting were well balanced (SMD < 0.2).

The incidence rate and HR with 95% CI for each of the outcomes among patients with and without a COVID-19 diagnosis, 30 days after infection, are summarised in Table 14. High incidence rates (per 1000 person-days) in hospitalisation (COVID-19 group: 321.78 [95% CI: 296.99,348.09], non-COVID-19 group: 296.34 [95% CI: 281.16,312.13]) and A&E attendance (COVID-19 group: 520.66 [95% CI: 486.86,556.19], non-COVID-19 group: 479.28 [95% CI: 458.80,500.44]) were observed in both cohorts. However, no significant difference was observed in the risk of these outcomes during the post-acute phase of COVID-19, except for pneumonia (Adjusted HR: 1.79 [95% CI: 1.09,2.94], p = 0.02).

Table 15 provides the results from the subgroup analyses. In both cohorts, results largely consistent with the main analysis were observed for different subgroups. The subgroup analysis did not find any statistically significant subgroup effects based on sex (female versus male), age (<65 years versus ≥65 years), vaccination status (< 2 doses versus ≥ 2 doses), or CCI (CCI < 3 versus CCI ≥3), except that patients who received less than two doses of COVID-19 vaccines were more likely to have a higher risk of hospitalisation than those received two or more doses. Table 16 summarise the results from the sensitivity analysis and these remain consistent with the main analysis.

Figure 4. Flowchart of selection procedure for objective 3

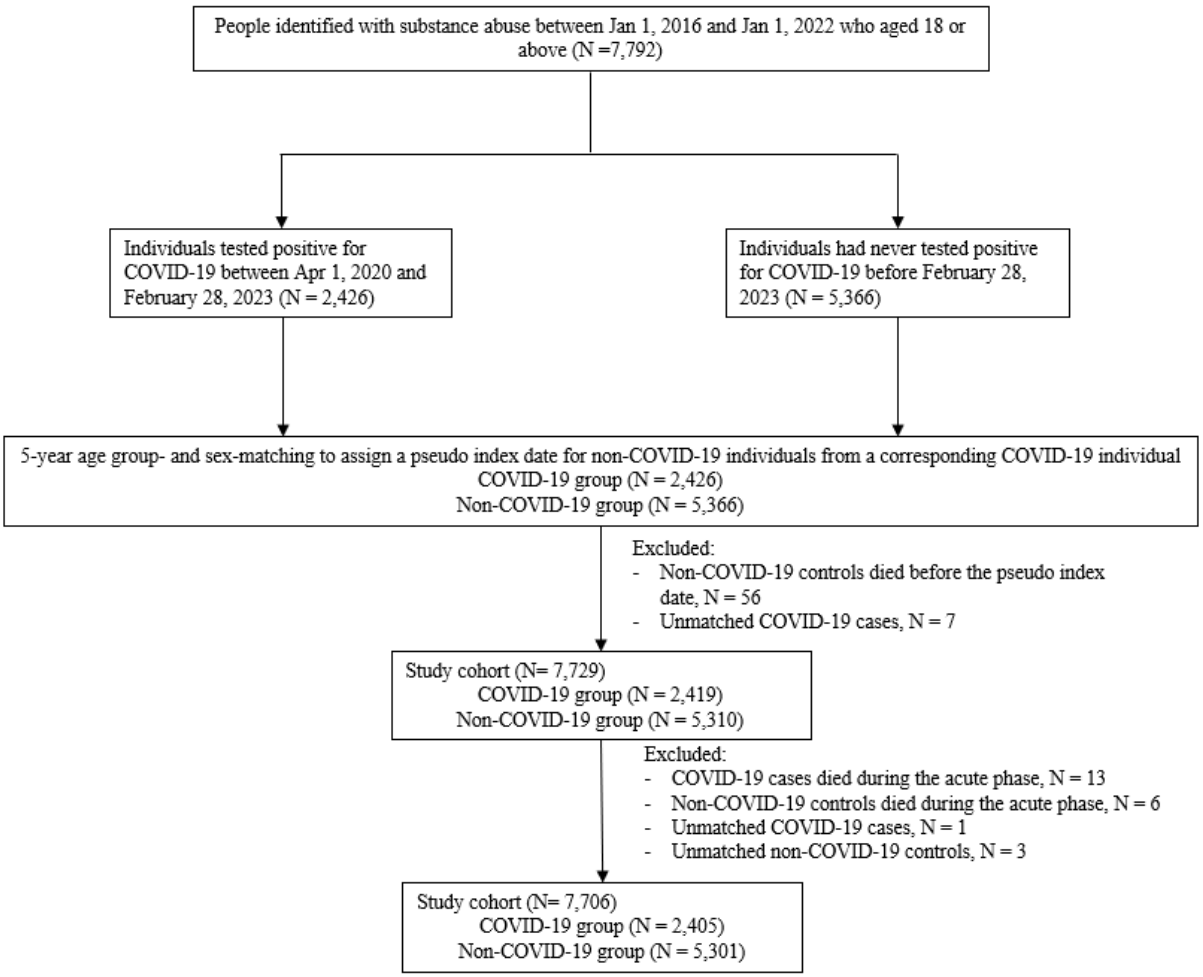

Table 13. Baseline characteristics before and after weighting (Post-acute phase)

	Before weighting			After weighting		
Baseline characteristics	COVID-19 (N=2,405)	Non-COVID-19 (N=5,301)	SMD	COVID-19 (N=2,405)	Non-COVID-19 (N=5,301)	SMD
Age, years (mean (SD))	46.66 (14.54)	47.27 (13.81)	0.043	47.16 (14.39)	47.06 (13.86)	0.007
Sex, male (%)	1412 (58.7)	3113 (58.7)	<0.001	1417.7 (58.9)	3103.2 (58.5)	0.008
Charlson Comorbidity Index (mean (SD))	0.35 (0.88)	0.27 (0.79)	0.099	0.30 (0.81)	0.29 (0.81)	0.002
Pre-existing comorbidities						
Tobacco abuse (%)	39 (1.6)	105 (2.0)	0.027	45.2 (1.9)	99.5 (1.9)	<0.001
Alcohol abuse (%)	228 (9.5)	483 (9.1)	0.013	227.0 (9.4)	490.2 (9.2)	0.007
Myocardial infarction (%)	19 (0.8)	23 (0.4)	0.046	12.8 (0.5)	27.3 (0.5)	0.003
Congestive Heart Failure (%)	23 (1.0)	65 (1.2)	0.026	25.8 (1.1)	61.4 (1.2)	0.008
Cerebrovascular disease (%)	97 (4.0)	171 (3.2)	0.043	80.8 (3.4)	184.0 (3.5)	0.006
Chronic obstructive pulmonary disease (%)	153 (6.4)	249 (4.7)	0.073	129.1 (5.4)	276.4 (5.2)	0.007
Dementia (%)	11 (0.5)	16 (0.3)	0.025	9.3 (0.4)	17.9 (0.3)	0.008
Paralysis (%)	5 (0.2)	14 (0.3)	0.012	5.1 (0.2)	13.2 (0.2)	0.007
Chronic renal failure (%)	30 (1.2)	29 (0.5)	0.074	18.7 (0.8)	38.7 (0.7)	0.006
Mild liver disease (%)	25 (1.0)	29 (0.5)	0.056	16.7 (0.7)	33.9 (0.6)	0.007
Moderate-severe liver disease (%)	9 (0.4)	27 (0.5)	0.020	10.1 (0.4)	25.7 (0.5)	0.009
Ulcers (%)	60 (2.5)	85 (1.6)	0.063	44.3 (1.8)	100.2 (1.9)	0.004
Rheumatoid arthritis and other inflammatory polyarthropathies (%)	6 (0.2)	11 (0.2)	0.009	6.0 (0.2)	11.8 (0.2)	0.005
Malignancy (%)	37 (1.5)	67 (1.3)	0.023	32.7 (1.4)	71.5 (1.3)	0.001
Metastatic solid tumour (%)	7 (0.3)	14 (0.3)	0.005	6.7 (0.3)	13.9 (0.3)	0.003
Major Cardiovascular diseases (%)	172 (7.2)	335 (6.3)	0.033	152.4 (6.3)	347.4 (6.6)	0.009
Coronary artery disease (%)	64 (2.7)	130 (2.5)	0.013	55.9 (2.3)	135.5 (2.6)	0.015
Stroke (%)	98 (4.1)	178 (3.4)	0.038	81.5 (3.4)	190.6 (3.6)	0.011
Heart failure (%)	23 (1.0)	68 (1.3)	0.031	25.8 (1.1)	64.8 (1.2)	0.014
Asthma (%)	79 (3.3)	155 (2.9)	0.021	74.4 (3.1)	161.6 (3.0)	0.003
Hypertension (%)	373 (15.5)	751 (14.2)	0.038	352.5 (14.7)	780.4 (14.7)	0.002
Diabetes (%)	229 (9.5)	395 (7.5)	0.074	197.7 (8.2)	432.9 (8.2)	0.002
Hyperlipidemia (%)	244 (10.1)	454 (8.6)	0.054	216.1 (9.0)	485.9 (9.2)	0.006
Cardiovascular diseases (%)	463 (19.3)	926 (17.5)	0.046	431.8 (18.0)	961.7 (18.1)	0.005
Neoplasms (%)	39 (1.6)	69 (1.3)	0.027	34.8 (1.4)	73.3 (1.4)	0.005
Major Mental Illness (%)	655 (27.2)	1375 (25.9)	0.029	631.4 (26.3)	1398.4 (26.4)	0.003
Medication use within 90 days						
Renin-angiotensin-system agents (%)	206 (8.6)	413 (7.8)	0.028	189.1 (7.9)	426.4 (8.0)	0.007
Beta blockers (%)	313 (13.0)	587 (11.1)	0.060	281.3 (11.7)	622.3 (11.7)	0.001
Calcium channel blockers (%)	334 (13.9)	590 (11.1)	0.083	289.1 (12.0)	635.5 (12.0)	0.001
Diuretics (%)	63 (2.6)	130 (2.5)	0.011	59.1 (2.5)	132.7 (2.5)	0.003
Nitrates (%)	43 (1.8)	73 (1.4)	0.033	34.9 (1.5)	78.7 (1.5)	0.003
Lipid lowering agents (%)	332 (13.8)	631 (11.9)	0.057	304.2 (12.6)	667.2 (12.6)	0.002
Insulins (%)	55 (2.3)	90 (1.7)	0.042	46.1 (1.9)	100.1 (1.9)	0.002
Antidiabetic drugs (%)	207 (8.6)	369 (7.0)	0.061	184.3 (7.7)	401.0 (7.6)	0.004
Oral anticoagulants (%)	30 (1.2)	47 (0.9)	0.035	23.1 (1.0)	52.5 (1.0)	0.003
Antiplatelets (%)	157 (6.5)	275 (5.2)	0.057	131.7 (5.5)	296.5 (5.6)	0.005
Immunosupressants (%)	14 (0.6)	9 (0.2)	0.067	8.2 (0.3)	13.9 (0.3)	0.015

Vaccination status			0.082		0.011
Dose status (%)	219 (9.1)	508 (9.6)	226.7 (9.4)	493.6 (9.3)	
…No vaccination before	253 (10.5)	583 (11.0)	258.9 (10.8)	577.5 (10.9)	
…First dose before	855 (35.6)	1796 (33.9)	823.8 (34.3)	1831.2 (34.5)	
…Second dose before	960 (39.9)	2226 (42.0)	1000.8 (41.6)	2184.0 (41.2)	
…Booster dose before	118 (4.9)	188 (3.5)	94.7 (3.9)	214.8 (4.1)	

Notes: SMD = standard mean difference; SD = standard deviation

Table 14. Post-acute phase Incidence rate and Adjusted hazard ratio of outcomes in Non-COVID-19 and COVID-19 groups after weighting

	COVID		Non-COVID			
	Event	Incidence Rate† (95% CI)	Event	Incidence Rate† (95% CI)	Adjusted hazard ratio (95% CI)	P-value
Hospitalisations	622	321.78 (296.99,348.09)	1426	296.34 (281.16,312.13)	1.04 (0.95,1.15)	0.386
A&E attendance	882	520.66 (486.86,556.19)	2059	479.28 (458.80,500.44)	1.05 (0.96,1.13)	0.281
All-cause mortality	55	20.48 (15.43,26.66)	92	15.55 (12.54,19.07)	1.18 (0.84,1.66)	0.351
Major Cardiovascular Disease	16	6.44 (3.68,10.46)	28	5.06 (3.36,7.31)	1.20 (0.64,2.25)	0.58
Coronary artery disease	3	1.15 (0.24,3.35)	7	1.21 (0.49,2.50)	0.91 (0.23,3.59)	0.897
Heart failure	10	3.77 (1.81,6.93)	9	1.54 (0.70,2.93)	2.15 (0.85,5.40)	0.105
Stroke	6	2.34 (0.86,5.09)	18	3.15 (1.87,4.98)	0.66 (0.25,1.72)	0.39
Depression	5	2.34 (0.76,5.47)	4	0.85 (0.23,2.19)	2.78 (0.74,10.51)	0.131
Anxiety	1	0.39 (0.01,2.16)	2	0.35 (0.04,1.27)	1.07 (0.10,11.81)	0.958
Suicide	0	0.00 (0.00,2.20)	0	0.00 (0.00,0.96)	NA	NA
COPD	5	1.99 (0.65,4.64)	12	2.13 (1.10,3.72)	0.92 (0.32,2.61)	0.869
Pneumonia	30	12.05 (8.13,17.21)	37	6.58 (4.63,9.07)	1.79 (1.09,2.94)	0.02

Notes: CI = confidence interval; A&E = Accident and Emergency; COPD = Chronic obstructive pulmonary disease; † per 1000 person-days

Table 15. Subgroup analysis for incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Non-COVID-19 and COVID-19 groups after weighting (Post-cute phase)

	Sex				
	Female		Male		P value for interaction
	Events	Adjusted hazard ratio (95% CI)	Events	Adjusted hazard ratio (95% CI)	
Hospitalisation	246	0.96 (0.83,1.12)	376	1.10 (0.97,1.25)	0.187
A&E attendance	357	1.00 (0.88,1.14)	525	1.08 (0.97,1.19)	0.404
All-cause mortality	16	1.40 (0.74,2.65)	39	1.09 (0.73,1.64)	0.521
Major Cardiovascular Disease	2	0.54 (0.12,2.53)	14	1.51 (0.74,3.06)	0.237
Coronary artery disease	1	2.43 (0.15,38.89)	2	0.68 (0.13,3.47)	0.439
Heart failure	1	0.49 (0.05,4.77)	9	2.99 (1.04,8.63)	0.159
Stroke	1	0.43 (0.05,3.64)	5	0.76 (0.26,2.27)	0.643
Depression	3	3.63 (0.60,22.04)	2	1.99 (0.27,14.41)	0.659
Anxiety	1	1.08 (0.10,11.97)	0	1.00 (0.93,1.07)	0.95
Suicide	0	NA	0	NA	NA
COPD	2	0.65 (0.13,3.13)	3	1.28 (0.30,5.40)	0.534
Pneumonia	9	1.46 (0.61,3.51)	21	1.98 (1.09,3.61)	0.573
	Age				
	< 65		**⩾ 65**		P value for interaction
	Events	Adjusted hazard ratio (95% CI)	Events	Adjusted hazard ratio (95% CI)	
Hospitalisation	533	1.07 (0.96,1.19)	89	0.93 (0.72,1.21)	0.342
A&E attendance	765	1.04 (0.96,1.14)	117	1.08 (0.86,1.36)	0.768
All-cause mortality	28	1.02 (0.65,1.62)	27	1.34 (0.80,2.23)	0.448
Major Cardiovascular Disease	14	1.21 (0.62,2.37)	2	1.06 (0.17,6.62)	0.892
Coronary artery disease	2	0.60 (0.12,2.97)	1	NA	NA
Heart failure	8	2.32 (0.82,6.56)	2	1.46 (0.20,10.39)	0.683

Stroke	4	0.61 (0.20,1.93)	2	0.78 (0.13,4.72)	0.825
Depression	5	3.93 (0.93,16.66)	0	NA	NA
Anxiety	1	1.08 (0.10,11.93)	0	1.00 (0.85,1.18)	0.95
Suicide	0	NA	0	NA	NA
COPD	3	0.71 (0.19,2.57)	2	1.86 (0.26,13.25)	0.419
Pneumonia	22	2.78 (1.46,5.30)	8	0.94 (0.40,2.20)	0.046

Vaccination status					
	<2 doses		**⩾2 doses**		P value for interaction
	Events	Adjusted hazard ratio (95% CI)	Events	Adjusted hazard ratio (95% CI)	
Hospitalisation	172	1.27 (1.05,1.53)	450	0.98 (0.88,1.10)	0.022
A&E attendance	197	1.08 (0.91,1.28)	685	1.04 (0.95,1.14)	0.71
All-cause mortality	24	1.84 (1.05,3.21)	31	0.91 (0.59,1.41)	0.053
Major Cardiovascular Disease	8	2.15 (0.76,6.12)	8	0.83 (0.36,1.91)	0.164
Coronary artery disease	1	0.99 (0.09,11.06)	2	0.88 (0.17,4.55)	0.933
Heart failure	5	2.57 (0.59,11.15)	5	1.87 (0.56,6.24)	0.74
Stroke	3	1.56 (0.33,7.39)	3	0.39 (0.11,1.43)	0.181
Depression	0	1.00 (0.88,1.13)	5	2.76 (0.73,10.44)	0.135
Anxiety	0	NA	1	NA	NA
Suicide	0	NA	0	NA	NA
COPD	2	1.35 (0.22,8.09)	3	0.78 (0.21,2.87)	0.626
Pneumonia	11	1.40 (0.64,3.04)	19	2.20 (1.15,4.20)	0.38

CCI group					
	CCI < 3		**CCI ⩾3**		P value for interaction
	Events	Adjusted hazard ratio (95% CI)	Events	Adjusted hazard ratio (95% CI)	
Hospitalisation	595	1.04 (0.95,1.15)	27	1.19 (0.73,1.96)	0.604
A&E attendance	851	1.04 (0.96,1.13)	31	1.19 (0.76,1.86)	0.58
All-cause mortality	46	1.10 (0.77,1.59)	9	2.19 (0.76,6.28)	0.231
Major Cardiovascular Disease	14	1.17 (0.60,2.25)	2	1.83 (0.16,20.36)	0.724
Coronary artery disease	3	0.91 (0.23,3.59)	0	1.00 (0.69,1.45)	0.9
Heart failure	8	1.85 (0.70,4.90)	2	NA	NA
Stroke	4	0.58 (0.19,1.80)	2	1.10 (0.15,7.85)	0.581
Depression	5	2.78 (0.74,10.51)	0	1.00 (0.67,1.50)	0.15
Anxiety	1	1.07 (0.10,11.79)	0	1.00 (0.69,1.44)	0.959
Suicide	0	NA	0	NA	NA
COPD	5	0.92 (0.32,2.62)	0	1.00 (0.68,1.48)	0.88
Pneumonia	25	1.63 (0.96,2.77)	5	4.51 (1.03,19.67)	0.203

Notes: CI = confidence interval; CCI = Charlson Comorbidity Index; A&E = Accident and Emergency; COPD = Chronic obstructive pulmonary disease

Table 16. Sensitivity analysis for incidence rate and Adjusted hazard ratio of COVID-19-related outcomes in Non-COVID-19 and COVID-19 groups after weighting (Post-acute phase)

Changing the duration of acute phase to 21 days		
	Adjusted hazard ratio (95% CI)	P-value
Hospitalisation	1.07 (0.98,1.18)	0.146
A&E attendance	1.07 (0.98,1.15)	0.113
All-cause mortality	1.22 (0.87,1.72)	0.249
Major Cardiovascular Disease	1.19 (0.63,2.23)	0.591
Coronary artery disease	0.87 (0.22,3.38)	0.835
Heart failure	2.05 (0.83,5.04)	0.119
Stroke	0.70 (0.26,1.83)	0.463
Depression	3.02 (0.80,11.45)	0.104
Anxiety	0.99 (0.09,10.96)	0.993
Suicide	NA	NA
COPD	1.13 (0.39,3.23)	0.825
Pneumonia	1.83 (1.11,3.02)	0.018
Considering all-cause mortality as the competing risk		
	Adjusted hazard ratio (95% CI)	P-value
Hospitalisation	1.04 (0.95,1.15)	0.38
A&E attendance	1.05 (0.97,1.14)	0.266
Major Cardiovascular Disease	1.20 (0.64,2.25)	0.576
Coronary artery disease	0.91 (0.23,3.59)	0.898
Heart failure	2.15 (0.85,5.40)	0.105
Stroke	0.66 (0.25,1.72)	0.391
Depression	2.79 (0.74,10.52)	0.13
Anxiety	1.07 (0.10,11.82)	0.958
Suicide	NA	NA
COPD	0.92 (0.32,2.62)	0.873
Pneumonia	1.80 (1.10,2.94)	0.020

Notes: CI = confidence interval; A&E = Accident and Emergency; COPD = Chronic obstructive pulmonary disease

4.4 Result of Objective 4 (To compare vaccine effectiveness among vaccinated individuals with or without substance abuse)

Figure 5 shows the flowchart of selection procedure. The baseline characteristics before and after inverse probability treatment weighting were presented based on different cohorts (substance abuse vs. without substance abuse) and different phases (acute vs. post-acute) (Table 17a – 17d). The average age in the substance abuse cohort was approximately 46 years, with a CCI of about 1.1. In contrast, the without substance abuse cohort had an average age of 54 years and a CCI of around 1.6. The proportion of males was approximately 61% in the substance abuse cohort and 45% in the without substance abuse cohort.

The vaccine effectiveness of full vaccination against COVID-19 outcomes during acute phase were presented in Table 18. The incidence rate and adjusted hazard ratio of 12 health-related exposures were examined for both substance abuse cohort and without substance abuse cohort. Significant risk reductions were observed in two exposures among fully-vaccinated individuals with substance abuse during acute phase of COVID-19, including hospitalisation (Adjusted HR: 0.60 [95% CI: 0.45,0.81]) and A&E attendance (Adjusted HR: 0.66 [95% CI: 0.51,0.87]). Similar estimates of risk reductions were observed among fully-vaccinated individuals without substance abuse, where the adjusted hazard ratios were 0.52 (95% CI: 0.51,0.53) for hospitalisation, 0.72 (95% CI: 0.71,0.73) for A&E attendance, 0.60 (0.56,0.64) for all-cause mortality, 0.79 (95% CI: 0.69,0.92) for major CVD, 0.53 (95% CI: 0.37, 0.74) for heart failure, and 0.41 (95% CI: 0.37, 0.46) for pneumonia.

The vaccine effectiveness of full vaccination against COVID-19 outcomes during post-acute phase were presented in Table 19. The incidence rate and adjusted hazard ratio of 12 health-related outcomes were examined for both substance abuse cohort and without substance abuse cohort. Significant risk reductions were observed among fully-vaccinated individuals without substance abuse, where the adjusted hazard ratio were 0.93 (95% CI: 0.92, 0.94) for hospitalisation, 0.98 (95% CI: 0.97, 0.99) for A&E attendance, 0.54 (95% CI: 0.52, 0.56) for all-cause mortality, 0.82 (95% CI: 0.78, 0.86) for major CVD, 0.60 (95% CI: 0.55, 0.66) for heart failure, and 0.83 (95% CI: 0.78, 0.89) for stroke, 0.79 (95% CI: 0.70, 0.88) for COPD, and 0.52 (95% CI: 0.49, 0.55) for pneumonia. In contrast, no significant risk reductions were observed in 12 exposures among fully-vaccinated individuals with substance abuse.

Figure 5. Flowchart of selection procedure for objective 4

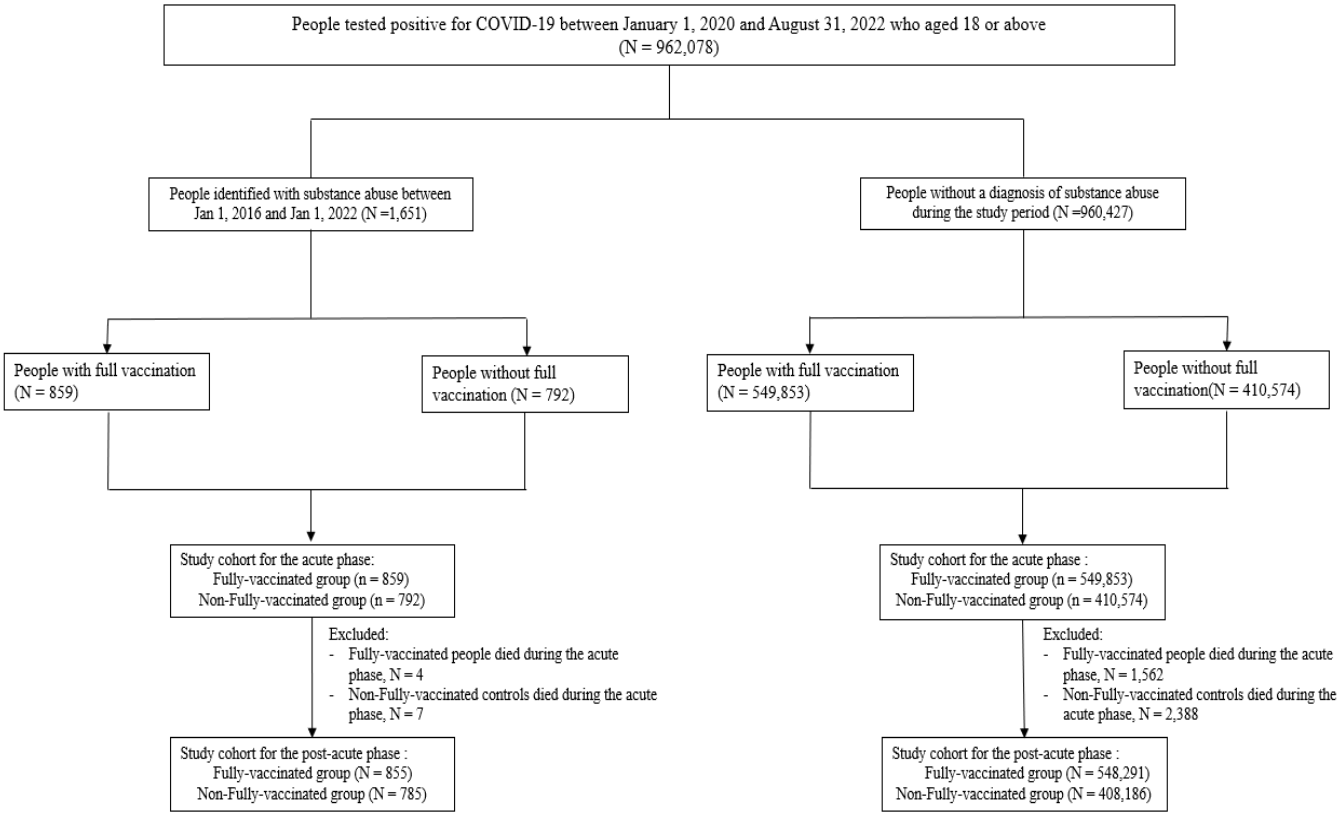

Table 17a. Baseline characteristics for Substance Abuse cohort before and after weighting (Acute phase)

	Before weighting			After weighting		
Baseline characteristics	**Fully vaccinated (N=859)**	**Non-fully-vaccinated (N=792)**	**SMD**	**Fully vaccinated (N=859)**	**Non-fully-vaccinated (N=792)**	**SMD**
Age, years (mean (SD))	46.22 (14.02)	47.41 (15.33)	0.081	46.98 (14.86)	47.15 (14.93)	0.012
Sex, male (%)	533 (62.0)	482 (60.9)	0.024	529.6 (61.6)	492.7 (62.2)	0.011
Charlson Comorbidity Index (mean (SD))	0.97 (1.52)	1.16 (1.72)	0.115	1.09 (1.68)	1.10 (1.62)	0.010
Pre-existing comorbidities						
Tobacco abuse (%)	14 (1.6)	16 (2.0)	0.029	16.4 (1.9)	14.6 (1.8)	0.005
Alcohol abuse (%)	93 (10.8)	73 (9.2)	0.054	85.0 (9.9)	78.4 (9.9)	<0.001
Myocardial infarction (%)	5 (0.6)	7 (0.9)	0.035	5.0 (0.6)	5.6 (0.7)	0.017
Congestive Heart Failure (%)	5 (0.6)	10 (1.3)	0.071	5.2 (0.6)	6.7 (0.8)	0.028
Cerebrovascular disease (%)	32 (3.7)	37 (4.7)	0.047	37.6 (4.4)	34.9 (4.4)	0.002
Chronic obstructive pulmonary disease (%)	48 (5.6)	65 (8.2)	0.103	58.4 (6.8)	58.2 (7.3)	0.022
Dementia (%)	2 (0.2)	10 (1.3)	0.120	10.5 (1.2)	6.1 (0.8)	0.045
Paralysis (%)	2 (0.2)	2 (0.3)	0.004	1.6 (0.2)	1.6 (0.2)	0.005
Chronic renal failure (%)	9 (1.0)	13 (1.6)	0.052	9.5 (1.1)	10.8 (1.4)	0.023
Mild liver disease (%)	15 (1.7)	6 (0.8)	0.089	9.6 (1.1)	15.5 (2.0)	0.068
Moderate-severe liver disease (%)	1 (0.1)	4 (0.5)	0.070	1.5 (0.2)	2.4 (0.3)	0.027
Ulcers (%)	26 (3.0)	24 (3.0)	<0.001	32.9 (3.8)	21.6 (2.7)	0.062
Rheumatoid arthritis and other inflammatory polyarthropathies (%)	2 (0.2)	1 (0.1)	0.025	1.2 (0.1)	0.7 (0.1)	0.012
Malignancy (%)	15 (1.7)	10 (1.3)	0.040	13.4 (1.6)	11.0 (1.4)	0.014
Metastatic solid tumour (%)	2 (0.2)	2 (0.3)	0.004	1.3 (0.2)	1.5 (0.2)	0.009
Major Cardiovascular disease (%)	50 (5.8)	67 (8.5)	0.103	57.4 (6.7)	57.3 (7.2)	0.022
Coronary artery disease (%)	15 (1.7)	26 (3.3)	0.098	15.9 (1.8)	19.1 (2.4)	0.039
Stroke (%)	32 (3.7)	38 (4.8)	0.053	37.6 (4.4)	35.6 (4.5)	0.006
Heart failure (%)	5 (0.6)	10 (1.3)	0.071	5.2 (0.6)	6.7 (0.8)	0.028
Asthma (%)	28 (3.3)	28 (3.5)	0.015	26.8 (3.1)	27.7 (3.5)	0.021
Hypertension (%)	128 (14.9)	126 (15.9)	0.028	127.6 (14.9)	117.6 (14.8)	<0.001
Diabetes (%)	86 (10.0)	81 (10.2)	0.007	96.3 (11.2)	77.4 (9.8)	0.047
Hyperlipidemia (%)	84 (9.8)	77 (9.7)	0.002	82.0 (9.5)	77.1 (9.7)	0.006
Cardiovascular diseases (%)	161 (18.7)	163 (20.6)	0.046	160.3 (18.7)	150.5 (19.0)	0.009
Neoplasms (%)	15 (1.7)	10 (1.3)	0.040	13.4 (1.6)	11.0 (1.4)	0.014
Major Mental Illness (%)	239 (27.8)	189 (23.9)	0.091	224.7 (26.2)	207.2 (26.2)	<0.001
Medication use within 90 days						
Renin-angiotensin-system agents (%)	73 (8.5)	73 (9.2)	0.025	79.9 (9.3)	66.9 (8.5)	0.030
Beta blockers (%)	122 (14.2)	92 (11.6)	0.077	109.0 (12.7)	97.5 (12.3)	0.011
Calcium channel blockers (%)	102 (11.9)	124 (15.7)	0.110	118.9 (13.8)	110.8 (14.0)	0.004
Diuretics (%)	13 (1.5)	34 (4.3)	0.166	24.1 (2.8)	24.9 (3.1)	0.020
Nitrates (%)	9 (1.0)	22 (2.8)	0.127	12.0 (1.4)	15.0 (1.9)	0.039
Lipid lowering agents (%)	114 (13.3)	120 (15.2)	0.054	126.8 (14.8)	113.3 (14.3)	0.013
Insulins (%)	15 (1.7)	27 (3.4)	0.105	28.6 (3.3)	20.4 (2.6)	0.044
Antidiabetic drugs (%)	81 (9.4)	71 (9.0)	0.016	82.6 (9.6)	69.8 (8.8)	0.028
Oral anticoagulants (%)	4 (0.5)	17 (2.1)	0.148	5.4 (0.6)	9.4 (1.2)	0.059
Antiplatelets (%)	51 (5.9)	60 (7.6)	0.065	58.5 (6.8)	52.9 (6.7)	0.005

Notes: SMD = standard mean difference; SD = standard deviation

Table 17b. Baseline characteristics for Substance Abuse cohort before and after weighting (Post-acute phase)

	Before weighting			After weighting		
Baseline characteristics	**Fully vaccinated (N=855)**	**Non-fully-vaccinated (N=785)**	**SMD**	**Fully vaccinated (N=855)**	**Non-fully-vaccinated (N=785)**	**SMD**
Age, years (mean (SD))	46.20 (14.04)	47.15 (15.13)	0.066	46.63 (14.57)	46.87 (14.85)	0.016
Sex, male (%)	530 (62.0)	477 (60.8)	0.025	516.5 (60.4)	487.4 (62.1)	0.035
Charlson Comorbidity Index (mean (SD))	0.97 (1.53)	1.13 (1.69)	0.098	1.04 (1.60)	1.06 (1.59)	0.014
Pre-existing comorbidities						
Tobacco abuse (%)	13 (1.5)	16 (2.0)	0.039	18.6 (2.2)	14.9 (1.9)	0.020
Alcohol abuse (%)	92 (10.8)	73 (9.3)	0.049	85.6 (10.0)	78.8 (10.0)	0.001
Myocardial infarction (%)	5 (0.6)	6 (0.8)	0.022	4.9 (0.6)	5.3 (0.7)	0.012
Congestive Heart Failure (%)	5 (0.6)	9 (1.1)	0.061	7.9 (0.9)	7.4 (0.9)	0.002
Cerebrovascular disease (%)	32 (3.7)	36 (4.6)	0.042	32.7 (3.8)	32.1 (4.1)	0.013
Chronic obstructive pulmonary disease (%)	48 (5.6)	63 (8.0)	0.096	55.6 (6.5)	55.6 (7.1)	0.023
Dementia (%)	2 (0.2)	7 (0.9)	0.088	10.9 (1.3)	4.3 (0.5)	0.078
Paralysis (%)	2 (0.2)	2 (0.3)	0.004	1.3 (0.2)	1.7 (0.2)	0.015
Chronic renal failure (%)	9 (1.1)	12 (1.5)	0.042	9.1 (1.1)	9.0 (1.1)	0.008
Mild liver disease (%)	15 (1.8)	6 (0.8)	0.089	9.5 (1.1)	14.7 (1.9)	0.064
Moderate-severe liver disease (%)	1 (0.1)	4 (0.5)	0.070	1.3 (0.1)	2.3 (0.3)	0.031
Ulcers (%)	24 (2.8)	24 (3.1)	0.015	26.3 (3.1)	21.3 (2.7)	0.021
Rheumatoid arthritis and other inflammatory polyarthropathies (%)	2 (0.2)	1 (0.1)	0.025	1.1 (0.1)	0.6 (0.1)	0.016
Malignancy (%)	15 (1.8)	10 (1.3)	0.039	13.5 (1.6)	11.0 (1.4)	0.015
Metastatic solid tumour (%)	2 (0.2)	2 (0.3)	0.004	1.3 (0.2)	1.2 (0.2)	0.001
Major Cardiovascular diseases (%)	50 (5.8)	65 (8.3)	0.095	54.8 (6.4)	54.9 (7.0)	0.023
Coronary artery disease (%)	15 (1.8)	25 (3.2)	0.092	15.7 (1.8)	19.3 (2.5)	0.043
Stroke (%)	32 (3.7)	37 (4.7)	0.048	32.7 (3.8)	32.8 (4.2)	0.018
Heart failure (%)	5 (0.6)	9 (1.1)	0.061	7.9 (0.9)	7.4 (0.9)	0.002
Asthma (%)	28 (3.3)	27 (3.4)	0.009	27.0 (3.2)	25.2 (3.2)	0.003
Hypertension (%)	127 (14.9)	124 (15.8)	0.026	129.1 (15.1)	117.9 (15.0)	0.002
Diabetes (%)	86 (10.1)	79 (10.1)	<0.001	93.2 (10.9)	71.1 (9.1)	0.062
Hyperlipidemia (%)	83 (9.7)	76 (9.7)	0.001	81.8 (9.6)	71.9 (9.2)	0.014
Cardiovascular diseases (%)	160 (18.7)	160 (20.4)	0.042	163.2 (19.1)	147.0 (18.7)	0.009
Neoplasms (%)	15 (1.8)	10 (1.3)	0.039	13.5 (1.6)	11.0 (1.4)	0.015
Major Mental Illness (%)	236 (27.6)	186 (23.7)	0.090	225.3 (26.4)	198.4 (25.3)	0.025
Medication use within 90 days						
Renin-angiotensin-system agents (%)	73 (8.5)	71 (9.0)	0.018	73.9 (8.6)	64.1 (8.2)	0.017
Beta blockers (%)	121 (14.2)	91 (11.6)	0.076	111.6 (13.1)	97.6 (12.4)	0.019
Calcium channel blockers (%)	101 (11.8)	121 (15.4)	0.105	115.0 (13.4)	108.8 (13.9)	0.012
Diuretics (%)	13 (1.5)	32 (4.1)	0.155	20.0 (2.3)	24.3 (3.1)	0.047
Nitrates (%)	9 (1.1)	21 (2.7)	0.120	11.5 (1.3)	14.3 (1.8)	0.039
Lipid lowering agents (%)	114 (13.3)	116 (14.8)	0.042	125.5 (14.7)	106.9 (13.6)	0.030
Insulins (%)	15 (1.8)	27 (3.4)	0.106	31.1 (3.6)	20.0 (2.6)	0.063
Antidiabetic drugs (%)	80 (9.4)	69 (8.8)	0.020	86.2 (10.1)	64.4 (8.2)	0.065

Oral anticoagulants (%)	4 (0.5)	16 (2.0)	0.142	7.3 (0.9)	9.1 (1.2)	0.030
Antiplatelets (%)	51 (6.0)	57 (7.3)	0.052	58.8 (6.9)	49.1 (6.3)	0.025
Immunosupressants (%)	9 (1.1)	1 (0.1)	0.121	5.1 (0.6)	3.8 (0.5)	0.014

Notes: SMD = standard mean difference; SD = standard deviation

Table 17c. Baseline characteristics for Without Substance Abuse cohort before and after weighting (Acute phase)

	Before weighting			**After weighting**		
Baseline characteristics	**Fully vaccinated (N= 549,853)**	**Non-fully-vaccinated (N= 410,574)**	**SMD**	**Fully vaccinated (N= 549,853)**	**Non-fully-vaccinated (N= 410,574)**	**SMD**
Age, years (mean (SD))	54.02 (17.00)	52.33 (19.04)	0.094	53.14 (17.46)	53.54 (18.53)	0.022
Sex, male (%)	251582 (45.8)	185397 (45.2)	0.012	251398.3 (45.7)	185197.8 (45.1)	0.012
Charlson Comorbidity Index (mean (SD))	1.57 (1.71)	1.55 (1.94)	0.014	1.55 (1.78)	1.58 (1.86)	0.013
Pre-existing comorbidities						
Tobacco abuse (%)	4497 (0.8)	2898 (0.7)	0.013	4293.3 (0.8)	3096.1 (0.8)	0.003
Alcohol abuse (%)	1217 (0.2)	1024 (0.2)	0.006	1277.8 (0.2)	953.1 (0.2)	<0.001
Myocardial infarction (%)	3131 (0.6)	3488 (0.8)	0.033	3727.5 (0.7)	2871.6 (0.7)	0.003
Congestive Heart Failure (%)	4071 (0.7)	5879 (1.4)	0.067	5586.8 (1.0)	4372.6 (1.1)	0.005
Cerebrovascular disease (%)	15660 (2.8)	16873 (4.1)	0.069	18702.2 (3.4)	13969.6 (3.4)	<0.001
Chronic obstructive pulmonary disease (%)	10100 (1.8)	9162 (2.2)	0.028	11023.3 (2.0)	8292.7 (2.0)	0.001
Dementia (%)	1335 (0.2)	2853 (0.7)	0.066	2137.0 (0.4)	1908.0 (0.5)	0.012
Paralysis (%)	825 (0.2)	1218 (0.3)	0.031	1149.0 (0.2)	889.7 (0.2)	0.002
Chronic renal failure (%)	5509 (1.0)	5945 (1.4)	0.041	6500.4 (1.2)	4987.7 (1.2)	0.003
Mild liver disease (%)	711 (0.1)	666 (0.2)	0.009	788.5 (0.1)	591.7 (0.1)	<0.001
Moderate-severe liver disease (%)	491 (0.1)	455 (0.1)	0.007	536.8 (0.1)	402.5 (0.1)	<0.001
Ulcers (%)	5152 (0.9)	4472 (1.1)	0.015	5497.5 (1.0)	4134.5 (1.0)	0.001
Rheumatoid arthritis and other inflammatory polyarthropathies (%)	2304 (0.4)	1652 (0.4)	0.003	2252.9 (0.4)	1712.1 (0.4)	0.001
Malignancy (%)	14221 (2.6)	11684 (2.8)	0.016	14872.3 (2.7)	11149.3 (2.7)	0.001
Metastatic solid tumour (%)	1979 (0.4)	2057 (0.5)	0.022	2340.7 (0.4)	1720.4 (0.4)	0.001
Major Cardiovascular disease (%)	36330 (6.6)	33647 (8.2)	0.061	40171.3 (7.3)	29964.9 (7.3)	<0.001
Coronary artery disease (%)	19295 (3.5)	15210 (3.7)	0.010	20026.6 (3.6)	14491.0 (3.5)	0.006
Stroke (%)	16499 (3.0)	17741 (4.3)	0.070	19542.5 (3.6)	14859.8 (3.6)	0.004
Heart failure (%)	4346 (0.8)	6162 (1.5)	0.067	5881.6 (1.1)	4648.9 (1.1)	0.006
Asthma (%)	5529 (1.0)	4176 (1.0)	0.001	5543.1 (1.0)	4169.1 (1.0)	0.001
Hypertension (%)	128027 (23.3)	87630 (21.3)	0.047	123927.3 (22.5)	91715.7 (22.3)	0.005
Diabetes (%)	64976 (11.8)	44236 (10.8)	0.033	63187.9 (11.5)	46060.0 (11.2)	0.009
Hyperlipidemia (%)	82632 (15.0)	51989 (12.7)	0.069	78176.2 (14.2)	56287.2 (13.7)	0.015
Cardiovascular diseases (%)	137304 (25.0)	96631 (23.5)	0.033	134503.6 (24.5)	99578.6 (24.3)	0.005
Neoplasms (%)	14690 (2.7)	12136 (3.0)	0.017	15404.1 (2.8)	11550.3 (2.8)	0.001
Major Mental Illness (%)	7845 (1.4)	6801 (1.7)	0.019	8484.9 (1.5)	6279.4 (1.5)	0.001

Medication use within 90 days						
Renin-angiotensin-system agents (%)	79244 (14.4)	54964 (13.4)	0.030	77581.3 (14.1)	56803.5 (13.8)	0.008
Beta blockers (%)	47488 (8.6)	36575 (8.9)	0.010	48252.1 (8.8)	36155.5 (8.8)	0.001
Calcium channel blockers (%)	111291 (20.2)	77033 (18.8)	0.037	108138.6 (19.7)	80287.8 (19.6)	0.003
Diuretics (%)	14666 (2.7)	14926 (3.6)	0.055	16881.8 (3.1)	12771.7 (3.1)	0.002
Nitrates (%)	10844 (2.0)	10291 (2.5)	0.036	12025.3 (2.2)	9174.2 (2.2)	0.003
Lipid lowering agents (%)	113381 (20.6)	75313 (18.3)	0.058	109697.1 (20.0)	79113.0 (19.3)	0.017
Insulins (%)	8748 (1.6)	8146 (2.0)	0.030	9588.6 (1.7)	7302.4 (1.8)	0.003
Antidiabetic drugs (%)	63144 (11.5)	41798 (10.2)	0.042	60898.2 (11.1)	44178.0 (10.8)	0.010
Oral anticoagulants (%)	5318 (1.0)	6029 (1.5)	0.046	6518.4 (1.2)	4938.8 (1.2)	0.002
Antiplatelets (%)	40288 (7.3)	34375 (8.4)	0.039	42805.9 (7.8)	32107.4 (7.8)	0.001
Immunosupressants (%)	2732 (0.5)	2016 (0.5)	0.001	2729.5 (0.5)	2046.5 (0.5)	<0.001

Notes: SMD = standard mean difference; SD = standard deviation

Table 17d. Baseline characteristics for Without Substance Abuse cohort before and after weighting (Post-acute phase)

	Before weighting			**After weighting**		
Baseline characteristics	**Fully vaccinated (N=548,291)**	**Non-fully-vaccinated (N=408,186)**	**SMD**	**Fully vaccinated (N=548,291)**	**Non-fully-vaccinated (N=408,186)**	**SMD**
Age, years (mean (SD))	53.94 (16.94)	52.14 (18.92)	0.100	53.05 (17.40)	53.37 (18.40)	0.018
Sex, male (%)	250649 (45.7)	183979 (45.1)	0.013	250525.0 (45.7)	183771.8 (45.0)	0.013
Charlson Comorbidity Index (mean (SD))	1.56 (1.70)	1.52 (1.91)	0.020	1.54 (1.76)	1.56 (1.84)	0.008
Pre-existing comorbidities						
Tobacco abuse (%)	4483 (0.8)	2862 (0.7)	0.013	4283.3 (0.8)	3062.7 (0.8)	0.004
Alcohol abuse (%)	1209 (0.2)	1011 (0.2)	0.006	1270.7 (0.2)	942.4 (0.2)	<0.001
Myocardial infarction (%)	3050 (0.6)	3363 (0.8)	0.032	3614.8 (0.7)	2771.8 (0.7)	0.002
Congestive Heart Failure (%)	3862 (0.7)	5561 (1.4)	0.065	5286.9 (1.0)	4143.6 (1.0)	0.005
Cerebrovascular disease (%)	15332 (2.8)	16279 (4.0)	0.066	18198.6 (3.3)	13548.6 (3.3)	<0.001
Chronic obstructive pulmonary disease (%)	9921 (1.8)	8893 (2.2)	0.026	10792.2 (2.0)	8069.7 (2.0)	0.001
Dementia (%)	1188 (0.2)	2618 (0.6)	0.065	1906.4 (0.3)	1744.7 (0.4)	0.013
Paralysis (%)	800 (0.1)	1172 (0.3)	0.030	1104.2 (0.2)	861.3 (0.2)	0.002
Chronic renal failure (%)	5333 (1.0)	5657 (1.4)	0.038	6249.9 (1.1)	4774.0 (1.2)	0.003
Mild liver disease (%)	702 (0.1)	648 (0.2)	0.008	774.5 (0.1)	578.0 (0.1)	<0.001
Moderate-severe liver disease (%)	479 (0.1)	437 (0.1)	0.006	521.3 (0.1)	389.0 (0.1)	<0.001
Ulcers (%)	5080 (0.9)	4350 (1.1)	0.014	5420.4 (1.0)	4021.9 (1.0)	<0.001
Rheumatoid arthritis and other inflammatory polyarthropathies (%)	2289 (0.4)	1629 (0.4)	0.003	2239.5 (0.4)	1685.1 (0.4)	0.001
Malignancy (%)	14031 (2.6)	11445 (2.8)	0.015	14699.8 (2.7)	10888.5 (2.7)	0.001
Metastatic solid tumour (%)	1900 (0.3)	1955 (0.5)	0.021	2237.7 (0.4)	1642.1 (0.4)	0.001
Major Cardiovascular disease (%)	35708 (6.5)	32620 (8.0)	0.057	39308.6 (7.2)	29177.1 (7.1)	0.001
Coronary artery disease (%)	19054 (3.5)	14840 (3.6)	0.009	19708.9 (3.6)	14190.3 (3.5)	0.006
Stroke (%)	16143 (2.9)	17111 (4.2)	0.067	19006.3 (3.5)	14405.2 (3.5)	0.003
Heart failure (%)	4130 (0.8)	5826 (1.4)	0.065	5570.3 (1.0)	4401.8 (1.1)	0.006
Asthma (%)	5495 (1.0)	4129 (1.0)	0.001	5520.7 (1.0)	4114.9 (1.0)	<0.001
Hypertension (%)	127212 (23.2)	86334 (21.2)	0.049	123028.9 (22.4)	90489.1 (22.2)	0.006

Diabetes (%)	64514 (11.8)	43522 (10.7)	0.035	62660.3 (11.4)	45384.2 (11.1)	0.010
Hyperlipidemia (%)	82283 (15.0)	51431 (12.6)	0.070	77808.4 (14.2)	55742.9 (13.7)	0.015
Cardiovascular diseases (%)	136302 (24.9)	95063 (23.3)	0.037	133362.9 (24.3)	98134.3 (24.0)	0.007
Neoplasms (%)	14490 (2.6)	11878 (2.9)	0.016	15216.5 (2.8)	11274.7 (2.8)	0.001
Major Mental Illness (%)	7794 (1.4)	6709 (1.6)	0.018	8391.3 (1.5)	6211.3 (1.5)	0.001
Medication use within 90 days						
Renin-angiotensin-system agents (%)	78722 (14.4)	54178 (13.3)	0.031	77019.9 (14.0)	56067.8 (13.7)	0.009
Beta blockers (%)	47091 (8.6)	35966 (8.8)	0.008	47820.9 (8.7)	35580.5 (8.7)	<0.001
Calcium channel blockers (%)	110572 (20.2)	75940 (18.6)	0.040	107384.4 (19.6)	79208.9 (19.4)	0.005
Diuretics (%)	14287 (2.6)	14314 (3.5)	0.052	16348.1 (3.0)	12318.1 (3.0)	0.002
Nitrates (%)	10681 (1.9)	10029 (2.5)	0.035	11827.3 (2.2)	8948.9 (2.2)	0.002
Lipid lowering agents (%)	112700 (20.6)	74268 (18.2)	0.060	108957.0 (19.9)	78135.8 (19.1)	0.018
Insulins (%)	8553 (1.6)	7890 (1.9)	0.028	9347.1 (1.7)	7088.2 (1.7)	0.002
Antidiabetic drugs (%)	62754 (11.4)	41222 (10.1)	0.043	60489.8 (11.0)	43606.0 (10.7)	0.011
Oral anticoagulants (%)	5191 (0.9)	5830 (1.4)	0.044	6340.4 (1.2)	4792.2 (1.2)	0.002
Antiplatelets (%)	39727 (7.2)	33479 (8.2)	0.036	42086.4 (7.7)	31358.7 (7.7)	<0.001
Immunosupressants (%)	2702 (0.5)	1990 (0.5)	0.001	2706.7 (0.5)	2004.0 (0.5)	<0.001

Notes: SMD = standard mean difference; SD = standard deviation

Table 18. Vaccine effectiveness of full vaccination of COVID-19 Vaccine against COVID-19 outcomes during acute phase

Exposure	Event	Follow-up time	Incidence Rate† (95% CI)	Adjusted HR (95% CI)	Vaccine Effectiveness % (95% CI)	P value
Substance Abuse cohort						
Hospitalisation						
Non-fully-vaccinated	124	57	2,175.44 (1,809.42,2,593.76)	(reference)		
Fully-vaccinated	81	65	1,246.15 (989.63,1,548.86)	0.60 (0.45,0.81)	39.90 (19.09,55.36)	0.001
A&E attendance						
Non-fully-vaccinated	140	56	2,500.00 (2,103.05,2,950.10)	(reference)		
Fully-vaccinated	105	64	1,640.63 (1,341.87,1,986.08)	0.66 (0.51,0.87)	33.79 (13.30,49.44)	0.003
All-cause mortality						
Non-fully-vaccinated	7	65	107.69 (43.30,221.89)	(reference)		
Fully-vaccinated	4	70	57.14 (15.57,146.31)	0.52 (0.14,1.91)	47.90 (-90.79,85.77)	0.325
Major Cardiovascular Disease						
Non-fully-vaccinated	0	59	0 (NA)	(reference)		
Fully-vaccinated	1	66	15.15 (0.38,84.42)	NA	NA	NA
Coronary artery disease						
Non-fully-vaccinated	0	63	0 (NA)	(reference)		
Fully-vaccinated	0	69	0 (NA)	NA	NA	NA
Heart failure						
Non-fully-vaccinated	0	64	0 (NA)	(reference)		
Fully-vaccinated	0	70	0 (NA)	NA	NA	NA
Stroke						
Non-fully-vaccinated	0	62	0 (NA)	(reference)		
Fully-vaccinated	1	68	14.71 (0.37,81.94)	NA	NA	NA
Depression						
Non-fully-vaccinated	0	55	0 (NA)	(reference)		
Fully-vaccinated	0	58	0 (NA)	NA	NA	NA
Anxiety						
Non-fully-vaccinated	0	62	0 (NA)	(reference)		
Fully-vaccinated	0	68	0 (NA)	NA	NA	NA
Suicide						
Non-fully-vaccinated	0	39	0 (NA)	(reference)		
Fully-vaccinated	0	45	0 (NA)	NA	NA	NA
COPD						
Non-fully-vaccinated	0	59	0 (NA)	(reference)		
Fully-vaccinated	0	66	0 (NA)	NA	NA	NA
Pneumonia						

Non-fully-vaccinated	2	58	34.48 (4.18,124.56)	(reference)		
Fully-vaccinated	0	67	0 (NA)	NA	NA	NA
Without Substance Abuse cohort						
Hospitalisation						
Non-fully-vaccinated	34409	31365	1,097.05 (1,085.49,1,108.70)	(reference)		
Fully-vaccinated	22602	43690	517.33 (510.60,524.12)	0.52 (0.51,0.53)	47.68 (46.78,48.56)	<0.001
A&E attendance						
Non-fully-vaccinated	38573	31038	1,242.77 (1,230.40,1,255.23)	(reference)		
Fully-vaccinated	36014	42745	842.53 (833.85,851.28)	0.72 (0.71,0.73)	27.92 (26.86,28.96)	<0.001
All-cause mortality						
Non-fully-vaccinated	2388	33620	71.03 (68.21,73.94)	(reference)		
Fully-vaccinated	1562	45113	34.62 (32.93,36.38)	0.60 (0.56,0.64)	39.89 (35.83,43.69)	<0.001
Major Cardiovascular Disease						
Non-fully-vaccinated	334	30891	10.81 (9.68,12.04)	(reference)		
Fully-vaccinated	393	42139	9.33 (8.43,10.30)	0.79 (0.69,0.92)	20.62 (8.07,31.46)	0.002
Coronary artery disease						
Non-fully-vaccinated	127	32383	3.92 (3.27,4.67)	(reference)		
Fully-vaccinated	156	43531	3.58 (3.04,4.19)	0.92 (0.73,1.17)	8.09 (-16.51,27.50)	0.486
Heart failure						
Non-fully-vaccinated	85	33127	2.57 (2.05,3.17)	(reference)		
Fully-vaccinated	57	44764	1.27 (0.96,1.65)	0.53 (0.37,0.74)	47.49 (26.21,62.63)	<0.001
Stroke						
Non-fully-vaccinated	212	32183	6.59 (5.73,7.54)	(reference)		
Fully-vaccinated	257	43762	5.87 (5.18,6.64)	0.84 (0.70,1.01)	16.14 (-0.77,30.21)	0.06
Depression						
Non-fully-vaccinated	11	33191	0.33 (0.17,0.59)	(reference)		
Fully-vaccinated	19	44564	0.43 (0.26,0.67)	1.30 (0.62,2.75)	-30.47 (-175.29,38.17)	0.485
Anxiety						
Non-fully-vaccinated	3	33451	0.09 (0.02,0.26)	(reference)		
Fully-vaccinated	6	44858	0.13 (0.05,0.29)	1.35 (0.34,5.46)	-35.48 (-445.81,66.37)	0.669
Suicide						
Non-fully-vaccinated	0	33540	0.00 (0.00,0.11)	(reference)		
Fully-vaccinated	0	45030	0.00 (0.00,0.08)	NA	NA	NA
COPD						
Non-fully-vaccinated	40	32879	1.22 (0.87,1.66)	(reference)		
Fully-vaccinated	41	44289	0.93 (0.66,1.26)	0.75 (0.48,1.16)	25.29 (-15.99,51.88)	0.194
Pneumonia						
Non-fully-vaccinated	871	32576	26.74 (24.99,28.57)	(reference)		

Fully-vaccinated	431	44348	9.72 (8.82,10.68)	0.41 (0.37,0.46)	58.70 (53.53,63.30)	<0.001

Notes: CI = confidence interval; A&E = Accident and Emergency; COPD = Chronic Obstructive Pulmonary Disease; NA = Not applicable; † per 1000 person-days

Table 19. Vaccine effectiveness of full vaccination of COVID-19 Vaccine against COVID-19 outcomes during post-acute phase

Exposure	Event	Follow-up time	Incidence Rate† (95% CI)	Adjusted HR (95% CI)	Vaccine Effectiveness % (95% CI)	P value
			Substance Abuse cohort			
Hospitalisation						
Non-fully-vaccinated	249	694	358.79 (315.61,406.23)	(reference)		
Fully-vaccinated	256	833	307.32 (270.83,347.37)	0.89 (0.74,1.08)	10.82 (-7.93,26.31)	0.24
A&E attendance						
Non-fully-vaccinated	331	607	545.30 (488.14,607.33)	(reference)		
Fully-vaccinated	366	717	510.46 (459.50,565.53)	0.89 (0.76,1.05)	10.60 (-5.46,24.21)	0.184
All-cause mortality						
Non-fully-vaccinated	29	1071	27.08 (18.13,38.89)	(reference)		
Fully-vaccinated	18	1113	16.17 (9.58,25.56)	0.89 (0.44,1.77)	11.43 (-76.74,55.61)	0.731
Major Cardiovascular Disease						
Non-fully-vaccinated	9	978	9.20 (4.21,17.47)	(reference)		
Fully-vaccinated	5	1045	4.78 (1.55,11.17)	0.63 (0.20,1.96)	36.86 (-95.67,79.63)	0.426
Coronary artery disease						
Non-fully-vaccinated	1	1036	0.97 (0.02,5.38)	(reference)		
Fully-vaccinated	2	1092	1.83 (0.22,6.62)	2.05 (0.18,24.06)	-105.30 (-2,305.68,82.48)	0.567
Heart failure						
Non-fully-vaccinated	5	1056	4.73 (1.54,11.05)	(reference)		
Fully-vaccinated	3	1105	2.71 (0.56,7.93)	0.54 (0.13,2.32)	46.19 (-131.66,87.50)	0.405
Stroke						
Non-fully-vaccinated	4	1018	3.93 (1.07,10.06)	(reference)		
Fully-vaccinated	1	1069	0.94 (0.02,5.21)	0.30 (0.03,2.76)	69.81 (-175.59,96.69)	0.288
Depression						
Non-fully-vaccinated	1	911	1.10 (0.03,6.12)	(reference)		
Fully-vaccinated	2	921	2.17 (0.26,7.84)	2.18 (0.20,24.03)	-118.02 (-2,302.75,80.22)	0.524
Anxiety						
Non-fully-vaccinated	1	1027	0.97 (0.02,5.43)	(reference)		
Fully-vaccinated	0	1075	0 (NA)	NA	NA	NA
Suicide						
Non-fully-vaccinated	0	646	0 (NA)	(reference)		
Fully-vaccinated	0	713	0 (NA)	NA	NA	NA
COPD						
Non-fully-vaccinated	2	987	2.03 (0.25,7.32)	(reference)		
Fully-vaccinated	2	1051	1.90 (0.23,6.87)	1.07 (0.14,8.19)	-6.75 (-718.96,86.08)	0.95
Pneumonia						

Non-fully-vaccinated	12	969	12.38 (6.40,21.63)	(reference)		
Fully-vaccinated	12	1052	11.41 (5.89,19.93)	1.33 (0.53,3.31)	-32.51 (-231.42,47.02)	0.547
Without Substance Abuse cohort						
Hospitalisation						
Non-fully-vaccinated	67948	463126	146.72 (145.61,147.82)	(reference)		
Fully-vaccinated	84815	621069	136.56 (135.65,137.49)	0.93 (0.92,0.94)	6.82 (5.87,7.77)	<0.001
A&E attendance						
Non-fully-vaccinated	1E+05	436190	244.13 (242.67,245.61)	(reference)		
Fully-vaccinated	1E+05	570184	234.60 (233.35,235.86)	0.98 (0.97,0.99)	2.04 (1.24,2.83)	<0.001
All-cause mortality						
Non-fully-vaccinated	9156	565816	16.18 (15.85,16.52)	(reference)		
Fully-vaccinated	5320	703586	7.56 (7.36,7.77)	0.54 (0.52,0.56)	45.86 (43.96,47.70)	<0.001
Major Cardiovascular Disease						
Non-fully-vaccinated	3066	520619	5.89 (5.68,6.10)	(reference)		
Fully-vaccinated	3433	656877	5.23 (5.05,5.40)	0.82 (0.78,0.86)	18.47 (14.35,22.39)	<0.001
Coronary artery disease						
Non-fully-vaccinated	1300	545138	2.38 (2.26,2.52)	(reference)		
Fully-vaccinated	1483	678781	2.18 (2.08,2.30)	0.89 (0.83,0.96)	10.91 (3.91,17.41)	0.003
Heart failure						
Non-fully-vaccinated	1137	557908	2.04 (1.92,2.16)	(reference)		
Fully-vaccinated	813	698269	1.16 (1.09,1.25)	0.60 (0.55,0.66)	40.08 (34.33,45.32)	<0.001
Stroke						
Non-fully-vaccinated	1641	542179	3.03 (2.88,3.18)	(reference)		
Fully-vaccinated	1825	682359	2.67 (2.55,2.80)	0.83 (0.78,0.89)	16.84 (11.02,22.28)	<0.001
Depression						
Non-fully-vaccinated	179	558627	0.32 (0.28,0.37)	(reference)		
Fully-vaccinated	188	694977	0.27 (0.23,0.31)	0.90 (0.73,1.11)	9.86 (-10.94,26.77)	0.327
Anxiety						
Non-fully-vaccinated	63	562975	0.11 (0.09,0.14)	(reference)		
Fully-vaccinated	49	699631	0.07 (0.05,0.09)	0.64 (0.44,0.93)	36.40 (7.24,56.39)	0.019
Suicide						
Non-fully-vaccinated	0	564501	0 (NA)	(reference)		
Fully-vaccinated	0	702311	0 (NA)	NA	NA	NA
COPD						
Non-fully-vaccinated	610	553782	1.10 (1.02,1.19)	(reference)		
Fully-vaccinated	577	690891	0.84 (0.77,0.91)	0.79 (0.70,0.88)	21.32 (11.65,29.93)	<0.001
Pneumonia						
Non-fully-vaccinated	3990	548720	7.27 (7.05,7.50)	(reference)		

Fully-vaccinated	2382	691881	3.44 (3.31,3.58)	0.52 (0.49,0.55)	48.02 (45.26,50.65)	<0.001

Notes: CI = confidence interval; A&E = Accident and Emergency; COPD = Chronic Obstructive Pulmonary Disease; NA = Not applicable; † per 1000 person-days

Chapter 5 Discussion

5.1 Interpretation of study results

5.1.1 The risk of COVID-19 infection in individuals with substance abuse

Our population-based study showed that there is no increased risk of COVID-19 infection but significantly increased the risk of COVID-19-related hospitalisation and COVID-19-related mortality in individuals with substance abuse compared to those without substance abuse.

Regarding the COVID-19 infection, this finding was inconsistent with results from a previous case-control study that individuals with substance abuse had a significantly higher risk of COVID-19 infection than patients without substance abuse [5]. The inconsistency may be due to differences in study design and subject inclusion period. Our cohort study design should provide more rigorous and less biased results compared to the case-control study design. Additionally, the previous case-control study covered the early COVID-19 period (up to June 15, 2020), while our study covered a longer COVID-19 period (up to January 1, 2021), during which different COVID-19 variants may have emerged. Therefore, direct comparison between the studies requires caution. In fact, individuals with substance abuse may be reluctant to report that they have COVID-19, as they may fear that their substance abuse could be discovered during medical check-ups. As a result, the COVID-19 infection rate among individuals with substance abuse may be underreported, particularly if their COVID-19 symptoms are mild.

Our results showed that substance abuse significantly increased the risk of COVID-19-related hospitalisation and COVID-19-related mortality. These findings were consistent with previous studies that substance use was associated with an increased risk of hospitalisation and mortality among patients diagnosed with COVID-19 [5, 33]. The long-recognised relationship between substance abuse and immunosuppression may contribute to the increased risk of COVID-19-related hospitalisation among patients with substance abuse. Previous study showed that the immunomodulatory effects of drugs of abuse may be an important factor contributing to susceptibility of infection diseases [2]. Common mechanisms involved in the immunomodulatory effects of drugs abuse include inhibition of Th_1- or elevation of Th_2-associated cytokines for illegal drugs of abuse (e.g., Cocaine, Cocaine, Opioid) and specific interactions with acetylcholine receptors in the central nervous system (CNS) and periphery for legal drugs (e.g., antidepressant drugs, caffeine, nicotine) [34]. The greater susceptibility to infection among patients with substance abuse may result in lower levels of protective

antibodies in the blood and more severe and longer lasting illnesses compared to those without substance abuse [35]. Additionally, substance abuse may acutely or chronically alter organ function, with pulmonary and respiratory involvement accounting for a major part of illicit drug-related morbidities [36], making patients with substance abuse particularly vulnerable to the adverse respiratory effects of COVID-19 and potentially increasing the severity of COVID-19-related adverse outcomes. Moreover, COVID-19 infection may also increase the risk of hospitalisation due to the damage on immune system. The virulence of SARS-CoV-2 family stems from non-structural proteins that disrupt immune responses, causing excessive inflammation and impaired immunity. This can lead to tissue damage where the virus invades, increasing pathogenicity [37]. The damage to the immune system may lead to greater susceptibility to infection among patients diagnosis with COVID-19 and may result in more severe symptoms of COVID-19. Additionally, SARS-CoV-2 may also affect respiratory system and other major organ systems, such as the gastrointestinal tract , hepatobiliary, cardiovascular, renal, and central nervous systems [38], which may lead to the higher prevalence of related comorbidities and risk of COVID-related hospitalisation.

Our findings confirmed that substance abuse increases the risk of COVID-19 complications, highlighting the need for attention, screening, and treatment of substance abuse in the context of COVID-19 infection.

5.1.2 Short- and long-term burden of COVID-19 among individuals with substance abuse

Our findings showed higher short- and long-term burden of COVID-19 in individuals with substance abuse. For short term burden, we found that compared to uninfected individuals with substance abuse, individuals with both substance abuse and COVID-19 infection were associated with higher risks of hospitalisation, A&E attendance, and all-cause mortality during the acute phase. The risk measures for each outcome showed a more than three-fold increase during this phase, indicating the short-term severity of COVID-19 infection among individuals with substance abuse. This might be related to the baseline health conditions of individuals with substance abuse. Several studies have shown that individuals with substance abuse issues may have compromised immune systems or pre-existing health conditions, making them more susceptible to severe illness and adverse outcomes caused by the virus during the acute phase of COVID-19 [1, 2]. Additionally, substance abuse can lead to respiratory and cardiovascular issues [3, 4, 7], which may further contribute to the increased risks of healthcare service

utilisation and mortality. The results also found that patients who were older than 65 years and received less than two doses of COVID-19 vaccines were more likely to have a higher risk of hospitalisation or A&E attendance. Therefore, monitoring this vulnerable population during the acute phase of COVID-19 is crucial, especially for those aged above 65 years or who received less than two doses of vaccination.

Regarding long-term burden, our study found that individuals with substance abuse with COVID-19 infection had no significantly increased risk of hospitalisation, A&E attendance, and all-cause mortality during this phase. There is no previous study evaluating the long-term impact of COVID-19 in individuals with substance abuse. This may be attributed to the inherent higher risk of healthcare service utilisation and mortality among individuals with substance abuse [39]. Previous study showed that a progressive reduction in risk of all-cause mortality was observed over one year between patients with and without COVID-19 in Hong Kong general population [40]. Furthermore, several nationwide population-based studies have provided evidence of gradual improvements in recovery among individuals infected with COVID-19 [41, 42]. These improvements are characterised by a decrease in the prevalence of self-reported symptoms and the proportion of infected individuals reporting non-recovery from health outcomes associated with the infection [41, 42]. Additionally, a reduced risk of post-infection clinical complications was reported six months after the initial infection in individuals with mild SARS-CoV-2 infections. Regarding the risk of cardiovascular and respiratory outcomes except for pneumonia, our study did not find any significant difference between the exposed group and the unexposed group during both the acute and post-acute phases. However, the findings may be primarily attributed to the limited sample size that the number of observed cases for these outcomes was small in both groups. Hence, this resulted in insufficient statistical power to detect significant differences in these outcomes. The finding of the increased risk of pneumonia during the post-acute phase was consistent with previous findings [43, 44]. Additionally, it was noted that full COVID-19 vaccination appeared to have a protective effect against health care utilisation during both the acute and post-acute phases of COVID-19. To further evaluate this protective effect of full COVID-19 vaccination against clinical outcomes and all-cause mortality among infected individuals, we compared the risk of these outcomes between fully vaccinated and non-fully vaccinated individuals, among those infected with or without substance abuse, in Objective 4. To sum up, given that increased risk of hospitalisation and A&E attendance during post-acute phase, this highlights the need for close long-term

monitoring and management of health conditions in individuals with substance abuse following recovery from COVID-19.

5.1.3 Vaccine effectiveness among vaccinated individuals with or without substance abuse

Our results showed a similar trend of vaccine effectiveness during the acute phase of COVID-19 between individuals with and without substance abuse. Fully-vaccinated patients had a risk reduction in hospitalisation, A&E attendance, and all-cause mortality compared to non-fully-vaccinated patients. A slight risk reduction was observed in hospitalisation, A&E attendance, and all-cause mortality during the post-acute phase in individuals without substance abuse. In contrast, no significant reduced risk was observed in hospitalisation, A&E attendance, and all-cause mortality during the post-acute phase in individuals with substance abuse. This difference might be due to the impaired immune systems and rapid waning immunity among individuals with substance abuse [1]. It was also noted that there was a wide confidence interval for these outcomes, especially for the all-cause mortality among individuals with substance abuse. Furthermore, most of the vaccine effectiveness measures lacked statistical significance in this group. This may be attributable to the limited sample size, which resulted in inadequate statistical power to detect meaningful differences in these outcomes. Hence, further studies with larger sample size are needed. There is no previous study evaluating the effectiveness of COVID-19 vaccination against the risk of post-acute sequelae after COVID-19 in individuals with substance abuse. The findings of a reduced risk of several post-acute sequelae in the individuals without substance abuse were consistent with previous literature focusing on the general population [45]. Our findings validate that COVID-19 vaccination is effective during the acute phase in individuals with substance abuse as well, underscoring the vital role of early vaccination intervention in controlling the pandemic and mitigating associated health burdens during both the acute and post-acute stages of COVID-19.

5.2 Clinical implications

Substance abuse poses tremendous threats, impacting the physical and mental health and social well-being of patients and their families. With the pandemic, the epidemic of substance abuse may also add to the burden of healthcare services. To our knowledge, this is the first study to describe the COVID-19 related outcomes of individuals with substance abuse, evaluate the effectiveness of vaccination on COVID-19 related outcomes, and explore this effectiveness

among substance abuse population. Findings in current study provided a current and comprehensive picture of substance abuse among this special patient group. The importance of screening and treatment of substance abuse was also emphasised due to its influence on COVID-19 related outcomes. Ultimately, the findings can inform the public on the consequences of substance abuse to their health and improve the management of individuals with substance abuse.

5.3 Limitations

There are several limitations in this study. First, similar to other retrospective epidemiological studies using electronic medical record data, there might be residual confounding; Second, hidden individuals with substance abuse or cases will not be captured in the HA database if individuals have not ever used healthcare services from public hospitals or clinics. However, we are confident there will be a representative sample as approximately 80% of Hong Kong residents use public hospitals and healthcare services [46], and the prevalence of substance abuse in the general population is low [47]; Although the number of patients with substance use disorder could have been under-reported during the pandemic years, we identified the study population based on medical records since 2016; therefore, people who were missed were probably new patients with substance use disorder who presented after 2020. The small proportion of missing cases is unlikely to change our study conclusions; Third, considering the relatively small sample size in our study, the risk of some secondary outcomes cannot be estimated due to limited power. Moreover, we cannot explore specific drug abuse for each drug. Lastly, our study used ICD-9-CM codes for identification of patients with substance abuse and outcomes measure, which were primarily for administrative purpose rather than research purpose. The outcome identification greatly depends on coding quality of doctor by using ICD-9-CM diagnosis codes and might not reflect the exact details on stimulants users.

Chapter 6 Conclusion

By understanding the impact of substance abuse on COVID-19 infection and its related outcomes and vaccination effectiveness, this study provides insights into the impact of substance abuse on COVID-19 infection, related outcomes, and vaccination effectiveness, highlights the significance of COVID-19 vaccination among people with substance abuse. It serves as a crucial alert to health policymakers and clinicians regarding the potential burden of COVID-19. Individuals with substance abuse who contracted COVID-19 are more likely to require emergency department visits and hospitalisation in both the short-term and long-term, imposing greater strain on public healthcare resources. To mitigate the downstream utilisation of resources, it is imperative to establish sustainable, accessible, and effective management for substance abuse, ensuring early care and treatment provision.

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